Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Recommendations
February 2023

In response to enquiries from a clinical bacteriophage specialist

Bacteriophage therapy for patients with difficult to treat bacterial infections

Recommendations for NHSScotland

Conventional antibiotic therapies may be insufficient for a small and diverse group of patients with difficult to treat bacterial infections. This population is characterised by one or more of the following:

- antibiotic resistance
- antibiotic sensitivity but clinical recalcitrance
- high risk of death or significant complications if surgical intervention is used to manage their infection
- patient specific factors that preclude the use of conventional antibiotics.

Bacteriophage therapy may, at the discretion of the responsible clinician, be appropriate management for patients with difficult to treat bacterial infections. A bacteriophage laboratory is being trialled within NHS Tayside. Bacteriophage therapy is not currently licensed by the Medicines and Healthcare Products Regulatory Agency and use must comply with their guidance on the supply of unlicensed medicinal products, available here.

Published evidence on bacteriophage therapy primarily consists of a heterogeneous collection of small single arm cohort studies, small case series and individual case studies. The majority of patients in these studies received bacteriophage therapy in combination with conventional antibiotic therapies. This means that there is a limited evidence base regarding the clinical effectiveness and safety of bacteriophage therapy.

The use of bacteriophage therapy is supported by a small number of randomised controlled trials suggesting that bacteriophage therapy may be effective for patients with difficult to treat bacterial infections.

Exploratory SHTG economic modelling and analysis suggest that the addition of bacteriophage therapy to standard of care is likely to be a cost effective use of resources within a subpopulation of patients with treatment-refractory diabetic foot infection at high risk of lower extremity amputation.

The 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.

NHSScotland is required to consider Scottish Health Technologies Group recommendations

What were we asked to look at?

A Clinical Director for Surgery and a clinical bacteriophage specialist asked us to review the evidence for the use of bacteriophage therapy in patients with difficult to treat bacterial infections who continue to experience significant infection-related disability despite optimal management. Consultants from medical and surgical specialties across NHSScotland confirmed the relevance of this topic for the health service.

Why is this important?

The incidence of antimicrobial tolerant and resistant bacterial infections is increasing worldwide, contributing to the strain on healthcare services due to longer hospital stays, rising medical costs and increased mortality.[1] During 2016, it was estimated that multi-drug resistant bacterial infections alone caused 700,000 deaths globally each year; if current practices continue this figure is expected to rise to 10 million deaths by 2050.[2] Bacteriophage therapy represents an option to address this problem in the near future.

What was our approach?

We produced an SHTG Recommendation based on a review of published evidence on the clinical effectiveness, safety and patient preferences regarding bacteriophage therapy for the treatment of patients with difficult to treat bacterial infections. De novo economic modelling by SHTG was used to assess the cost effectiveness of bacteriophage therapy in patients with severe treatment-refractory diabetic foot infections who are at risk of amputation. Further information on our SHTG Recommendations product can be found on the SHTG website.

What next?

Our recommendations will be used to inform the development of bacteriophage therapy across NHSScotland. The SHTG Recommendation will be made available to clinicians and the public via the SHTG website.

Key points from the evidence

1. The secondary literature regarding the clinical effectiveness and safety of bacteriophage therapy for patients with difficult to treat bacterial infections consists of seven systematic reviews based primarily on single-arm observational studies and case series.[3-9] Three of these systematic reviews were excluded from the evidence synthesis due to the degree of overlap in included studies.[7-9]

2. Evidence on the clinical effectiveness and safety of bacteriophage therapy should be interpreted with caution owing to a high risk of bias and indirectness (caused by studies including healthy volunteers or patients with acute infections) in primary studies.

Clinical effectiveness

3. The most recent systematic review (53 studies; two comparative; n=2,218) compared patients receiving bacteriophage therapy with a control group receiving standard of care or placebo across several medical and surgical specialties.[3] Based on a pooled analysis of randomised controlled trials (RCTs), patients in the control group were more likely to show clinical improvement than patients who received bacteriophage therapy (50% vs 43.8%; two RCTs). Conversely, patients treated with bacteriophage therapy were more likely to achieve bacterial eradication than those in the control group (16.6% vs 0.0%; 1 RCT).

4. A second systematic review (20 studies; 0 comparative; n=51) outlined the effect of bacteriophage therapy, with or without conventional antibiotic therapy, on patients with bone and joint infections.[4] Criteria for success following treatment were satisfied in 71% of treatment episodes; success by indication was 57% for patients with periprosthetic joint infections and 88% for patients with osteomyelitis.

5. A third systematic review (27 studies; two comparative; n=1,579) reported results for the effectiveness of bacteriophage therapy, with or without conventional antibiotic therapy, in patients with three different infection types:[5]
    a. **burn wound infections:** 49.6% of patients achieved clinical resolution, 27.9% showed improvement, and 22.5% showed no improvement. Excluding three studies that did not clearly report on clinical resolution, or where the bacteriophage therapy dropped below the therapeutic dose, resulted in 89.2% of patients achieving clinical resolution.
    b. **chronic wound or ulcer infections:** 65.8% achieved clinical resolution, 20.3% showed improvement, and 13.9% showed no improvement.
    c. **dermatological infections:** 87.3% achieved clinical resolution, 6.8% showed improvement, and 5.9% showed no improvement.

6. The fourth systematic review (30 studies; three comparative; n>1,152, one study did not report patient numbers) reported results for bacteriophage therapy in patients with multi-drug resistant infections.[6] Twenty-six of the 30 studies included showed that bacteriophage therapy successfully decreased or halted bacterial growth.

Safety

7. Safety data on bacteriophage therapy came from the four systematic reviews described under the clinical effectiveness subheading above.[3-6] Not all of the studies included in the reviews reported safety outcomes, hence the number of included studies and patient numbers differ between the clinical effectiveness and safety sections.

8. The most recent systematic review (51 studies; nine comparative; n=731) found that, based on a pooled analysis of nine RCTs, patients treated with bacteriophage therapy were less likely to experience adverse events than those in the control group (7.6% vs 14.9%; 9 RCTs).[3] No adverse events were reported in the observational studies. A pooled analysis of case series found an adverse event rate comparable to that observed in the RCTs.

9. The second systematic review (20 studies; n=51) noted that eight of the 20 studies included reported adverse events associated with bacteriophage therapy, finding that adverse events occurred in 8% of treatment episodes, all of which were considered to be minor: elevation of liver function tests, mild pruritis associated with an elevation of Tumour Necrosis Factor alpha, or redness and pain.[4]

10. The third systematic review (15 studies; n=1,095) included three studies in patients with burn wound infections that found no adverse events, five studies in patients with chronic wound or ulcer infections, four of which identified no adverse events, and eight studies in patients with dermatological infections, seven of which did note adverse events.[5] Adverse events were described on an individual study basis, were relatively mild and were not thought to be directly related to bacteriophage therapy. Adverse event data from this review was primarily from studies conducted between 1929 and 1987 and therefore should be interpreted with caution.

11. The fourth systematic review (22 studies; n=not reported) reported that 20 studies found no adverse events.[9] The remaining two studies noted subsequent infections after treatment, eczema, increased pain, nausea and vomiting, but had limited data to confirm whether these were related to bacteriophage therapy. No studies reported an association between phage administration and death.

Patient and social aspects

12. The literature on patient and social aspects is limited to a single study on patient preferences around bacteriophage therapy and antibiotic therapy for diabetic foot ulcer infections. The study explored patient awareness and concern about antibiotic resistance, and perceptions of bacteriophage therapy, through a survey (n=55) and focus group (n=5) with Scottish patients and found that:
    a. patients' levels of concern about antibiotic versus bacteriophage therapy were not statistically significantly different
    b. after reading information about bacteriophage therapy, 87% of patients stated they would accept bacteriophage therapy if it was recommended by their doctor
    c. all focus group participants were supportive of bacteriophage therapy, and four of the five strongly expressed a willingness to use bacteriophage therapy in lieu of intravenous antibiotics if possible, citing ease of use, the potential not to be admitted to hospital and the likelihood of a significantly reduced side effect profile.

13. The views of patients were captured via a patient organisation submission received from Antibiotic Research UK which noted that:
    a. patients with antibiotic resistant infections feel there is a lack of acceptance or confirmation of their ongoing suffering and a need to travel to private clinics in England, or even abroad, to access alternative treatments
    b. recurrent and resistant infection's dramatically reduce quality of life for patients and their families. They severely affect mental health; many patients say life is not worth living and admit to having suicidal thoughts.
    c. antibiotic resistant infections represent an economic burden for patients through being unable to work and to the NHS due to long-term care needs.

Cost effectiveness

14. No published cost effectiveness evidence was identified during the literature search. An economic model was therefore developed by SHTG to inform the recommendations on the use of bacteriophage therapy for the treatment of patients with difficult to treat bacterial infections.

15. The economic evaluation estimated the cost effectiveness of bacteriophage therapy plus standard of care versus standard of care only for the treatment of adults with severe treatment-refractory diabetic foot infections who were at risk of amputation despite conventional antibiotic therapy. This population represents a subset of the overall patient

population who may be suitable for bacteriophage therapy, and was selected for analysis based on the availability clinical expertise to inform the analysis.

16. Base case results indicate that bacteriophage therapy plus standard of care is less costly and more effective than standard of care only. The cost savings associated with bacteriophage therapy plus standard of care stem from a lower proportion of patients requiring minor or major lower extremity amputation, leading to an overall lower cost of care and higher quality-adjusted life years (QALYs). Of note:
    a. probabilistic sensitivity analysis estimated that bacteriophage therapy plus standard of care has approximately an 85% probability of being cost effective using a willingness to pay threshold of £20,000 per QALY.
    b. individual scenario analyses indicate that the cost effectiveness of bacteriophage therapy plus standard of care versus standard of care only is relatively stable, with the majority of scenarios estimating that bacteriophage therapy plus standard of care remains a dominant (that is, less costly and more effective) treatment strategy despite changes in key parameters.
    c. the cost effectiveness of bacteriophage therapy plus standard of care was less clear when a number of conservative assumptions regarding its clinical effectiveness and cost were combined (for example, a 75% reduction in the probability of clinical resolution and a 200% increase in the cost of treatment).

SHTG Council considerations

1. In reaching their recommendations, the Council took into account the range of information and evidence that was gathered as part of the health technology assessment (HTA) process, including the published literature, the SHTG economic evaluation, and public and patient experiences gathered through engagement with Antibiotic Research UK.

