

Phage therapy for severe infections tested in the first multicentre trial

An alternative to antibiotics has been around for the past 100 years. Ironically, the discovery of antibiotics meant their use faltered in the west, until now. Clare Sansom reports.

For Frederick Twort's paper on bacteriophages see *Lancet* 1915; 2: 1241-43

For more on the Phagoburn trial see <http://www.phagoburn.eu/>

It is common knowledge that antibiotic resistance is one of this century's most important medical challenges. Journalists often speculate about a dystopian post-antibiotic future and, in 2014, the public chose combating it as the challenge for the £10 million Longitude Prize. Yet one potential alternative to antibiotics has been in clinical use for almost a century. This is phage therapy: the use of viruses that specifically infect and destroy bacteria to treat refractory infections.

The first paper to describe bacteriophages was published by Frederick Twort in the *Lancet* in 1915. He referred to bacteriophages as "the transmissible bacterial lyses". 4 years later, and still 10 years before the discovery of penicillin, they were first used as anti-infective agents. However, phage therapy stalled in developed countries after penicillin was discovered. During and immediately after the Cold War, use of bacteriophages was restricted to some countries in eastern Europe, largely because of the difficulty in obtaining antibiotics there. "We have decades of experience of this approach in Poland, and anecdotal evidence of its efficacy and safety, but this has not been

rigorous enough to enable any phage therapy to be licensed", says Andrzej Górski of the L Hirsfeld Institute of Immunology and Experimental Therapy (Wroclaw, Poland).

"We are ready to discuss regulatory approaches for further developments of phage therapy for difficult-to-treat infections..."

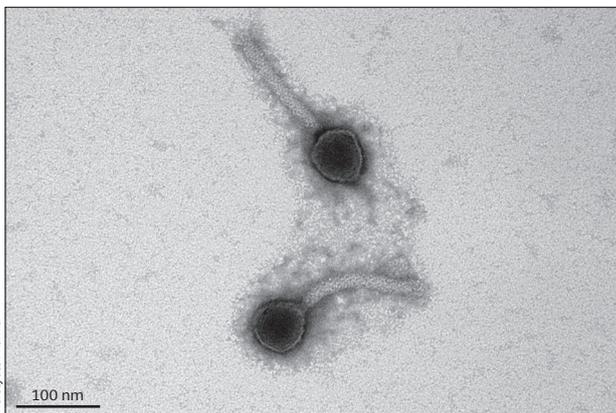
Now, however, a phage therapy is being tested in a multicentre, randomised controlled trial for the first time. Phagoburn (NCT02116010) is a phase 1-2 trial in patients with burns with severe infections, set up by the French biotech company Pherecydes Pharma, and Patrick Jault, a clinician working in the burns unit at Percy military hospital (Clamart, France), with an European Union Framework 7 grant. "We are testing naturally derived phage cocktails in patients infected with *Escherichia coli* and *Pseudomonas aeruginosa*", says Jault.

The trial began in July, 2015, and the investigators eventually aim to recruit 220 patients from intensive care units in 11 major burns facilities in France, Switzerland, and Belgium. Ideally for the sample size, half the patients will be infected with each bacterium. After random assignment to treatment, each patient is treated once per day for 7 days with swabs of either the relevant phage cocktail or the current standard treatment, silver sulfadiazine. The primary outcome measure is the time taken before the bacteria are eradicated from the infection site, or bacterial counts significantly reduced at the site.

The phages used in the trial have been manufactured by a French biopharmaceutical company, Clean

Cells. "This was the first time we had to produce significant quantities of phages to good laboratory practice and good manufacturing practice standards, and it took a long time to set up the facilities and get full approval", says Laurent Bretau, Clean Cells' research director. Patients with *E coli* infection are treated with a cocktail of 13 phages, and patients with *P aeruginosa* are treated with 12; each phage was individually purified and characterised before mixing. "All the phages we use have to be lytic—that is, they have to break open and destroy the bacteria they infect", says Jerome Gabard, CEO of Pherecydes Pharma. "We therefore analysed all the phage genomes and rejected any that carry genes that suggest they might become lysogenic."

Regulatory agencies view fixed phage cocktails like these as biological products, and so need to apply similar standards of efficacy and safety as with other biological products such as antibodies. The European Medicines Agency (EMA) organised a workshop in June, 2015, to discuss practical issues related to their registration. "The Phagoburn trial is one of the very first phage therapy trials to be conducted to the level of rigour that we need to see in clinical development as a starting point towards licensing", says Marco Cavaleri, head of anti-infectives and vaccines at the EMA. Even if this trial is wholly successful, however, the agency will require evidence from further trials before the therapy can be registered, and these will take at least 5 years. "We are ready to discuss regulatory approaches for further developments of phage therapy for difficult-to-treat infections, and some of these could be much more complex", adds Cavaleri.



