HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: The Antimicrobial Potential of Bacteriophages, HC 886

Wednesday 8 February 2023

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Watch the meeting

Members present: Greg Clark (Chair); Aaron Bell; Dawn Butler; Tracey Crouch; Katherine Fletcher; Rebecca Long Bailey; Stephen Metcalfe; Carol Monaghan.

Questions 1 - 111

Witnesses

I: Professor Cath Rees, Professor of Microbiology, University of Nottingham; Professor Joanne M Santini, Professor of Microbiology, University College London; and Professor Martha Clokie, Professor of Microbiology, University of Leicester.

II: Dr Josh Jones, Clinical Phage Specialist, NHS Tayside; and Dr James Soothill, Consultant Microbiologist, Great Ormond Street Hospital Laboratory Medicine.

III: Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd; and Mr David Browning, Chief Executive Officer, Fixed Phage Ltd.

Examination of witnesses

Witnesses: Professor Rees, Professor Santini and Professor Clokie.

Q1 **Chair:** The Science and Technology Committee this morning begins a new inquiry into the antimicrobial potential of bacteriophages. This subject was pitched to us competitively through a process in which we invited submissions from the public, and particularly from the scientific community. This is the one that attracted most support from members of the Committee. We are delighted to learn all about bacteriophages and their potential, starting today.

I am very pleased to introduce our first panel of witnesses. Professor Martha Clokie is professor of microbiology at the University of Leicester and director of the university's centre for phage research. Thank you for joining us.

Professor Cath Rees is professor of microbiology at the University of Nottingham. She co-founded PBD Biotech, which I think I am correct in saying has developed a phage-based diagnostic for tuberculosis.

Finally, Professor Joanne Santini is professor of microbiology at University College London. Professor Santini's work focuses on understanding the interactions between microbes and the environments in which they live.

Thank you very much indeed for coming and joining us. This subject matter is not well known to most people, and, indeed, the Committee has not looked into it before, so, perhaps starting with Professor Santini, will you give us a basic primer on what phages are and what use they can have? I shall then ask your colleagues to supplement what you say.

Professor Santini: Bacteriophages are viruses—good viruses—that kill bacteria. They are probably the most prevalent biological entity on this earth. They are found everywhere you find bacteria, and you will find more bacteriophages, or phages, than bacteria. They have been used for over 100 years to kill bacteria in people.

Q2 **Chair:** What is the derivation and relevance of the word "phage"?

Professor Clokie: It comes from the Greek "to eat"—so a bacteriophage is a bacteria eater.

Q3 **Chair:** I see. That is a very helpful piece of etymology. Since you have the floor, Professor Clokie, perhaps you will advance our understanding. They can be useful in eating harmful bacteria, and that, obviously, has medical uses.

Professor Clokie: Bacteriophages are part of the natural microbial world. Bacteria have been in existence for nearly 4 billion years, and, as they evolved, bacteriophages, their predators, evolved with them. All bacteria have these very specific viruses. In the same way that we will get a flu or a particular type of virus, bacteria have their own types that can affect them. Therefore, in a way, nature has done the work to find the things that kill bacteria that affect us. One approach to treating diseases is to find the natural bacteriophages and figure out how to use

them in a targeted way. To put that in context, antibiotics come from bacterial-bacterial interactions: bacteria try to kill each other in the soil, and so on, so they have made these compounds. We learned how to get these compounds from bacteria and use them as antibiotics. We have this other set of natural enemies of the bacteria—the phages—so we can exploit them.

The difference between an antibiotic and a phage is that a phage is a whole organism. They are quite big viruses. They tend to have genomes of perhaps between 50 and 200 genes, and we know quite a lot about how they work. They attach to bacteria and turn the bacteria essentially into phage-making machines and release their progeny. They then find more bacteria and kill them, and so on. When we have a bacterial disease, the bacteria have got out of balance in our bodies and are causing infection. We can therefore use a phage to selectively remove that one bacterial infection.

Q4 **Chair:** Thank you very much. That is very clear. Perhaps I can ask Professor Rees to comment. My understanding is that you have been working on a phage-based diagnostic for TB.