2. The Council acknowledged that antimicrobial resistance is a global public health challenge and that bacteriophage therapy offers a promising alternative or adjunct to conventional antibiotics.

3. The Council recognised the significant impact that difficult to treat bacterial infections have on patients' quality of life and that of their family members.

4. Clinical experts outlined the burden of difficult to treat bacterial infections for patients across NHSScotland and highlighted the potential value of bacteriophage therapy as an adjunctive treatment for these patients.

5. The Council agreed that the focus of the research question was on patients with difficult to treat bacterial infections, and that bacteriophage therapy would not be considered for use in a general patient population until sufficient clinical evidence exists. An overview of the current use of bacteriophage therapy across Western Europe and North America on a compassionate use basis was provided, and recent guidelines for the use of bacteriophage therapy in clinical practice produced by the Antimicrobial Resistance Leadership Group in the United States of America were highlighted.

6. The Council noted the differences in the reported efficacy of bacteriophage therapy between observational evidence and RCTs. Clinical experts outlined the complexity of conducting clinical trials with a biological medicine such as bacteriophage therapy versus chemical medicines such as conventional antibiotics. They explained that for efficacy to be observed, a therapeutic amount of the correct bacteriophages must be delivered to the correct area to treat infections containing a sufficient number of susceptible bacterial cells. It was noted that trials that have not demonstrated efficacy are unlikely to have fulfilled one or more of these requirements.

7. The Council discussed the history of bacteriophage from their discovery in the early 20th century to their subsequent manipulation and therapeutic use. It was noted that as naturally occurring organisms, bacteriophage are non-patentable and it was suggested that this may have hindered their use in modern medical settings.

8. The Council asked about the availability of guidance for the clinical use of bacteriophage in patients with different types of infection. Clinical experts explained that further research is required to establish a recommended dose and duration of treatment in specific clinical indications. Experts went on to say that dose and duration is currently guided by the published literature as well as being based on each individual patient's response to treatment.

9. The Council discussed the potential for long-term adverse events associated with bacteriophage therapy, and stated the importance of gathering this safety data. Clinical experts were not aware of any long-term adverse events, but noted that antibodies to a particular bacteriophage can develop during prolonged treatment. The Medicines and Healthcare Products Regulatory Agency's Yellow Card System facilitates the collection of adverse event data.

10. The Council acknowledged the value of the SHTG economic evaluation in informing its decision making, while noting that it was an exploratory analysis within a specific subpopulation of patients within the overall population of the recommendation.

11. The Council debated the practicalities of accessing bacteriophage products and expertise from the bacteriophage laboratory hosted within NHS Tayside. It was explained that the bacteriophage laboratory is grant funded for one-year. It was suggested that, if NHSScotland was to manufacture its own bacteriophage products, this should be consolidated within a single specialist centre for financial reasons and to aid the development of expertise.

12. The Council highlighted potential equality issues regarding access to treatment between urban and rural health boards. It was explained that patients could be treated with bacteriophage therapy at their local hospital regardless of their geographical location which may mitigate equality of access concerns.

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Introduction

Difficult to treat bacterial infections can occur in patients from almost all medical and surgical specialties. The continuation of infection for patients stems from factors that can be categorised as either ineffective clearance of the causative pathogen by the patient's immune system or ineffective killing of the pathogen by conventional antibiotics.[10]

Ineffective clearance by the immune system occurs when a pathogen alters a patient's immune response through initiation of an inappropriate anti-inflammatory response that decreases the likelihood of pathogen clearance. Alternatively, bacteria may change the expression of their surface antigens to avoid detection by the immune system.

Ineffective killing by conventional antibiotics can be caused by inadequate dispersion of drugs within infected tissues, or the presence of bacteria that are able to either tolerate or resist the bactericidal effects of conventional antibiotics through various mechanisms.[11] Inadequate dispersion of drugs within infected tissues may lead to an insufficient concentration of antibiotics at the site of infection to inhibit bacterial growth. Antibiotic tolerance allows bacteria to survive transient exposure to high concentrations of antibiotics by slowing bacterial processes, allowing the re-emergence of the pathogen after treatment is discontinued. Antibiotic resistance enables the growth of bacteria at high concentrations of an antibiotic irrespective of treatment duration through genetic adaptation or horizontal gene transfer.

The rising incidence of difficult to treat bacterial infections has contributed to a strain on healthcare services worldwide, because it leads to longer hospital stays, rising medical costs and increased mortality.[1] Antimicrobial resistance among bacterial pathogens is recognised as a major global public health threat. Multi-drug resistant bacteria are increasingly being identified not only in the hospital environment, but in community settings as well. A report published in 2016 estimated that antimicrobial resistance will cause 10 million deaths per year by 2050, with a loss of up to £64 trillion to the global economy.[2] This situation is compounded by a decreasing pipeline of antibiotics coming onto the market, which means clinicians may be faced with fewer reliable alternatives for the treatment of patients with multi-drug resistant infections. Bacteriophages represent an alternative treatment option for difficult to treat bacterial infections, and in the global fight against antimicrobial resistance.

Research questions

1. Are naturally occurring (unmodified) lytic bacteriophage clinically effective, cost effective, and safe for the treatment of patients with difficult to treat bacterial infections who continue to experience significant infection-related disability despite optimal management?

2. What are patients' experiences and views of bacteriophage therapy for difficult to treat bacterial infections?

Literature search

A systematic search of the secondary literature was carried out between 9 March 2022 and 5 April 2022 to identify systematic reviews and meta-analyses, health technology assessments and other evidence based reports. The Medline and Embase databases were searched.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

A separate search for patient and social aspects was undertaken. This involved a search of selected websites, and the Medline and PsycInfo databases using search filters to identify qualitative studies. Details of the search filters used are available on request.

All results were limited to English language and studies conducted in humans. No limits regarding the publication date were applied following advice from the topic referrers.

Concepts used in all searches included: phages and bacteriophages. A full list of resources searched and terms used is available on request.

Health technology description

Bacteriophages (phages) are naturally occurring viruses ranging between 20 to 200 nm in size that selectively target bacteria in a species-specific and sometimes strain-specific manner.[12] Phages are the most common biological entities in nature, with $1x10^{32}$ phages estimated to be on the planet and more phages on or inside of the human body than there are human cells composing it.

The two main classes of phages, lytic (virulent) and lysogenic (temperate), are categorised by the characteristics of their life cycle.[13] During the lytic life cycle, phage bind to specific receptors on the surface of the bacterial cell and inject their genetic material into its cytoplasm. This leads to degradation of bacterial cell DNA, allowing the phage to acquire control of the biosynthetic machinery of the cell to produce structural and non-structural phage proteins. After biosynthesis of these proteins, viral assembly takes place generating approximately 50 to 200 new phage that exert pressure on the bacterial cell wall. The rupturing of the cell wall occurs due to the accumulation of phage lysis proteins, releasing new phages that are then able to start another infection cycle. By comparison, during the lysogenic life cycle, phage DNA is replicated alongside bacterial DNA, thereby establishing a stable relationship. At a later stage, a switch from the lysogenic to the lytic form can occur leading to the activation of the lytic life cycle.

The therapeutic administration of phages (phage therapy [PT]) has been carried out since the early 20th century, primarily in the former Soviet Union and Eastern Europe, as an alternative or adjunct to conventional antibiotic therapy.[14] Lytic phage have several properties for use as a treatment for bacterial infections:[13]

- lytic phages exhibit high specificity for particular bacterial species and are therefore believed to leave commensal flora unaffected
- the specificity of phages means they are less likely to induce cross-resistance among bacterial species than conventional antibiotics
- phages are unaffected by the tolerance or resistance of bacteria to conventional antibiotics and may resensitise bacteria to antibiotics[15]
- PT can be administered in combination with conventional antibiotics through multiple delivery mechanisms including oral, local, inhalation, intravenous, or topical administration
- phages self-amplify as part of their lifecycle in the presence of their target bacteria but are self-limiting in its absence
- Select species of phages contain polysaccharide depolymerases that can degrade biofilms, a common feature in difficult to treat bacterial infections that prevents antibiotic penetration in susceptible infections.[13]

The usage of PT across the United Kingdom (UK) has been limited to a small number of patients. Topical anti-staphylococcal PT, in combination with conventional antibiotics, was provided to 10 patients with diabetic foot infection (DFI) at high risk of amputation despite conventional antibiotic therapy at the Royal Infirmary in Edinburgh and Queen Elizabeth University Hospital in Glasgow (unpublished, 2022). Two paediatric patients with cystic fibrosis have received intravenous anti-mycobacterial PT at Great Ormond Street Hospital in London.[16]

There are currently no phages suitable for therapeutic use manufactured in the UK, in part due to a requirement that unlicensed medicinal products for human use must be manufactured according to Good Manufacturing Process (GMP) standards (Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 23 August 2022). This requirement does not apply to phages imported from outside the UK, therefore the phage products used to treat the patients with DFI at the Royal Infirmary in Edinburgh and Queen Elizabeth University Hospital in Glasgow and the paediatric cystic fibrosis patients at Great Ormond Street Hospital in London were sourced from the Queen Astrid Military Hospital in Belgium and an academic laboratory at the University of Pittsburgh in the United States (US), respectively.

Regulatory status

The Medicines and Healthcare Products Regulatory Authority (MHRA) categorises PT as a biological medicine and notes that there are currently no medicinal products containing phage as an active ingredient registered in the UK. PT may be provided as an unlicensed medicinal product for human use (such products are commonly described as ‘specials’) subject to appropriate authorisation (Mr

Malcolm Hawkins, Senior Executive Officer, MHRA. Personal communication, 13 September 2022). This policy on unlicensed medicines exists for situations where, in the opinion of the patient's clinician(s), licensed treatments are unable to meet the patient's clinical needs and unlicensed options may be in the best interest of the patient. In the context of PT, this may include the following situations: antibiotic resistant infections; antibiotic susceptible but clinically recalcitrant chronic infections; where patient-specific factors prevent the use of appropriate antibiotics (for example, for patients with renal failure or allergy); or where further medical intervention is preferred to surgery (for example, in patients at high risk surgical candidates). The MHRA advises that phages can be imported into the UK for therapeutic use provided specific criteria are met. This requires all of the following criteria to be met in full:[17]

- 'Supplied in response to an unsolicited order.'
- 'Are manufactured and assembled to the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber.'
- 'Are for use by a patient for whose treatment that person is directly responsible for, in order to fulfil the special needs of that patient.'[17]

Further details on the regulatory requirements for unlicensed medicines can be found in MHRA Guidance Note 14.