Almost certainly, further phage trials will be underway before the Phagoburn investigators report their results next summer. AmpliPhi, a biopharmaceutical company with bases in Australia and the USA that focuses on the development of therapeutic phages, plans to launch two major trials of a three-phage cocktail against severe *Staphylococcus aureus* infection within the next 6 months. "We have approval for the first trial in patients with chronic rhinosinusitis complicated by *S aureus* infections that have not been effectively treated. We expect to be recruiting patients before the end of the year", says Scott Salka, CEO of AmpliPhi. "This type of infection is far more than just a bad cold; some patients even resort to surgery to open their sinuses." Three groups of three patients will be given different concentrations of phages in nasal washes that are similar to those they regularly use with saline solution. This is a first-in-man trial

designed mainly to examine safety and establish appropriate doses, but the investigators are also hoping to detect a reduction in bacterial load.

The second trial planned by AmpliPhi will be a phase 1 study of the same phage cocktail as a treatment for severe skin infections. "This will initially be a safety study: we will be applying gauze dressings soaked in phage cocktail to the intact skin of healthy volunteers", says Sandra Morales, AmpliPhi's Vice-President of Research. This study is designed in collaboration with the US army, which is very interested in using phages to treat infected wounds. "Our collaborators in the army have very clear ideas about the types of wound that they would like to test this on first, assuming that this trial shows that it is safe", adds Morales.

Both Pherecydes Pharma and AmpliPhi have notably chosen to partner with military hospitals to develop phage therapies that could be used in treating battle injuries,

for which infections can be severe and the anti-infective agent can be applied topically. Other forms of delivery are possible, however, and both companies are exploring the development of inhaled phage therapy for acute or chronic lung infections. "Phage could be a potential alternative therapy for the recurrent lung infections that plague people with cystic fibrosis", suggests Cavaleri. Other indications that are likely to be suitable for this approach include persistent infections of the bone and inner ear.

Jault and Gabard are hopeful that Phagoburn and other trials will lead to the licensing of phage products as anti-infective agents. "This is a new tool for the treatment of severe and resistant infections, and we think it [is] a promising one", says Jault. "But it will not, on its own, defeat multidrug resistance. If we are to do that, we will need to reduce antibiotic use further."

Clare Sansom

Infectious disease surveillance update

Zika virus in Colombia

The National Institute of Health in Colombia has confirmed the presence of Zika virus in the Bolívar, Córdoba, Norte de Santander, San Andrés, and Sucre departments. As of Oct 16, 2015, nine of 98 samples taken from patients in the Bolívar department were laboratory confirmed as Zika virus, the first cases detected in the country. The virus is transmitted by the *Aedes aegypti* mosquito, which also transmits dengue and chikungunya viruses.

Update on MERS-CoV

Between Oct 17, and Oct 23, 2015, the National International Health Regulations (IHR) Focal Point for Saudi Arabia reported 12 cases of Middle East respiratory syndrome coronavirus (MERS-CoV), including one death. Seven cases were from Riyadh city, and three were identified through contact-tracing activities. On Oct 12,

the National IHR Focal Point for South Korea reported a relapse in a male patient aged 35 years who had been discharged from hospital on Oct 3, 2015, after two PCR-negative results. On Oct 11, this patient developed symptoms including fever and tested PCR-positive for MERS-CoV on Oct 12. Between Sept 24, 2012, and Oct 29, 2015, WHO has been notified of 1611 laboratory confirmed cases, including at least 575 related deaths.

Visceral leishmaniasis in South Sudan

The UN Office for Coordination of Humanitarian Affairs has reported that more than 150 people have died from visceral leishmaniasis (VL) in South Sudan in 2015. 4939 cases have been reported since January, 2015, including 152 deaths. In the week beginning Oct 19, 300 people affected by VL were reportedly admitted to

the Médecins Sans Frontières clinic in Lankien, and 800 other patients receive treatment daily. Ten deaths were also reported during this week. In 2013, 1614 cases of VL were registered and 45 deaths recorded in South Sudan. The increase in cases is probably due to conflict-related displacement, which might have resulted in non-immune populations moving into endemic areas.

Shigellosis outbreak in the USA

An outbreak of shigellosis has been reported in San Jose, CA (USA). As of Oct 27, 2015, 190 people have fallen ill with shigella-like symptoms in the region; 92 of these cases have been laboratory confirmed. The outbreak has been linked to the Mariscos San Juan No 3 restaurant in San Jose. Almost all those who have fallen ill ate at the restaurant on Oct 16 or 17, 2015.

Ruth Zwizwai

For more on **Zika in Colombia** see <http://www.promedmail.org/post/20151018.3723954>
For more on **MERS-CoV in Saudi Arabia** see <http://www.who.int/csr/don/29-october-2015-mers-saudi-arabia/en/> and
For more on **MERS-CoV in South Korea** see <http://www.who.int/csr/don/25-october-2015-mers-korea/en/>
For more on **visceral leishmaniasis in South Sudan** see <http://www.promedmail.org/post/3749052>
For more on **shigellosis in San Jose** see <https://foodpoisoningbulletin.com/2015/shigella-outbreak-linked-to-mariscos-san-juan-in-ca-grows-again/>