Professor Rees: Yes.

Q5 **Chair:** So how does the diagnostic potential work?

Professor Rees: As Martha has explained, the whole point about these viruses is that they have specific targets. As we understand with viruses ourselves, not all viruses that infect animals will infect humans. If you think of bacteria as different animals, different types of bacteria have different viruses. If we choose a virus that infects one particular type of bacteria, we can then use that to allow us to detect the presence.

The advantage of a virus over the bacteria, as Martha was explaining, is that one virus goes in and usually 50 to 100 come out. They grow really quickly. If we are looking for bacterial diagnostics we often have to go one, two, four, eight, 16, until we get enough to find it. With viruses it goes one, 50, 50^2—someone can do the maths. They grow very quickly and we can take advantage of that. So we have specificity and speed and can make combinations.

Again, we come back to the idea in phage therapy: when these agents go in—unlike with an antibiotic, where, when it is added to the body, bacteria will start to break it down and it gets diluted out—if they have hosts in there that they can replicate on, they will make more, to kill the next bacteria. They are self-replicating, which is one of the big advantages we see in this idea of therapy—not being diluted out.

Q6 **Chair:** We will come into this in more detail. Obviously, the whole country is familiar with antibiotics; given the potential, and the biological effects of phages on bacteria, why are they less well known and, by implication, therefore less well used than antibiotics, which have become familiar to us?

Professor Rees: It is quite a long history. Partly, about 100 years ago, it was, "We have got a new reagent and we will say that it cures everything, including broken legs." It was a bit of a snake oil, which did its reputation no good whatsoever.

Then we got to the point where the technology was being developed, and there were applications, and antibiotics came along. There were political issues. The eastern bloc had particular expertise in phage therapy, and we were going with antibiotics in the west, so it kind of fell out of fashion in our sphere; but in the wider scientific world of phage biology it has been very well established.

Professor Clokie: It is also to do with the simplicity. It is relatively easy to develop an antibiotic. It is one compound. We have pathways and processes to develop a simple compound that kills bacteria, but bacteriophages are more complex, as we have been talking about. They are replicating biological entities; but, actually, it is this complexity that we need, now, because it is the complexity that means it is hard for bacteria to become resistant in the same way.

Until recently it was probably a little bit difficult to understand that complexity, but we have a lot of tools, now. We can do it, and it is a complexity that we need. A simple solution is always favoured, and antibiotics were seen as simple and a panacea to all diseases, so they were used; but now we can see that there are significant problems to them.

I do not see it as a question of either bacteriophages or antibiotics. One of the things that phages can do is help us preserve our antibiotics. There is a lot of research now showing how phages can actually resensitise bacteria to antibiotics, so we can use them in a really sensible way to protect the antibiotics that we have currently.

Q7 **Tracey Crouch:** Sorry if this is a really stupid question. There is a spotlight on gut health at the moment. Are there natural sources of phages?

Professor Clokie: It is not a stupid question at all. Wherever you find bacteria you find phages, so in your guts already you have—in a healthy gut—phages playing crucial roles in controlling the bacterial populations.

Q8 **Tracey Crouch:** And are there certain foods that can help encourage that?

Professor Clokie: Yes, certainly certain foods like fermented foods have the particular bacteria that are favourable and bacteriophages associated with them. It is somehow a little counterintuitive. When people are looking for phages to use in therapy, you find them where you have high concentrations of bacteria and you will actually sometimes find them associated with healthy people. People look for phages in sewage—not because sewage is dirty; just because you have high numbers of bacteria, and among those bacteria will be phages that are effective on bacteria that we wish to treat. Phage scientists hang around in not very

salubrious places, and go to places like anaerobic mud, which I go to quite a lot for some of my anaerobic bacteria; and we go to sewage farms and find the right viruses. We purify them, of course, away from everything else, and make them into single viral preparations—but, yes, they are just present naturally, and they are present in healthy guts and healthy microbiota.