Manufacturing phage products

The manufacture of unlicensed medicinal products or 'specials' within the UK or the importation of these products into the UK is subject to the regulatory requirements described in MHRA Guidance Note 14.[17] NHSScotland is required to adhere to these regulations if it chooses to manufacture phage products.

Epidemiology

The research questions posed by the topic referrers comprises patients across a wide variety of medical and surgical specialties. The broad scope of these questions means that it is not feasible to provide an accurate estimate of the number of patients expected to be eligible for PT across NHSScotland based on published literature sources.

A partial perspective on the number of patients expected to be eligible for PT across NHSScotland can be provided using the results of a survey of NHSScotland consultants across multiple specialties organised by the topic referrers during 2021. The results of this survey are presented in *Table 1* (Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 23 August 2022). Consultants were asked to estimate the number of patients at their hospital receiving care in their specialty who

would be eligible for PT due to their 'special clinical needs' as described above. A total of 21 consultants from 11 different hospitals across 11 health boards responded to the survey. Based on the information provided, there are estimated to be at least 906 patients who would be eligible to receive PT across NHSScotland. These figures may underestimate the total number of eligible patients given the relatively small number of responses received and that not all hospitals or health boards participated in the survey.

Table 1: Estimated number of patients eligible for PT by infection type across NHSScotland

Infection type	Estimated number of eligible patients	
Diabetic Foot	457	
Surgical Site	165	
Bone/Prosthetic	120	
Vascular	20	
Urinary	100	
Respiratory	32	
Dermatological	10	
Other	2	
Total	**Eligible patients**	**906**
	Respondents	**21**
	Hospitals	**11**
	Health boards	**11**

Note: health boards not included in survey results are NHS Dumfries and Galloway, NHS Orkney, NHS Shetland, NHS Western Isles, Golden Jubilee National Hospital, and The State Hospital

Guidance

During 2020, the National Institute of Allergy and Infectious Diseases and the Antibacterial Resistance Leadership Group (ARLG) phage task force in the US produced a series of evidence based suggestions for the experimental use of PT in clinical practice.[18] The ARLG task force suggests the following:

- 'Experimental phage therapy may be considered for a variety of infections refractory to conventional antibiotics including respiratory tract infections, infections involving devices that cannot be removed, osteo-articular infections, urinary tract infections, gastrointestinal infections, endovascular infections and other source infections.
- 'If phage therapy is used, it should be in conjunction with conventional antibiotics.'
- 'Phage therapy is generally safe to administer, with adverse events rarely reported.

Clinical effectiveness

Seven acceptable or high quality systematic reviews reported on the clinical effectiveness of PT for treating patients with difficult to treat bacterial infections.[4-9, 19] Three of the seven reviews were excluded from the evidence synthesis because of the large degree of overlap in included studies.[7-9] None of the systematic reviews identified a meta-analysis due to heterogeneity between studies caused by the variety of pathologies, pathogens, treatments with different phages (single versus cocktails) via different administration routes, and the fact that PT was sometimes combined with other treatments.

The most recent systematic review incorporated 53 studies comparing PT, with or without conventional antibiotics, through different administration routes, with a control group in patients with difficult to treat bacterial infections across several medical specialties.[19] The control group received either standard of care (SoC) defined as conventional antibiotics, surgery, or a placebo. Approximately 58% of patients receiving PT also received concomitant broad-spectrum antibiotics. The most common causative pathogens were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Escherichia coli*. The authors of the review assessed the risk of bias in included trials using the Cochrane risk of bias tool and assessed non-randomised studies using the risk of bias in non-randomised studies of interventions tool. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was used to assess the strength of the evidence for each outcome. The authors considered the quality of evidence to be very low to moderate, mainly due to a high risk of bias and indirectness. The risk of bias arose from the types of evidence included (for example, uncontrolled or non-blinded observational trials and case series) and loss of patients to follow-up. Since publication, the authors' assessment of the strength of the evidence has received criticism, with a comment made that evidence based on RCTs should be rated as low on the basis of imprecision due to the small sample sizes involved.[20] In addition, it was noted that evidence based on observational trials should be rated as very low due to the risk of bias among the included studies. The authors acknowledged that, while they did not consider the impact of imprecision for one RCT, they did assess the risk of bias in observational trials and stand by their conclusions.[21]

Results from the pooled analysis component of the systematic review are presented in *Table 2*. A pooled analysis of the two RCTs found that 43.8% of patients treated with PT achieved clinical improvement (defined as a subjective or objective improvement in quality of life, reduction in bacterial load or reduction in biofilm mass) compared with 50.0% of patients in the control group. Bacterial eradication was achieved in 16.6% of patients who received PT compared with no patients in the control group. The magnitude of the treatment effect associated with PT for these outcomes was larger when observational trials and case series were analysed; specifically, 74.2% of observational trial patients and 86.4% of case study patients achieved clinical improvement with PT. Similarly, 55.5% of observational trial patients and 79.2% of case study patients had bacterial eradication with PT. No data from observational trials or case studies was available to estimate the

treatment effect for the control group. The review authors considered the evidence underpinning these outcomes to be of moderate quality based on RCT evidence, low quality for observational trials, and very low quality for case study data.

Table 2: Pooled analysis comparing PT with a control group comprised of SoC or placebo in patients with difficult to treat bacterial infections[19]

	Comparative risk		Duration of follow-up	GRADE assessment of quality of evidence
	PT	Control group		
Clinical improvement				
n=66 (2 RCT)	43.8% (n=14/32)	50.0% (n=17/34)	42 days to 6 months	Moderate (due to indirectness)
n=1,983 (8 OBS)	74.2% (n=1,333/1,797)	NA	7 days to 3 months	Low (due to risk of bias)
n=169 (43 CS)	86.4% (n=146/169)	NA	1 month to 24 months	Very low (due to risk of bias and indirectness)
Bacterial eradication				
n=24 (1 RCT)	16.6% (n=2/12)	0.0%	42 days	Moderate (due to risk of bias)
n=274 (7 OBS)	55.5% (n=152/274)	NA	7 days to 3 months	Low (due to risk of bias)
n=53 (32 CS)	79.2% (n=42/53)	NA	1 month to 27 months	Very low (due to risk of bias and indirectness)

Abbreviations: PT = phage therapy; RCT = randomised controlled trials; OBS = observational trials; CS = case studies; NR = not reported; NA = not applicable; GRADE = Grading of Recommendations, Assessment, Development and Evaluations

A second systematic review focused on patients with bone and joint infections which included any infection of the bone (osteomyelitis), joint (septic arthritis) or implants related to these structures (that is, periprosthetic joint infections [PJI] or fracture-related infections [FRI] involving plates, screws, or intramedullary nails).[4] The review included 10 of the studies included in the most recent review[3], and a further 10 studies that were not captured by the search strategy of the more recent paper. The 20 studies (one cohort study, n=12; six case series, n=26; 13 case reports, n=13) identified for inclusion represented 51 patients and 52 treatment episodes (one patient received two separate rounds of PT). Almost all patients suffered from an infection located in the lower limbs, with the hip (27%, n=14/52), knee (27%, n=14/52) and toes (15%, n=8/52) being the most common. Over half of patients (54%, n=28/52) had a PJI, while the remainder (46%, n=24/52) had osteomyelitis (including FRIs). The organisms targeted by PT were mostly *Staphylococcus aureus* (58%, n=13/52), *Staphylococcus epidermis* (25%, n=13/52) and *Pseudomonas aeruginosa* (17%, n=9/52). Phages were tested for specificity to the targeted bacteria in 83% (n=43/52) of cases. PT was used to target one

pathogen in the majority of treatment episodes (87%, n=45/52) and targeted a maximum of two pathogens in seven cases (13%). Concomitant antibiotics were given in the majority of cases (79%, n=45/52).

Success following treatment was defined as clinical, microbiological and radiological evidence for resolution of infection and absence of infection relapse after administration of a PT treatment episode. Each of these three parameters did not have to be reported for inclusion, but all parameters that were reported had to indicate infection resolution. Criteria for success was satisfied in 71% (n=37/52) of treatment episodes, and success by indication was 57% for PJI (n=16/28) and 88% for osteomyelitis (n=21/24). For treatment episodes considered failures (29%, n=15/52), 4% (n=2/52) showed clinical signs of infection after PT without microbiological evidence of infection, 13% (n=7/52) were followed by a secondary infection with a different bacterial strain or species, 4% (n=2/52) did not result in any bacteriological and/or radiological resolution or were followed by a relapse with the same bacterial strain, and 8% (n=4/52) were negatively affected by a comorbidity. In failed cases, infection resolution was obtained for six cases after additional interventions and/or therapies (12%); the final outcome remained unfavourable in five cases (10%), and was negatively affected by a comorbidity in four cases (8%). 83% (n=43/52) of treatment episodes resulted in an eventual positive outcome.

The third systematic review focused on patients with dermatological infections, burn wound infections, chronic wound or ulcer infections.[5] This paper included 10 of the 65 studies included in the most recent review[3] and three of the 20 studies included in the second review[4], but also incorporated 14 other studies, the majority of which were published before 1 January 2000, that would not have been identified given the date limits applied in the search strategy of the most recent reviews. Twenty-seven studies (two RCTs, n=28; 25 case study or series, n=1,551) were identified for inclusion and divided into three groups pertaining to the treatment of dermatological (10 studies), burn wound (eight studies), chronic wound or ulcer (12 studies) infections. Bacterial genera and species for which reports of PT were identified included *Escherichia coli, Enterococcus, Klebsiella, Pseudomonas aeruginosa, Proteus, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus lugdenensis,* and *Streptococcus*.

Eight studies (n=156) that reported data for burn wound infections comprised one phase I/II clinical trial, one case report and six case series. Testing of the in vitro efficacy of phage against a patient's bacterial isolate (phage susceptibility testing) was reported or implied in six of the eight studies. The phage treatments used were unpurified phage lysates (n=1), phage cocktails (n=3), a phage-containing biodegradable bandage (n=1) or was unclear (n=3). The authors noted that a precise efficacy could not be derived, because coadministered therapies, type of phage used, reporting time points and methodologies differed between all studies. Despite these caveats, the authors stated that, given that most infections in the primary studies were refractory to antibiotics, a crude and cautionary estimate of efficacy could be derived after partially excluding one report in which outcome data were unclear for 45 out of 54 patients. The remaining data represented 111 patients, of whom: 49.6% achieved clinical resolution, 27.9% showed improvement and 22.5% showed no

improvement. Excluding three studies that did not clearly report on clinical resolution, or where the phage therapy dropped below the therapeutic dose, resulted in an estimated 89.2% of patients achieving clinical resolution. Bacterial resistance to phage was recorded for three patients that did not reach the primary endpoint in the PhagoBurn clinical trial. No other studies commented on bacterial resistance to PT.

Twelve studies (n=327) reported data for patients with chronic wound or ulcer infections, comprising one phase I safety trial, one case report and 10 case series.. The chronic wounds or ulcers included venous ulcers (n=195), diabetic foot infections (n=70), decubitus ulcers (n=21), non-specific chronic non-healing wounds (n=40) and community acquired methicillin resistant *Staphylococcus aureus* (n=1). The phage treatments used were unpurified phage lysate (n=2), monovalent phage suspension (n=3), phage cocktails (n=2), monovalent or cocktail based (n=2), a phage-containing biodegradable bandage (n=1) or unclear (n=2). As for burn wound infections, the caveats previously mentioned prevent a precise efficacy value. A cautionary crude estimate of efficacy was derived after excluding one report in which outcome data for all 17 patients was unclear. The remaining 11 studies represented 310 patients, of whom: 65.8% achieved clinical resolution, 20.3% showed improvement and 13.9% showed no improvement.

Ten studies (n=1,096) that reported data for patients with various bacterial skin infections included eight case series and two case reports. The infections treated were furunculosis (n=606), hidradenitis (n=94), acne (n=68), impetigo (n=67), carbunculosis (n=64), strepto-staphylococcal epidemitis (n=25), abscesses (n=14), sycosis vulgaris (n=14), folliculitis (n=11), dermatitis (n=7), ecthyma (n=8), cellulitis (n=5), pyoderma (n=4), paronychia (n=1) and 'various skin diseases' (n=102). The phage treatments used were unpurified phage lysate (n=3), monovalent and/or cocktail based (n=2) or unclear (n=5). A cautionary crude estimate of efficacy was derived, excluding two reports where outcome data for all 308 patients was unclear, and excluding 1/57 and 53/143 patients from two studies for whom outcome data were incomplete. The remaining eight studies represented 734 patients, of whom: 87.3% achieved clinical resolution, 6.81% showed improvement and 5.9% showed no improvement. One study commented on 'resistance to PT' and the development of 'antiphage.' Neither term was defined in the study, however the review authors took the former to mean the development of bacterial resistance to phage, of which there were nine cases, while the latter was interpreted as the action of antiphage antibodies, occurring in one case.

The fourth systematic review focused on patients infected with multi-drug resistant ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) organisms.[6] This paper included 16 of the 65 studies included in the most recent review[3], one of the 20 studies included in the second review[4], and seven of the 27 studies included in the review of superficial infections[5], but also incorporated 12 studies that had not been included elsewhere. Differences between reviews in the studies identified can be explained by use of a different range of publication dates in the search strategies, variation in inclusion criteria for type of studies and variation in databases searched.

The 30 studies in the review (three RCTs, n=103; nine observational trials, n=1,019; 17 case studies, n=30; one study did not report the design used or number of patients) included assessed PT, through different administration routes, in patients infected with one or more multi-drug resistant ESKAPE organisms. Patients had infections caused by *Escherichia coli* in two studies, *Staphylococcus aureus* in four, *Klebsiella pneumoniae* in one study, *Acinetobacter baumannii* in two, and *Pseudomonas aeruginosa* in nine studies. Twenty-six of the 30 (87%) studies showed phage efficacy against the respective target bacteria, successfully decreasing or halting bacterial growth (defined as 3 to 5 $\log_{10}$ of bacterial reduction).

Safety

Safety outcomes were reported in the same secondary literature described in the clinical effectiveness section.[4-6, 19] PT related adverse events included local redness and pain, mild pruritus, nausea and vomiting, eczema and hypotension. Two reviews noted that it was unclear if adverse events were directly related to PT or to the underlying health status of patients included in the studies reporting adverse events.[5, 6]

The most recent systematic review identified 51 studies (nine RCTs, n=526; five observational trials, n=136; 37 case studies, n=69) that reported on the safety of PT through different administration routes (*Table 3*).[19] These data showed that PT was well tolerated in the majority of cases; in RCTs adverse events were reported in 7.6% of patients after PT compared to 14.9% of patients in the control group. In case studies, 8.7% of patients reported adverse events associated with PT whereas no adverse events were reported across the five observational trials. The evidence quality for safety outcomes was judged by the review authors to be moderate based on RCT and observational trial results, for reasons of indirectness and risk of bias, respectively. Evidence quality for safety outcomes based on case study data was categorised as very low as a result of a combination of indirectness and risk of bias. Since publication, the authors' assessment of the strength of the evidence has received criticism, with a comment made that evidence based on observational trials should be rated as very low due to the risk of bias in the included studies.[20] The review authors have responded to this comment stating that the risk of bias was appropriately assessed and therefore their conclusions are unaffected.[21]

Table 3: Comparison of adverse events associated with PT compared with a control group comprised of SoC or placebo[19]

Adverse events	Comparative risk		Duration of follow-up	GRADE assessment of quality of evidence
	PT	Control group		
n=526 (9 RCT)	7.6% (n=21/277)	14.9% (n=37/249)	6 days to 15 months	Moderate (due to indirectness)
n=136 (5 OBS)	0.0% (n=0/136)	NA	7 days to 3 months	Moderate (due to risk of bias)
n=69 (37 CS)	8.7% (n=6/69)	NA	20 days to 48 months	Very low (due to risk of bias and indirectness)

Abbreviations: PT = phage therapy; RCT = randomised controlled trials; OBS = observational trial; CS = case studies; NA = not applicable; GRADE = Grading of Recommendations, Assessment, Development and Evaluations

The second systematic review on bone and joint infections included eight studies that reported adverse events linked to PT.[4] Adverse events were reported during 8% (n=4/52) of treatment episodes, all of which were considered to be minor: elevation of liver function tests (n=2), mild pruritus associated with an elevation of Tumour Necrosis Factor alpha (n=1), or redness and pain (n=1). Suppressive antimicrobial treatment was initiated during or after PT in 22% (n=8) of treatment episodes (of the 36 treatment episodes for which this information was reported).

The systematic review on burn wound infections, chronic wound or ulcer infections and dermatological infections identified 15 studies (n=1,095) that reported on adverse events; including three studies on burn wound infections that found no adverse events, five studies on chronic wounds or ulcers, four of which identified no adverse events, and eight studies on dermatological infections, one of which did not find any adverse events.[5]

One study on chronic wounds or ulcers from 1987 reported two instances of oral intolerance to raw phage lysate, one case of allergic symptoms following local application of phage, and hepatalgia and fever several days after oral PT. The remaining seven studies for dermatological infections were dated between 1929 and 1987. The earliest study reported that extremely mild adverse events were observed in the majority of patients that received injected subcutaneous raw staphylococcal phage lysate. Of the 149 patients for whom adverse events outcomes were recorded, 28.8% had no adverse events, 34.6% had mild localised erythema and soreness, 7.2% had generalised responses (fever, malaise), 1.0% had an undefined severe reaction and no data were available for the remaining 28.4%. A case series of 57 patients (1930) noted a severe local reaction for one patient, without further details. A third study (1938) documented localised and generalised adverse events associated with subcutaneous phage injections, typically seen within, and lasting no longer than, 24–48 hours. Two later studies reported similar localised and generalised adverse events following subcutaneous injection; local reactions (for example, redness and inflammation) were often noted at the injection site, but this was not considered by the study authors to be an indication that PT should

be halted. An allergic rash which rapidly disappeared was observed in 8% of patients. A sixth study (1963) reporting on subcutaneous injection of raw phage lysate for furuncles (boils) noted local reactions were mild and did not interfere with treatment and that there were no systemic reactions.

The fourth systematic review identified 22 studies that provided information regarding adverse events.[6] Twenty of these studies did not report on adverse events associated with phage administration, while the remaining two studies noted subsequent infections, eczema, increased pain, nausea and vomiting, but had limited data to confirm their relatedness to PT. No studies reported an association between phage administration and death.

Ongoing research

The details of five ongoing clinical trials are provided in *Table 4*. Protocols for seven systematic reviews or meta-analyses were also identified.

Table 4: Active clinical trials on the clinical effectiveness or safety of PT

Study title	Location Identifier	Number of patients	Primary completion date
CYstic Fibrosis bacterioPHage Study at Yale (CYPHY): A Single-site, Randomised, Double-blind, Placebo-controlled Study of Bacteriophage Therapy YPT-01 for Pseudomonas Aeruginosa Infections in Adults With Cystic Fibrosis	US NCT04684641	36	December 2022
A Phase 1b/2 a, Randomised, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Nebulised Bacteriophage Treatment in Outpatient Adult Cystic Fibrosis Subjects With Chronic Pseudomonas Aeruginosa Pulmonary Infection	US/Israel NCT05010577	32	March 2023
Phase 1b/2 a, Randomised, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of Safety, Tolerability, and Efficacy of Intravenous AP-SA02 as an Adjunct to Best Available Antibiotic Therapy for the Treatment of Adults With Bacteraemia Due to Staphylococcus Aureus	US NCT05184764	50	September 2023
A Pilot, Multicenter, Randomised, Non-Comparative, Double-Blind Study of Phage Therapy in Patients With Hip or Knee Prosthetic Joint Infection Due to Staphylococcus Aureus Treated With DAIR and Antibiotic Therapy.	France NCT05369104	64	December 2023
A Phase IIa Randomised, Parallel Group, Double-blind, Repeat Dose, Investigating the Safety, Tolerability, and Efficacy of Phage Treatment and Standard of Care Antimicrobials for Patients With Diabetic Foot Osteomyelitis	US NCT05177107	126	October 2024

Abbreviations: US = United States; DAIR = debridement, antibiotics, irrigation, and retention of the prosthesis

Patient and social aspects

A single Scottish study was identified that explored patient awareness and concerns about antibiotic resistance, and perceptions of PT through a survey and focus group.[22] The survey was made available to patients with diabetic foot ulcers (DFU) across Scotland. Eligible patients had either an active or resolved (healed or amputated) DFU and had consented to being contacted about research opportunities through the NHS Research Scotland Diabetes Network, or were patients from diabetic foot clinics at the Edinburgh Royal Infirmary or the Queen Elizabeth University Hospital in Glasgow. Participants were required to be aged 18 years or older and confident communicating in English.