Professor Santini: One of the big advantages of using phages over antibiotics—and I am not saying one or the other; a combination is obviously probably going to work best—is that phages will not kill all the good bacteria. Often, somebody who gets antibiotics will end up with some other problems, potentially, and the gut microbiome is adversely affected, in which case you lose some of the important species forever. That is why people have been talking about faecal transplants. That is really quite common now, and is becoming more common.

There are some phages in your gut that are probably doing some really good things in naturally keeping those pathogenic bacteria at bay—the nasty bacteria; because there are good ones, too, right? They are not all nasty. As Martha says, sewage is really good stuff—

Professor Rees: For phage hunters.

Professor Santini: For lots of things. Obviously, sewage was used as a diagnostic for SARS-CoV-2 in covid, so it has lots of advantages.

Chair: Well, that is an unexpected thing—in praise of sewage.

Q9 **Katherine Fletcher:** I am going to declare an interest, which is that I am utterly biased to Professor Rees, as a Nottingham university science department alumna.

Knocking around the House of Commons I often find that when we are interested in and passionate about a topic we forget the really basic brick level; so here is one I prepared earlier. Lots of people will hear "virus" and will think of that. Lots of people will hear "antibody" and will think of the stuff that we have generated to attack covid, and confuse that with a virus that is a phage and looks a little bit like a terminator. That will be confused with tiny little molecules that run around shattering cell walls, or whatever.

Would it be possible to explain why this is different from that, even though we use the colloquial term "virus"? Where I am going with this is that people are going to think, "Oh, they are going to release viruses into me." Covid has not given viruses a great reputation in the last couple of years. I don't know who to start with. I can see you all smiling.

Professor Rees: In essence, they are the same. What we are talking about with a virus is something that will infect something and take over. That is why we talk about computer viruses. They get in the computer and take over. The terminology is the same.

With different cell types we have different surfaces and different types of genes. You have to have a virus that recognises the right type of cell surface and has the right genetics to work in that cell.

Thankfully, bacterial cell surfaces and our cell surfaces are completely different. The molecules are not the same, the chemistry is not the same and the structure is not the same. The genetics of bacteria and humans are completely different. So even if we have those viruses in us, there is nothing for them to recognise. Even if they got into a human cell, there is nothing for them to do, because they do not recognise its genetics. The fear is perfectly understandable, but at our scientific end we say it is not a problem.

Professor Clokie: I think it is really important to have a good cultural narrative in which we will deploy phage products; and people do get it. People understand the concept of a probiotic, don't they—good bacteria in yogurt? So part of phages will be, "There are bad viruses that make us sick, and there are good viruses that kill them; the enemy of our enemy is our friend."

I think it is an important point and it is something that we have been investigating by working with colleagues from the humanities, to try to examine the current narrative. We did a study, funded by the Wellcome Trust, to look at people's perceptions of viruses, and the people who were surveyed did have some understanding of the differences already. I think there is more education in that area—

Q10 **Katherine Fletcher:** So there is a difference in the shape, because fundamentally they are attacking different things—brilliant. Can we be confident that we understand everything about phages? Can we look the public in the eye and say, "We have really nailed this, now. We know how this works," or are there any gaps in our understanding of it?

Professor Santini: Can I just take a step back? Animal viruses have evolved—they have come from phages, basically. There is a strong link. The thing about viruses, even with the virus that caused covid, is that when they infect they are very specific.

Q11 **Katherine Fletcher:** Lock and key.

Professor Santini: Yes, so a lot of the animals and humans that have been infected have got that key. Each bacterial virus—each bacteriophage—will have a separate key that it recognises, and that will be specific. It will be different for humans and animals, and—

Katherine Fletcher: That is brilliant. I just wanted to clear it up before we get on to the really technical stuff. Are there any gaps in our understanding of phages and how they work?

Professor Clokie: Yes. We have—connecting your last question with this question—a long history of understanding phages. We have 100 years of observing, and a lot of recent cases where people have used phages, and compassionate cases as well.

Huge numbers of trials have been done in the animal sector. In our lab, in the last year, we have done trials on thousands of birds, and we can see that they are effective. We know that they are safe.