A total of 55 digital and hardcopy survey responses were obtained and five of these respondents contributed to the focus group, although not all patients responded to every question. The sample population comprised of 22 females and 33 males, with a mean age of 57.4 years (standard deviation 11.0). The vast majority of respondents were familiar with antibiotic chemotherapy, with 98.2% of respondents having taken antibiotics for an illness. Respondents (n=53) had taken, on average, 3.5 courses of antibiotics for any illness in the 12 months prior to survey completion (range 0 to 15 courses). The sample population also regularly engaged with the healthcare system, having been an outpatient or inpatient for any reason within this timeframe, with an average number of hospital contacts of 16.2 (maximum 107).

There was a high level of awareness of antibiotic resistance among respondents, with 76.4% having heard of antibiotic resistance prior to completing the survey, and many noting their concern with the issue (42.6% extremely and 29.6% moderately concerned). The majority of patients were aware of viruses, with 76.4% stating that they had heard of them. Of this group who had heard of viruses, only 23.8% had heard of viruses that kill bacteria, such as phage. Even fewer patients were aware of the therapeutic applications of phage (n=5), the majority of whom stated they had heard of it through the media (n=4). Patients' level of concern around antibiotic versus PT was evaluated using an identical four part rating scale, the results of which are shown in *Table 5*. There were no statistically significant differences in the proportion of patients who were extremely concerned about antibiotics compared with PT (p=0.170). Comparison of overall levels of concern expressed across all response categories, found no statistically significant differences between antimicrobial strategies (p=0.546).

Table 5: Patients' level of concern about antibiotic therapy compared with PT[22]

Response	Antibiotic therapy (n=53)	PT (n=53)	p-value
Not concerned	49.1%	47.2%	NA
Slightly concerned	26.4%	35.8%	
Moderately concerned	15.1%	13.2%	
Extremely concerned	9.4%	3.8%	0.170

A free-text space was provided in the survey to allow patients to express any concerns they had around PT in their own words. The study authors qualitatively analysed the free-text responses and

grouped them into categories based on themes (*Table 6*). Key themes identified from survey responses were the safety of PT, its efficacy compared with antibiotics, and potential side effects associated with phage use.

Table 6: Themes identified among patient concerns about PT (n=43)[22]

Theme	% of patients	Number of patients
No concerns	44.2	19
Safety	23.3	10
Efficacy versus antibiotics	20.9	9
Side effects	14.0	6
More information	4.7	2
Why is it not used already?	4.7	2
Administration	4.7	2
Don't know	2.3	1
Uninterpretable	2.3	1

Following the free-text section, patients were provided with factual information about the history of phage, how PT works and the challenges associated with phage use. After reading this material, 86.8% of patients stated they would accept PT if it was recommended by their doctor, with 13.2% responding that they were not sure and no patients indicating refusal. When asked if they would consider PT as an alternative to foot amputation if there were no other treatment options, 98% stated they would try PT first.

The focus group (n=5) collected more detailed information regarding patients' thoughts and concerns around PT. The questions asked and the comments made by group members were divided into themes. Initial questions focused on an understanding and awareness of PT, before broadening out into comparisons between antibiotics and PT, how PT might work in practice and concerns around its use. All attendees were extremely supportive of PT, and four out of five strongly expressed a willingness to use PT in lieu of intravenous antibiotics if possible, citing ease of use, the potential not to be admitted to hospital and the likely significantly reduced side effect profile.

Patient organisation submission

A patient organisation submission was received from Antibiotic Research UK. The full submission can be located on the SHTG website here. A summary of the points highlighted by Antibiotic Research UK in support of the use of PT across NHSScotland are as follows:

- Bacterial infections that are tolerant or resistant to conventional antibiotics are a chronic condition for many patients and are associated with a significant risk of death. Several patients have received multiple courses of conventional antibiotics over a period of months, years or decades with no success in eradicating the causative bacteria. A significant number

of these patients are unable to tolerate further conventional antibiotic therapy. These patients now desperately seek alternative treatment options that can be delivered by the NHS within a reasonable distance from their homes.

- Over-reliance on substandard microbiological testing methods means that infections are frequently not detected despite the presence of symptoms. This leads patients to feel that they are, 'not believed,' by healthcare professionals or their family and friends. This situation is exemplified by the low sensitivity of dipstick tests for urinary tract infections (UTI), where treatment failure with conventional antibiotic therapy has led patients to access PT abroad.
- Symptoms of these infections include severe pain, fatigue, lethargy and brain fog, that directly contribute to major depression and anxiety among these patients, seriously diminishing the quality of their lives and their families. Some patients state that their life is not worth living with this condition and admit to having suicidal thoughts.
- The impact of resistant infections on patients' lives is compounded by other factors such as a lack of a confirmation and understanding of their suffering by healthcare professionals or their families, and the requirement to travel to the rest of the UK or abroad to access treatment options.
- There is a substantial economic burden for patients and their families due to being unable to continue employment, as well as an impact on health and social services through the need for continuing medical care and welfare benefits. This is in addition to impact on normal family life given the requirement for family members to care for the patient, their reduced ability to care for their children, and the challenges of attending leisure trips alongside their family.
- The burden of these infections are associated with significant level of inequality, as demonstrated by the extremely high proportion of women suffering with recurring UTIs.

Cost effectiveness

No published cost effectiveness evidence on the use of PT was identified during the literature search. A de novo economic evaluation was therefore developed to provide an indication of the relative cost effectiveness of PT compared to SoC for the treatment of patients with difficult to treat bacterial infections.

The research question posed by the topic referrers encompasses patients from a wide variety of medical and surgical specialties. It was therefore not feasible to provide an estimate of the cost effectiveness of PT for all patient populations covered by this recommendation. The economic evaluation was conducted in a patient population with DFI given that a subset of these patients are likely to be eligible for PT across NHS Scotland.

Patient population

The patient population used in the economic evaluation is adults (age ≥ 18 years) with severe treatment-refractory DFIs who are at risk of amputation.

The National Institute for Health and Care Excellence (NICE) guidance for the management of patients with diabetic foot problems categorises a DFI as severe if there is local infection with signs of a systematic inflammatory response (for example, temperature more than 38°C or less than 36°C, increased heart rate or increased respiratory rate).[23]

Patients are at high risk of amputation if any of the following apply: ulceration, spreading infection, critical limb ischaemia, gangrene, suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.[23] No defined criteria for when amputation is required currently exist (Dr M Young, Consultant Acute Medicine and Diabetes/Endocrinology, NHS Lothian. Personal communication, 22 August 2022).

Treatment-refractory was defined as situations where patients with DFIs have not responded to, or are not expected to respond to, any of the licensed or commonly used off-label treatments for their infection in the opinion of their clinician.

Intervention and comparators

The intervention in this evaluation is PT + SoC and the comparator is SoC only. The dose, duration and frequency of PT and SoC included in the economic evaluation are presented in *Table **7***. The ARLG Phage Task Force state that it is not possible to provide definitive recommendations on dose or duration of PT at present and therefore suggest that patient response should be used to inform dose and duration.[24] For the purpose of this analysis, the dose and duration of treatment for PT was assumed to be consistent with a clinical protocol used at the Royal Infirmary in Edinburgh and the Queen Elizabeth University Hospital in Glasgow for the treatment of patients with severe treatment-refractory DFI at risk of amputation. SoC was assumed to be delivered in accordance with conventional antibiotic therapy good practice recommendations for non-antibiotic naïve patients without penicillin allergy developed by clinicians across NHS Scotland.[25] A retrospective analysis of the microbiology samples taken from patients with DFIs at the Queen Elizabeth University Hospital in Glasgow found that, excluding fungal, mixed and samples without significant growth, 84.4% of monomicrobial results were positive for *Staphylococcus aureus*.[26] For simplicity, and to help guide the choice of antibiotics comprising SoC, all patients were assumed to be infected with *Staphylococcus aureus* and have infections uncomplicated by osteomyelitis.

Table 7: Dose, duration and frequency of treatment[25]

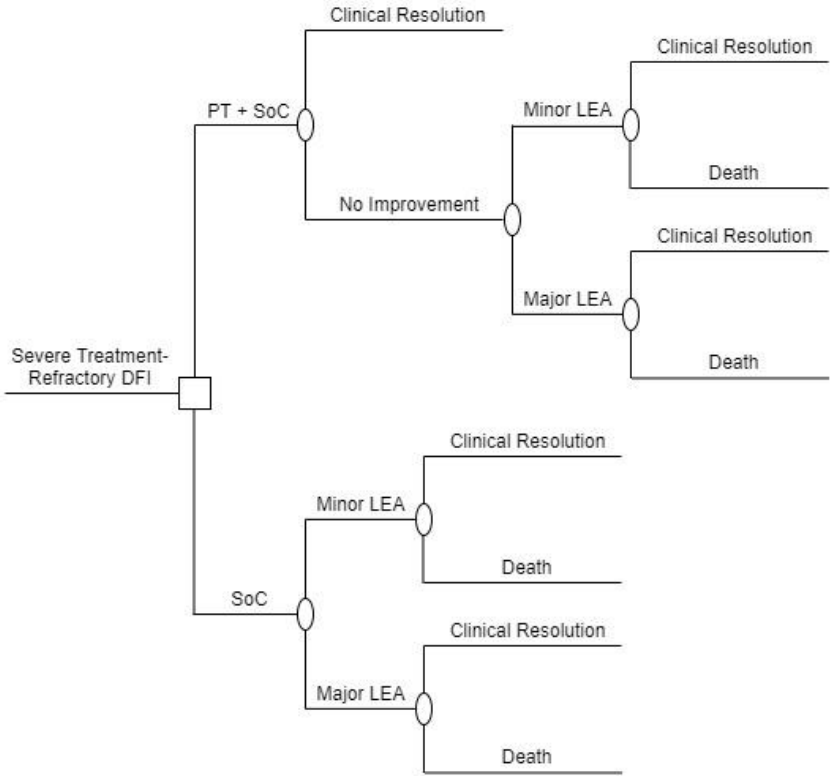
Treatment	Medicine	Dose	Duration	Frequency	Source
PT	Anti-Staphylococcal phage	2 ml volumes of 10^9 PFU/ml diluted to a concentration of 10^7 PFU/ml	Consistent with duration of conventional antibiotic therapy (14 days)	Once daily at wound dressing change	Clinical protocol (unpublished) Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 14 July 2022
SoC	Piperacillin-Tazobactam	4.5 g	14 days	Three times per day	Barwell *et al*[25]
	Clindamycin	600 mg		Four times per day	

Abbreviations: PT = phage therapy; SoC = standard of care; PFU = plaque forming units; ml = millilitres; mg = milligram; g = gram; kg = kilogram; IV = intravenous

Model type and structure

The model type used in the economic evaluation was a decision tree, in order to simulate the disease course, costs and outcomes of patients over a time horizon of one year. The model structure used is presented in *Figure 1*. All patients start in the DFI state and are assigned to receive PT + SoC or SoC only at the beginning of the model. Patients receiving PT + SoC can either experience clinical resolution of their infection following treatment or have no improvement. If no improvement is observed, patients are assumed to undergo either a minor or major lower extremity amputation (LEA). Following amputation, patients can experience clinical resolution of their infection or death. All patients receiving SoC only are assumed to undergo amputation and were able to experience any one of the post amputation states described above.

Figure 1: Model structure overview



Abbreviations: DFI = diabetic foot infection; PT = phage therapy; SoC = standard of care; LEA = lower extremity amputation

State-transition probabilities

The transition probabilities used in the economic evaluation are presented in *Table 8*. Supplementary data from a systematic review were used to derive the clinical effectiveness of PT + SoC; six studies (n=43) reported the outcome of PT in patients with DFIs, finding that 30 (69.7%) of patients achieved clinical resolution, six (14.0%) had no response, and outcomes were 'unclear' for the remaining seven (16.3%) patients.[5] It was conservatively assumed that where patient outcomes were unclear, these patients had no response to PT. The estimate for the proportion of patients achieving clinical resolution was used to represent the probability of transitioning from DFI to clinical resolution. The probability of transitioning from DFI to no improvement was assumed to be equal to 1 minus the probability of achieving clinical resolution. The probability of undergoing a minor or major LEA (if required) was estimated using the relative proportion of minor versus major LEA admissions found in a national patient level data analysis of diabetes patients across NHS England from 2014 to 2015.[27] Mortality rates one-year after first LEA from a population based cohort study were used to inform the probability of death following a minor or major LEA, and these probabilities were assumed to be equal regardless of treatment.[28] The probability of clinical resolution following amputation was assumed to be equal to 1 minus the probability of death.

Table 8: State-transition probabilities used in the economic evaluation[5, 27, 28]

Transition probabilities		Base case	Data source
PT + SoC	Clinical resolution	69.7%	Steele *et al*[5]
	No improvement	30.3%	1 – P(Clinical Resolution)
Amputation type	Minor LEA	57.1%	Kerr *et al*[27]
	Major LEA	42.9%	
Minor LEA	Clinical resolution	82.0%	1 – P(Death)
	Death	18.0%	Cascini *et al*[28]
Major LEA	Clinical resolution	67.0%	1 – P(Death)
	Death	33.0%	Cascini *et al*[28]

Abbreviations: PT = phage therapy; SoC = standard of care; LEA = lower extremity amputation; P = probability

State-utility values

The state-utility values used in the economic evaluation are presented in *Table 9*. A targeted literature review was conducted to identify health related quality of life studies in DFI patients regardless of severity of infection. This identified a vignette study that estimated the utility associated with 13 unique states based on the presence or type of DFI and amputation.[29] Members of the general population in the Netherlands were asked to indicate how undesirable each state was using the time trade-off method and their responses for each state were used to create utility values.

Table 9: Matching of economic evaluation state-utility values versus Redekop et al[29]

State		Mean-average utility value	95% confidence interval		Data Source
de novo economic evaluation	Redekop *et al*		Lower	Upper	
Clinical resolution	No active ulcer and no previous amputation	0.84	0.81	0.87	Redekop *et al*[29]
Minor LEA	More than one toe amputated plus active infected ulcer	0.65	0.60	0.69	
Major LEA	One leg amputated plus active infected ulcer	0.55	0.50	0.59	
Death	NA	0	NA		By definition

Abbreviations: NA = not applicable

Medication costs

The medicine acquisition costs for PT and SoC used in the economic evaluation are presented in *Table 10*. The per patient cost of SoC was estimated using the lowest available price of each antibiotic recorded in the British National Formulary and applying this price to the maximum recommended dosage of the relevant antibiotic outlined in good practice recommendations for antibiotic therapy in the population.[25, 30] The cost per patient of PT was informed using consultancy-derived estimates for the cost of establishing a GMP for phage in the UK (Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 6 December 2021). This included variable and fixed running costs to produce 3.25 litres of therapeutic phage, equipment maintenance costs, annual fees to the MHRA, and annual salaries for required staff members. If NHSScotland was to produce its own therapeutic phage, the cost of PT would reduce significantly after the initial investment required to establish a manufacturing process has been recovered. The impact of applying a lower cost for PT has been explored through a scenario analysis.

Table 10: Medicine acquisition costs used in the economic evaluation[30]

Medication		Cost (£)	Data source
SoC	Piperacillin-Tazobactam	153.30	British National Formulary[30]
	Clindamycin	554.40	
PT	Anti-Staphylococcal phage	698.10	Consultancy estimates for GMP phage within the UK
Total	**SoC**	**707.70**	**NA**
	PT + SoC	**1,405.80**	

Abbreviations: PT = phage therapy; SoC = standard of care; GMP = good manufacturing practice; UK = United Kingdom; NA = not applicable

Administration costs

The administration costs used in the economic evaluation are presented in *Table 11.* Conventional antibiotics within SoC were assumed to be delivered intravenously for the duration of treatment as recommended by good practice recommendations for antibiotic therapy in the population.[25] PT was assumed to be delivered topically via dripping of phage solution into wound cavities using a syringe and leaving it to soak into the wound for 15 minutes before dressings are applied which could also be soaked in phage solution as outlined in the clinical protocol. Patients with DFI typically receive two dressing changes per week when receiving conventional antibiotic therapy (Gillian Harkin, Lead Clinical Podiatrist, NHS Greater Glasgow & Clyde. Personal communication, 29 July 2022) only the cost of additional dressing changes associated with PT was included. The cost of consumables associated with dressing changes was considered by to be immaterial to economic results and was excluded. The type of healthcare professionals assumed to deliver treatment and the time taken by staff to administer PT and SoC were based on assumption. The cost per hour of healthcare professional time was set equal to that reported in the Unit Costs of Health and Social Care 2021 calculated by the Personal and Social Services Research Unit (PSSRU) at the University of Kent.[31]

Table 11: Administration costs used in the economic evaluation[30, 31]

Treatment	Delivery mechanism	Resource use	Number of administrations	Cost per hour (£)	Cost per administration (£)	Data source
Piperacillin-Tazobactam	IV	Nurse: band 6 15 minutes per administration	42	51.00	12.75	British National Formulary[30] PSSRU Unit Costs[31]
Clindamycin			56			
PT	Topical	Nurse: band 6 30 minutes per application	10		25.50	Clinical protocol PSSRU Unit Costs[31]
Total cost (£)	**SoC**	**1,249.50**	**NA**			
	PT + SoC	**1,504.50**				

Abbreviations: SoC = standard of care; PT = phage therapy; PSSRU = personal and social services research unit; NA = not applicable

Monitoring costs

The monitoring costs used in the economic evaluation are provided in *Table 12*. Resource use associated with monitoring for piperacillin-tazobactam and clindamycin was inferred from their respective Summary of Product Characteristics (SmPC).[32, 33] This unit costs for monitoring is valued using the National Schedule of NHS Costs 2020/21.[34]

Table 12: Monitoring costs used in the economic evaluation[32-34]

Treatment	Resource use	Quantity	Unit cost (£)	Total cost (£)	Data source
Piperacillin-Tazobactam	Haematology	4	3.63	14.52	SmPC[32]
	Clinical biochemistry		1.85	7.40	National Schedule of NHS Costs 2020/21[34]
Clindamycin	Haematology		3.63	14.52	SmPC[33]
	Clinical biochemistry		1.85	7.40	National Schedule of NHS Costs 2020/21[34]
Total cost (£)				**43.84**	**NA**

Abbreviations: SmPC = summary of product characteristics; NHS = National Health Service

Phage susceptibility testing costs

The cost of consumables and healthcare professional time required to conduct phage susceptibility testing prior to administration is presented in *Table 13*. The quantity and unit costs of consumables required to conduct testing was set equal to that provided by a clinical phage specialist (Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 14 July 2022) who also advised on the quantity of time required to set up testing and interpret results. The cost per hour of healthcare professional time was set equal to that reported in the Unit Costs of Health and Social Care 2021.[31] These costs assume the use of standard microbiological techniques that are relatively labour intensive but suitable for small numbers of patients. Large-scale testing platforms are available that may lower the cost per patient of testing but would require significant capital investment.