There are gaps in our understanding of the complexities of different types of viruses. We have said that their complexity is actually a good thing, but there are gaps in understanding the different nuances. I was saying they have been evolving for the whole time that bacteria have been in existence, so the different bacteria and viruses have solved the problem of killing each other in different ways. We have a lot to understand about the specifics of the different details, but we do not have to worry about the overall safety.

Q12 **Katherine Fletcher:** That is fair enough. I am not worried. I just wanted to get it cleared up and out of the way.

Professor Clokie: It is important to clarify.

Q13 **Katherine Fletcher:** Professor Santini, do you think we have identified their strengths? The key strengths are: they effectively do not touch human tissue, because they are not looking for it; they are replicable at speed; and they are highly specific. What else would you highlight as the strengths of bacteriophages for treating bacteria in human systems?

Professor Santini: There are different approaches depending on the organism that you want to kill. You could use specific phages—individual ones against particular organisms. You can use the large cocktails against those organisms. I was just trying to think of other advantages. They can be cheap and you could develop natural phages quite easily in low and middle-income countries, in particular.

Q14 **Chair:** Did Professor Rees want to say something on that?

Professor Rees: Yes, I was coming back to exactly that point. The drug discovery pipeline for antibiotics is getting tougher and tougher, but for phage the world is our oyster. There are limitless phage out there. Yes, they have to be isolated and purified, but the scientific community has identified those aspects of phage biology that we think could have a potential risk—and those are defined.

When you go for phage therapy there are criteria. We say, "You want a phage like this; it is lytic and does not have genes that would be transferred." The scientists have enough knowledge to say, "We can pull these out," and we can select from millions—billions.

Q15 **Katherine Fletcher:** That is a really interesting key point, Professor Rees. Lots of people have heard about personalised medicine and the mRNA vaccination that has been produced to attack covid, which is us moving pieces of DNA around to create an output. You are saying that the key strength of phages is that the world has created a panoply of varieties, and we just need to find the one that does the job that we want. Is that correct?

Professor Rees: In itself that creates the problem, because how do you market that? How does the business community engage with that? From my side in the business development world, it is often about how you make the business case. If you need that huge panoply of things, how do you do it? Part of the limitation is that there isn't a clear legislative framework for companies to be confident that the market will be there. It is a chicken and egg scenario. We need some regulation.

Q16 **Katherine Fletcher:** I know we want to come on to that, but I just want to do the last bit of quality nerdery, if that is acceptable. In terms of any risks and the clinical proposed use, would they be used in conjunction with or separately from antibiotics?

Professor Clokie: There will be some cases where we will use them with antibiotics, and some where we will not. There is a risk with bacteriophages, as with any other microbial agent, that you will generate resistance, but we know how to minimise that by combining particular bacteriophages and using ones where it is difficult for bacteria to become resistant to them. There will be many settings where we will use bacteriophages with antibiotics. One does not by nature preclude the other.

Q17 **Katherine Fletcher:** So there is a potential risk of its becoming ineffective over time. Are there any identified risks about use in mammalian systems?

Professor Clokie: The evidence suggests that when they are given orally or topically, or are nebulised, you do not mount a strong immune response. They are not a toxic product. If you inject them, that is different. A body of work needs to be done to find phages that are less immunogenic, and to work out how they could be used in that way; but there is not a direct risk. There are risks associated with producing a product, but we understand what those risks are, and we can monitor a product to make sure it is not going to cause any indirect effects.

Professor Santini: Can I follow up with one thing? It is really important that you understand the phages that you are using, because if there are unknown genes in there, you do not know what the potential risk will be in future. As you know, the virus that causes covid can recombine and change, so you really need to know what you are using to minimise any risk. People are taking these approaches, including starting from scratch in designing phages—engineering phages with known genes, so they know they are not going to be of risk.

Q18 **Katherine Fletcher:** I was going to ask, as my last question: is there anything that can kill a phage?

Professor Santini: The immune system.

Professor Rees: Protozoa love grazing on them, but that is another story.