Table 13: Phage susceptibility testing costs used in the economic evaluation[31]

Resource use	Quantity	Unit Cost (£)	Quantity	Data source
LB broth	3.50 ml	0.04	NA	Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 14 July 2022
Agarose	0.50 g	0.01		
Agar	7.50 ml	0.24		
Disinfectant	2.50 g	0.11		
Petri dish (90 mm)	16	1.60		
Bijous	16	1.20		
Eppendorf tubes (1.5 ml)	16	0.53		
Cuvette tube	4	0.49		
Plaque assay	**NA**	**4.22**	**2**	
LB broth	2.025 g	0.17	NA	Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 14 July 2022
Cuvette tube	9	1.08		
Conical polypropylene centrifuge tube (50ml)	8	2.65		
Planktonic killing assay	**NA**	**3.90**	**1**	
Hospital Scientific: band 6	2 hours set up 30 minutes interpretation	52.00 per hour	NA	Dr J Jones, Clinical Phage Specialist, NHS Tayside. Personal communication, 14 July 2022 PSSRU Unit Costs[31]
Healthcare professionals	**NA**	**130.00**		
Total cost (£)	**142.34**			

Abbreviations: PSSRU = personal and social services research unit; NA = not applicable

Amputation costs

The cost of minor or major LEAs used in the economic evaluation are provided in *Table 14*. The annual cost per admission was calculated using data on the total annual cost of care and number of admissions from a national patient level data analysis in patients with diabetes across NHS England from 2014 to 2015.[27] The annual cost per admission in 2015 was calculated by dividing the total annual cost of care by the total number of admissions during the year. This figure was subsequently inflated to account for changes in the cost of healthcare between 2015 and 2021 using the Consumer Price Index for Health produced by the Office for National Statistics in the UK.[35] The cost of amputation in this study was based on NHS England tariff prices for admissions involving non-traumatic amputations. Tariff prices represent the average cost of care from admission to discharge for standard groupings of clinically similar interventions and diagnoses that use comparable levels of healthcare resources. It is reasonable to assume that the actual cost of amputation for this patient population is greater than that applied in this analysis.

Table 14: Cost of minor or major LEAs used in the economic evaluation[27, 35]

Amputation type	Total annual cost of care (£)	Number of admissions	2015	2021	Data source
			Annual cost per admission (£)		
Minor LEA	16,910,258	4,015	4,211.77	4,805.63	Kerr *et al*[27]
Major LEA	24,772,523	3,016	8,213.70	9,371.83	

Abbreviations: LEA = lower extremity amputation

Post amputation care costs

The cost of after amputation care for patients receiving a minor or major LEA is presented in *Table 15*. The annual cost of outpatient care for patients post amputation was informed using data from the national patient level data analysis in diabetes patients across NHS England.[27] The estimates of resource use were calculated using data supplied by London Northwest University Healthcare Trust for all patients presenting with diabetes and ulcers (excluding Charcot foot) between 1 April 2014 and 31 March 2015. These figures were subsequently inflated to account for changes in the cost of healthcare between 2015 and 2021 using the Consumer Price Index for Health produced by the Office for National Statistics in the UK.[35]

Table 15: Cost of post amputation care[27]

Resource use	Minor	Major	Data source
	Cost (£)		
Non-consultant-led clinic attendance (including nurse or podiatrist visits)	308.07		Kerr *et al*[27]
Consultant-led clinic attendance	491.77		
Wheelchair assessment, provision and maintenance	171.15		Assumption
Physiotherapy	475.80	1,428.53	Kerr *et al*[27]
Transport	138.06		
Total cost (£)	**1,584.85**	**2,537.58**	

Note: inflation factor for 2015 to 207 = 1.141

Base case results

The base case economic evaluation results are presented in *Table 16* and indicate that over a one-year time horizon, PT + SoC is associated with incremental costs of -£5,008.96 (cost savings) and incremental quality-adjusted life years (QALYs) of 0.264 versus SoC only. Based on the assumptions listed above, PT + SoC was therefore estimated to be the dominant treatment strategy, providing additional QALYs at a lower cost compared with SoC. The cost savings associated with PT + SoC stem

from a lower proportion of patients requiring minor or major LEA and hence reduced post amputation healthcare services, leading to an overall lower cost of care.

Table 16: Base case economic evaluation results

	SoC	PT + SoC	Incremental
Treatment costs	707.70	1,405.80	698.10
Administration costs	1,249.50	1,504.50	255.00
Monitoring costs	43.84	43.84	-
Phage susceptibility testing	-	142.34	142.34
Minor LEA	2,744.02	831.44	-1,912.58
Major LEA	4,020.52	1,218.22	-2,802.30
Post amputation care	1,993.57	604.05	-1,389.52
Total cost	10,759.14	5,750.18	-5,008.96
QALYs	0.462	0.726	0.264
ICER	**Dominant**		

Abbreviations: SoC = standard of care; PT = phage therapy; LEA = lower extremity amputation; QALY = quality-adjusted life-year; ICER = incremental cost effectiveness ratio

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was carried out to estimate the impact of parametric uncertainty on the results of the economic evaluation. This was conducted by randomly sampling 10,000 sets of model inputs from selected probability distributions and using these inputs to generate estimates of the incremental cost effectiveness ratio (ICER) for PT + SoC versus SoC only. The probability distributions used to characterise uncertainty in model inputs are described in *Table 17*. Standard errors for parameters related to the effectiveness or cost of PT were assumed to be 50% of their base case value to reflect the greater level of uncertainty associated with these parameters. Standard errors for all other parameters were set equal to their estimated value where available or 20% of their base case value where absent.

Table 17: Parameter distributions used in probabilistic sensitivity analysis

Parameter		Base case	Standard error	Distribution	Alpha	Beta
Transition probability variables						
PT + SoC → Clinical resolution		0.697	0.349	Beta	0.515	0.224
Probability of minor LEA		0.571	0.114		10.153	7.627
Minor LEA → Clinical resolution		0.820	0.164		3.680	0.808
Major LEA → Clinical resolution		0.670	0.134		7.580	3.733
State-utility variables						
Clinical Resolution		0.84	0.17	Normal	NA	
Minor LEA		0.65	0.13			
Major LEA		0.55	0.11			
Death		0	NA			
Resource cost variables (£)						
SoC		707.70	141.54	Gamma	25	28.308
PT + SoC		1,405.80	702.90		4	351.450
Monitoring	SoC	43.84	8.77		25	1.754
	PT + SoC	43.84	8.77		25	1.754
Minor LEA		4,805.63	961.13		25	192.225
Major LEA		9,371.83	1,874.37		25	374.873
Post amputation care	Minor	1,584.85	316.97		25	63.394
	Major	2,537.58	507.52		25	101.503
Phage susceptibility testing		142.34	71.17		4	35.585
Administration	SoC	1,249.50	249.90		25	49.980
	PT + SoC	1,504.50	752.25		4	376.125

Abbreviations: PT, phage therapy; SoC, standard of care; LEA, lower extremity amputation: NA, not applicable

The ICERs estimated from these different input sets are plotted on the cost effectiveness plane presented in *Figure 2*. The majority of simulated ICERs are located below the willingness to pay (WTP) threshold of £20,000 per QALY (indicated by the diagonal line in this figure). The proportion of simulated ICERs situated below the WTP threshold when this is varied from £0 to £50,000 per QALY can be visualised in *Figure 3*. *Figure 3* indicates that PT + SoC has approximately an 85% probability of being cost effective using a WTP threshold of £0 per QALY and this increases marginally for WTP thresholds greater than or equal to £20,000 per QALY.

Figure 2: Cost effectiveness plane for PT + SoC versus SoC only

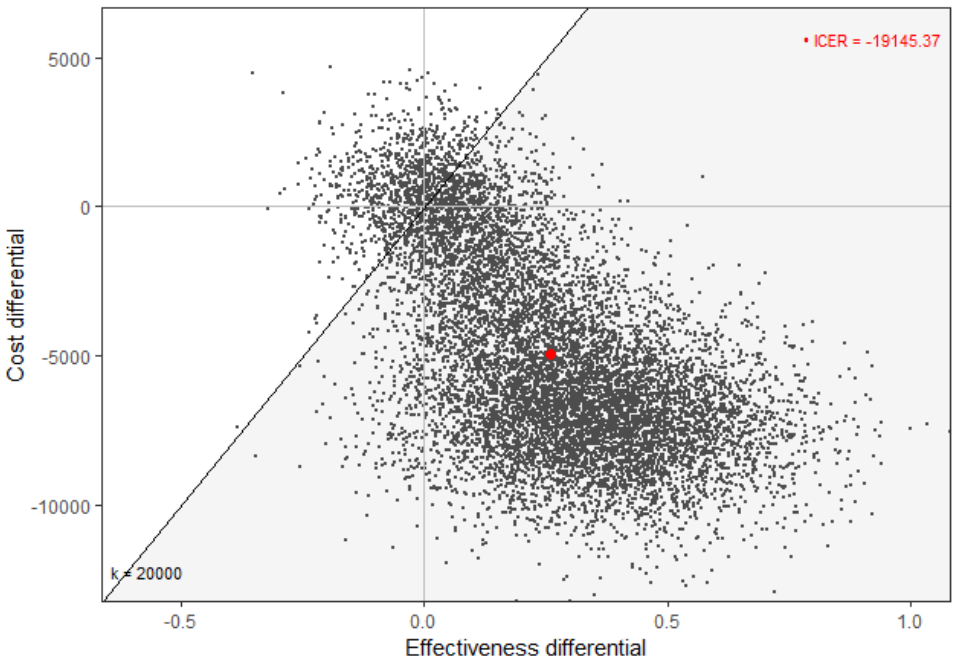
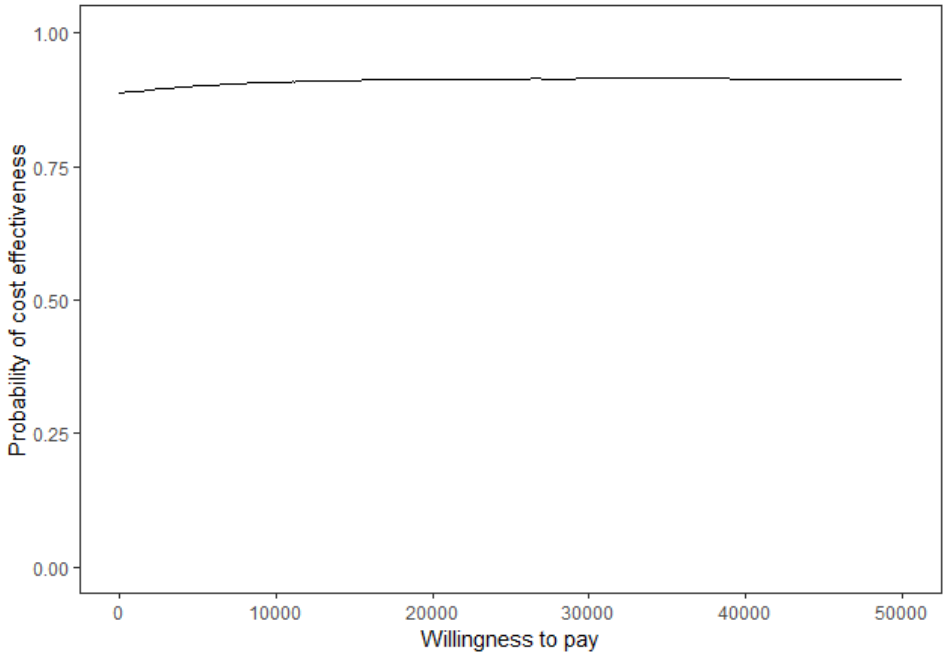


Figure 3: Cost effectiveness acceptability curve for PT + SoC versus SoC



Scenario analysis

A series of scenario analyses were conducted to estimate the impact of structural uncertainty on the results of the economic evaluation. The results of these analyses are provided in *Table 18* and indicate that overall the cost effectiveness of PT + SoC versus SoC is relatively stable, with the

majority of scenarios estimating that PT + SoC remains a dominant treatment strategy despite changes in key assumptions. It is only when relatively extreme changes in assumptions are combined, such as a 75% reduction in the probability of clinical resolution following PT + SoC and a 200% increase in the cost of PT + SoC (scenario 16) are assumed that there is a significant upwards impact on results.