Q19 **Carol Monaghan:** You were talking about the engineering of phages. Can I just check this? If a new virus comes along, probably, in the

thousands or millions of different phages, there will be something that will be a fit for that, and can attack it; but is there a possibility that if something new comes along you could manipulate a phage that is already there that is close, to attack it?

Professor Rees: Just to set things clear—I know it is a terminology thing, but in microbiology these phages are killing bacteria. They are viruses that kill bacteria. They will not kill viruses. As it is on the record, I just want to make sure we are clear about that.

To be honest, yes, there have been examples where people have taken the genetic route, but in the first instance there is such a plethora of phage out there, and our sequencing technologies and bioinformatics, and ability to understand the genetics, have really moved on in the last 10 years.

Getting a new phage and new genetic information about it, and doing those checks, is much easier, and our understanding is growing all the time. It is a worldwide programme, where we are gaining knowledge all the time of the genes that make the viruses.

The science is moving fast. Do not ask a scientist if we know everything, because we are going to say no. We will never admit we know everything—otherwise we are out of a job. There is always new knowledge, but we have a vast amount of knowledge, and that feeds into our safety criteria.

Q20 **Dawn Butler:** This is fascinating evidence, so thank you all very much.

Professor Santini, you talked about knowing what you are doing with regard to phages. Sometimes I feel that other countries are way ahead of where we are in the UK, so I just wondered how well developed we are here compared to other countries, in understanding what we are doing with phages.

Professor Santini: I am going to start with a positive and tell you that we could be world leaders, of course, with the right things put in place. We can certainly learn from other countries in terms of the regulations. They are more stringent here, but I am sure you are going to talk about that at some point. They are much stricter, and, actually, not that clear with respect to phages.

The other issue is that I think we can learn from places that have been using phages and checking their use—monitoring what happens to the patient over time. Belgium is one place that is doing this really nicely and providing phages for the UK. I think Josh Jones is going to talk about that. Australia has recently put out a very good protocol for how to use phages. This is on compassionate access grounds. Obviously, eastern Europe has been using phages for ages, so there is a lot to be learned there. The US now has quite a few clinical trials that the FDA has funded using phages, and there are some clinical trials in Europe as well.

Professor Clokie: I totally agree with Joanne. We have a lot of expertise in the UK. We have a very strong culture and history of microbiology

expertise, and it is internationally accepted that we have arguably more phage expertise in the UK than in other countries, but it is in little pockets. It is quite fragmented. We need to be much more co-ordinated in our response to maintain that position. Other countries are investing a lot more in the technology than we are, so we need to join up and capitalise on what we have. We are good at that aspect of it, and we are also good at translating things.

We have quite close connections with our clinical colleagues, so at Leicester and at many universities there are close connections with local hospitals. We have the ability to move forward now that we have a lot more clinical interest to drive projects. That is why we need policy support, the regulatory framework and those aspects—to join things together.

I think we need a co-ordinated institute of national research—a phage institute—where our banks of phages can be stored and we can have standard protocols. We could have banks of phages for people to access when they want to start their own projects.

We are in a good position to capitalise on what we have at the moment and turn it into a reality.

Q21 **Katherine Fletcher:** Do you mean something like a national phage library?

Professor Clokie: Yes.

Dawn Butler: It's good—you could do the whole thing.

Professor Santini: Just one thing: manufacturing is a problem. It is one case to manufacture for a compassionate access case—very personalised medicine—but when we are talking about clinical trials, we do not have GMP facilities. Good manufacturing practice facilities are a requirement from the MHRA for large-scale production of phages for, say, clinical trials. So infrastructure with respect to manufacture, together with regulation, would really help us to move forward.

Professor Rees: We do have the potential for GMP production. It is just that because there isn't a market, people do not invest.

Q22 **Dawn Butler:** As you say, it is a chicken and egg scenario. Is there information transfer between countries, or is it just done scientist to scientist? Do you have your close comrades that you talk to—

Professor Clokie: Yes, it is a very open and collegial community across the world. I saw that evidence was submitted from our Australian colleagues, as well as French and Belgian, and the community is aware of the urgent need for the technology. Historically it seems to be an open, warm community of the different elements.