Table 18: Scenario analyses applied in economic evaluation

#	Scenario	Alternate assumption		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
-	Base case	NA		-5,008.96	0.264	Dominant
1	Probability of clinical resolution following PT + SoC	Reduction from base case value	25%	-3,485.05	0.198	Dominant
2			50%	-1,961.14	0.132	Dominant
3			75%	-428.47	0.066	Dominant
4		Threshold analysis probability of clinical resolution = 5.5%		613.75	0.021	29,226.19
5	Probability of minor LEA	Increase from base case value	25%	-4,458.88	0.247	Dominant
6			50%	-3,870.34	0.229	Dominant
7	State-utility values	Minor LEA	0.70	-5,008.96	0.247	Dominant
8		Major LEA	0.65		0.243	Dominant
9		Scenarios 7 and 8 combined			0.226	Dominant
10	Medicine acquisition costs for PT + SoC	Increase from base case value	50%	-4,306.06	0.264	Dominant
11			100%	-3,603.16		Dominant
12			200%	-2,197.36		Dominant
13		Capital investment for GMP phage recovered		-5,594.44		Dominant
14	Combined scenarios	2 + 12		850.46	0.132	6,442.88
15		2 + 12 + 9			0.113	7,526.20
16		3 + 12		2,383.13	0.066	36,108.03
17		3 + 12 + 9			0.056	42,555.89

Abbreviations: ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life-year; PT = phage therapy; SoC = standard of care; LEA = lower extremity amputation: NA, not applicable

Discussion

This de novo economic evaluation, using base case parameter values, estimated that PT + SoC is a dominant treatment strategy versus SoC for the treatment of adults with severe treatment-refractory DFI who are at risk of amputation over a one-year time horizon. A probabilistic sensitivity analysis estimated that PT + SoC has approximately an 85% probability of being cost effective using a WTP threshold of £20,000 per QALY. These findings indicate that the use of PT + SoC may represent

value for money for the treatment of these patients across NHS Scotland. Nonetheless, this economic evaluation is associated with a number of significant limitations that should be considered when interpreting these results.

- The clinical effectiveness of PT + SoC was based on a pooled analysis of six case series comprising a small number of patients (n=43) that reported the outcome of PT in patients with DFIs.[5] There is significant heterogeneity between these studies due to the diverse array of pathogens, treatments with different phages (single versus cocktails) for varying durations, and PT was sometimes combined with other treatments. The impact of uncertainty regarding the clinical effectiveness of PT + SoC on results was explored in scenarios 1 to 4, finding that conclusions were generally robust to assumed reductions in the probability of clinical resolution following treatment. Threshold analysis indicated that PT + SoC may be cost effective if it provided clinical resolution of the infection in 5.5% or more of patients (all else equal).
- The cost of PT used in the economic evaluation was calculated by a consultancy commissioned to estimate the cost of establishing a GMP for therapeutic phage in the UK.[36] These estimates include multiple assumptions regarding the fixed capital and variable running costs required to establish this process that are inherently uncertain. The cost of PT was increased from this consultancy based estimated by factors of 50% to 200% in scenarios 10 to 12 but this was found not to affect conclusions regarding its cost effectiveness.
- State-utility values applied in the economic evaluation were sourced from a publication by Redekop *et al* conducted among members of the general population in the Netherlands.[29] It is possible that differences in preferences for included health states exist between the general population in Scotland versus the Netherlands that could alter results. Scenario analyses 7 to 9 investigated the impact of assuming that the general population in Scotland consider the difference in utility between minor versus major LEA health states to be smaller than that observed in this study. The impact of assuming a smaller difference in utility between these health states was not found to significantly impact results.
- The combined impact of uncertainty regarding the clinical effectiveness of PT + SoC, cost of PT, and variation in utility estimates was explored in scenarios 14 to 17. Results showed that the cumulative impact of these sources of uncertainty may have a significant impact on results, leading to an estimate for the cost effectiveness of PT + SoC that may not be considered value for the money. It is unclear if these assumptions represent a reasonable interpretation of the evidence base for PT + SoC.

Conclusion

The secondary literature on the clinical effectiveness and safety of PT for difficult to treat bacterial infections consists of seven systematic reviews based primarily on single-arm observational studies and case series.[4-9, 19] None of the systematic reviews included a meta-analysis due to heterogeneity between studies from a wide variety of pathologies caused by a diverse array of pathogens,

personalised treatments with different phages (single versus cocktails) via different administration routes, and the fact that PT was often combined with conventional antibiotic therapy. The evidence synthesis presented is limited to four of these systematic reviews due to the large degree of overlap in included studies between reviews.[4-6, 19]

Clinical effectiveness estimates were derived based on a pooled analysis of results by study design and for all study types combined. The most recent systematic review that compared PT to a control group receiving SoC or placebo estimated that, based on a pooled analysis of two RCTs, control group patients were more likely to experience clinical improvement than patients who received PT (50.0% vs 43.8%).[19] Conversely, this review also estimated that, based on one RCT, patients treated with PT were more likely to achieve bacterial eradication than those in the control group (16.6% vs 0.0%). The magnitude of the treatment effect associated with PT was larger when results from all study types were combined, finding that criteria for treatment success were satisfied in 65.8% to 89.2% of patients across all reviews included.[4-6, 19] No data from observational trials or case studies was available to estimate the treatment effect for a control group. Based on the available evidence, the true clinical effectiveness of PT is uncertain but expected to be somewhere between the estimates based on RCTs only and that for all study types combined.

Safety outcomes were reported in the same four systematic reviews.[4-6, 19] The most recent systematic review that compared PT with a control group estimated that, based on a pooled analysis of nine RCTs, adverse events were reported in 7.6% of patients after PT compared to 14.9% of patients in the control group.[19] A comparable rate of adverse events was observed in a pooled analysis of case studies included in this review, where 8.7% of patients reported adverse events associated with PT. No data from case studies were available to estimate the rate of adverse events for a control group in this review. These findings were consistent with the other reviews included in the evidence synthesis where adverse events were typically reported on an individual study basis, noting that these were mild and did not require treatment with PT to be discontinued.[4-6] No association between receipt of PT and death was reported in any reviews. The safety of PT is therefore expected to be comparable to that reported in this body of evidence.

The published literature on patient and social aspects of PT is limited to a single study on patient preferences for PT versus SoC.[22] The study found no statistically significant differences among Scottish patients in terms of their level of concern regarding treatment with PT or antibiotic therapy, with the majority of patients reporting that they would accept PT if it was recommended by their doctor. A patient organisation submission received from Antibiotic Research UK highlighted a number of points in support of the use of PT in Scotland.

An SHTG de novo economic evaluation comparing PT + SoC versus SoC only, for the treatment of adults with severe treatment-refractory DFIs who are at risk of amputation, estimated that PT + SoC is more effective and less costly than SoC over a time horizon of one-year. The value for money of PT + SoC was less clear when the combined impact of uncertainty regarding the clinical effectiveness

and cost of treatment with PT was investigated, and the reasonableness of the assumptions underpinning the results remains uncertain.

Identified research gaps

Additional RCTs comparing PT + SoC versus SoC only would be useful for accurately estimating the true effect of PT in specific populations of patients with difficult to treat bacterial infections. These RCTs could also provide a basis for an economic evaluation of PT + SoC in these populations of patients.

Other gaps in the existing published evidence include:

- data on the optimal dose, duration and frequency of PT administration, and
- information on standardised methods for conducting phage susceptibility testing.

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Appendix 1: definitions

Biofilm: a slime-enclosed community of bacterial colonies that is very difficult to eradicate even with the most powerful antibiotics or sterilising systems.[37]

Ecthyma: a pus forming, ulcerating and crusting inflammatory skin disease.[38]

Endotoxin: a toxin produced by certain bacteria and released upon destruction of the bacterial cells.[39]

Ex vivo: in an artificial environment outside a living organism.[40]

Furunculosis: a condition in which the patient suffers from recurrent episodes of boils.[41]

Hepatalgia: pain in the liver.[42]

Hidradenitis: inflammation of a sweat gland.[43]

Lytic: of or relating to lysis; the destruction of a living cell by disruption of its membrane.[44]

Paronychia: infection of the skin fold at the base or side of the nail.[45]

Pyoderma: a pus containing skin infection.[46]

Sycosis vulgaris: a chronic inflammation of the hair follicles, especially of the beard, characterised by eruption of pimples and nodules.[47]

Appendix 2: abbreviations

ARLG	Antibacterial Resistance Leadership Group
CPI	consumer price index
CS	case studies
DFI	diabetic foot infection
DFU	diabetic foot ulcer
DNA	deoxyribonucleic acid
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baummannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species
FRI	fracture-related infection
GMP	Good Manufacturing Process
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
ICER	incremental cost effectiveness ratio
LEA	lower extremity amputation
MHRA	Medicines and Healthcare Products Regulatory Authority
NA	not applicable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	not reported
OBS	observational trial
PFU	plaque forming units
PJI	periprosthetic joint infection
PSSRU	Personal and Social Services Research Unit
PT	phage therapy
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SHTG	Scottish Health Technologies Group
SoC	standard of care

UK	United Kingdom
US	United States of America
WTP	willingness to pay