Q23 **Tracey Crouch:** I find it quite inspiring to have three female professors sitting in front of us, on such an interesting, technical subject, and I wish you guys had been my biology teachers, because I would definitely have

shown more interest.

Professor Clokie, you partly answered my question when answering one of Dawn's about the relationship between universities, labs, hospitals and SMEs. I am interested to know whether you think that that relationship could be strengthened, and how it could become more universal. I assume that relationships between universities and their local hospitals are very strong, but what if you are in an area like mine that does not necessarily have a university where this is studied? How does it become more standard?

Professor Clokie: I think that it does need to become much more standardised. It is quite fragmented at the moment.

There are different levels of relationships. In a way, the relationships in the agricultural space are a bit more developed, because I think they can see a pathway to market. They have developed relationships with specific people who have the expertise in those viruses.

Having a network joining up phage researchers in general with that clinical need—a more formalised network, a phage taskforce: I think an institution could act as a centre of gravity. When relationships have been established between particular doctors and phage researchers, in a way you can then just roll that out to other people who are interested in treating particular diseases, because you need people with expertise in specific disease indications and how they will do the trials. I think it could be really valuable to have a co-ordinated central resource that can act as a place where people go to take the technology forward and develop it.

Professor Rees: I think that ultimately it has to move beyond specialism into generalism. Fortunately, quite a few of the phage specialist groups are attached to universities with med schools. With that forward-looking training, it is not just a niche offer for someone who happens to be interested in phage; it is accessible to lots of different types of clinicians, who can have the training and background knowledge. Fortunately, in the UK our medical schools happen to have quite a lot of phage biologists associated with their universities. So there are ways.

Professor Clokie: Yes. My best audience last year, in all the talks I gave, was our fifth-year medics. They were incredibly engaged. I was supposed to talk to them for an hour, and four hours later they let me go. I think embedding that within the educational programme, and embedding phages within, for example, the Government antimicrobial strategy documents, and politically in our different approaches, so that they are considered alongside other alternatives—

Professor Santini: Can I just add to that? I think Australia has done a really nice job linking up all the hospitals. Phage Australia is a link-up of all the hospitals, and all those hospitals have their own phage banks. They then share phages between the hospitals—well-characterised phage banks, which is really cool. That is for compassionate access, once again—very different from clinical trials.

I am pretty lucky at UCL that we have UCLPartners. I know clinicians from at least three other hospitals—GOSH, which is where Dr Soothill, who is going to speak to you, is from, UCLH and Royal Free—are very interested in using phages for their patients. They are quite keen that something moves forward—maybe a Phage Australia approach to that hospital base.

Q24 **Tracey Crouch:** You mentioned a link-up with the agriculture sector, and things like that, and we had a reference to bird flu earlier, but what about things like bovine TB?

Professor Clokie: We have the world expert on bovine TB among the Committee.

Professor Rees: Treatment of TB with phages is quite difficult, in a nutshell. It is not one that you would pick as a best target, just because of the nature of the disease and how it develops in the body. It is not one that you would think of as a great model for phage in the first instance. I am not ruling it out. I am just saying it is not one that we think of first, because it is quite hard.

In agriculture they are looking at control of campylobacter in poultry. One of our biggest causes of food poisoning is the organisms that do not affect the chickens coming into the food chain, but if you can reduce the number in the poultry you are going to reduce human infection, so treating carcases or birds to reduce human pathogens that come through the food chain has started to get movement. Salmonella in pigs is another one. It is about looking at the organisms that come through the food chain and targeting them.

It is interesting that in Europe phage are given a sort of organic status. There are products on sale in Europe that you can spray on meat or cheese. The cheese ones are to target listeria and the meat ones are to target E. coli. Those products exist but they come under the organic side of food regulation. So there is a lot of movement in that, but, again, it is about the financial model. There, you have phage that are going to be used—sprayed on a surface—and we are going to ingest them. We ingest phage anyway. It doesn't matter. It is relatively safe. It is not the same as a clinical application, but it does open up the business case, so supporting both sides, I think, is important. Having rules that cover both, to allow the whole sector to develop, will support both sides.

Professor Santini: We are talking about whole phages here. We can also use the phage enzymes, which would decrease channels of resistance, as well. Maybe, in some places where it is more difficult to administer the phages, the enzymes that can either kill, or remove the armour so that antibiotics and the immune system can work, could also be used. That will just expand it a bit.

Q25 **Tracey Crouch:** Professor Rees mentioned financial models, which brings me nicely on to my final question about funding arrangements. Do you think phage research requires more specific funding?

Professor Rees: Yes, of course—but what sort of phage research? This is the thing. Fundamental phage research is fundamental biology, and we are in competition with all other scientists in looking at all different aspects of biology, so, yes, that is something for which we have to fight our corner. It is sometimes harder to get phage biology funded than it is for maybe cell biology, cancer biology, because the obvious application is a bit further down the line, but we still have to fight our case.

I think that there is a big gap in translational funding. If you go to the UK funding agencies for fundamental research, they are looking for novelty. In some ways, phage therapy is not novel, now. It is an established idea, so who is going to fund this? Then it is, "Should the company be doing this?", and you come back to, "You can't until there is legislation." I think funding might have some sort of focus, where you say "We have got the expertise in the UK, and we have potential here. We have moved the science forward." If we could have a focus of funding that allowed or supported those early stages to get that fundamental movement from the lab to the application, that would benefit UK industry in the long term and help us to build that sector.

Q26 **Tracey Crouch:** Is there a big gap in the funding from big pharmaceutical companies? How can this be addressed?

Professor Rees: It is their business case. They have to have legislation and see markets. Until that is there—

Professor Santini: And you have got to use engineered phages or phage enzymes. It is impossible to patent natural phages. You might be able to patent cocktails of phages for certain organisms. Certainly, big pharma is interested in phage enzymes and engineered phages.

Professor Clokie: I think they are interested in phages. They are reluctant to invest if they do not have a mechanism to protect the product that they are then going to invest millions in. So that is where the gap is.

Q27 **Aaron Bell:** Thank you all very much for your time.

I want to follow up, Professor Santini, on your answer to Dawn Butler about regulation, when you were going through other countries. You said we had more stringent regulations. That is usually seen as a good thing, but I understood from the pitch we had that there is real concern that our regulations are not quite fit for purpose. Could you expand on that?

Professor Santini: You are going to get more from Josh Jones and James Soothill on this. There are no specific MHRA guidelines for phages. Because there are no specific mentions of phages in the guidelines, they are considered as medicines. Normally, a medicine has to be produced under good manufacturing practice. For phages, at the moment, we do not have such facilities, so that complicates things.

There are ways where they can be considered as specials—Dr Jones will tell you more about that in the next session—and they can be used for compassionate access use; but all the cases that I know of in the UK of

phage use for compassionate access have been with phages coming from abroad. They are from the US, Belgium or perhaps other places. I do not know of any examples of phage therapy in this country for compassionate access use with phages that come from here.

There was a clinical trial in this country in 2009 for the use of phages, and it showed that phages were effective against the particular bacterial pathogen, but there was no follow-up after that, because that was not approved. At that time, MHRA did not require phages to be produced under GMP, so the rules have changed, I guess.

Q28 **Aaron Bell:** So it is the production of them domestically that is the problem. Is it because the regulations did not really consider this?

Professor Santini: Maybe. I think it is a conversation that the MHRA should have with the phage community, the clinicians and perhaps regulators overseas.

Professor Clokie: Depending how a bacteriophage is regulated, that affects how they have to be produced. There is also not clarity in the veterinary and agricultural space as to whether a phage should be a feed additive or a veterinary medical product. Depending on how it is defined, it has to be made in different ways.

One conversation that can be very helpful within the regulators is about saying, "Actually, we need a phage to be produced to this particular standard." The Belgians, instead of producing their phages under strict GMP, which at the moment costs millions of pounds, have very stringent end-point monitoring. They make sure their products are safe, and they have good ways of monitoring that. At the moment, we do not have a mechanism to bring all those parts together.

Professor Rees: It is the very nature of phage that they are a biological agent, and they will not be identical every time. That is the difference between them and a pharmaceutical. If you are producing an antibiotic you can say, "It is this." There will be some biological variation, but it is in the same way as we think about transplants. We can do human transplants, but not all kidneys are the same. They are produced and harvested and treated to a standard. That is the important thing. It is setting the standards that have to be achieved for safety, rather than defining what it is as a very specific thing, which is much more difficult with a biological agent compared to a chemical.

Aaron Bell: Understood. Thank you.

Chair: Thank you, Aaron. I should point out to people watching that the MHRA, the regulator, will be giving evidence in one of our future sessions, and we will put these points to them.

Q29 **Dawn Butler:** You said that it is impossible to patent phage.

Professor Santini: Natural phages are unpatentable, because anyone can isolate them. You can just tweak them.

Q30 **Dawn Butler:** So does that mean that big pharma will be more reluctant to invest, because they will not make a lot of money?

Professor Santini: I have been speaking to GSK and they are reluctant: they are interested in engineered phages and use of phage enzymes. Other companies, I would say, are looking either to engineer them or to use their enzymes. It depends on what you are using it for. I am talking about it as a therapy.

Q31 **Dawn Butler:** We all often talk about maybe needing to change the relationship between medicines and profit, so that we start focusing on the patient rather than profit for big pharma; there will be more money to invest in research in things like phages. Is there another route to investment through the health industry or, dare I say, the diet industry? I whisper that bit.

Professor Clokie: I think there is. There is definite room for other models rather than the strict pharmaceutical industry model. We can certainly learn from them. We need that expertise, but there could easily be another method—whether it is a social enterprise type of method where the phages are collated and used and the companies have a subscription model, like the Netflix model, a little bit like the Government's incentive for being able to produce a drug and delinking that from the amount of drug that is sold. There could easily be models like that which could be implemented across the entire NHS.

Dawn Butler: Great, thank you.

Q32 **Chair:** Thank you very much, Dawn.

On the point about the good manufacturing process and GMP facilities not being available, is this specific to phages, or is it a more general problem in the life sciences in the UK? Is it a reflection of a general problem, or is it a specific one?

Professor Clokie: It is a little bit specific to phages. We have good manufacturers, in general, of biologicals, and we have companies that are interested in moving into the phage space. Phages are a little bit different in the way that you make them, because normally, when you manufacture a biological, you make a high density of the bacteria and give them a signal to make the protein, the biological, that you need to have made. With the dynamics of making phages, you need to carefully understand the amount of bacteria that you have, before you add the phage. There are complexities with that dynamic.

I think, with more investment, companies are really keen. They could be incentivised to apply the body of knowledge that they have into the phage space. I think we could capitalise on our ability to produce other biologicals and bring that technology to phages.

Q33 **Tracey Crouch:** How long does it take to make a phage?

Professor Clokie: Just 20 minutes—overnight. The time it takes to make a phage is linked to how long it takes bacteria to divide. In general, when

you are fermenting a phage, you do an overnight fermentation to get a high concentration of phages from a low concentration. They are relatively quick to make. You need bacteria that they replicate well on. Conceptually, it is not difficult to make large numbers of phages expensively. What is difficult is that, when you apply so many checks to every single aspect of the production that need to be done, to make it consistent with the way you make other things, the cost associated with that can be completely prohibitive to getting the phages to do a trial with. I have seen that myself. I have sometimes approved quite large grants, or tried to encourage them, and they fall down because they cannot get hold of the correct amount of GMP phages to be able to do the trial. Conceptually, it is not difficult. More investment and incentives need to be put into that space.

Q34 **Chair:** I find it extraordinary that there has just been one single clinical trial.

Professor Clokie: That is in the UK. There have been several other trials across the world.

Q35 **Chair:** But in the UK, just a single one—in 2009, I think you said. Is that because there isn't the manufacturing capability here? Is that what has stopped it, or is it funding?

Professor Clokie: I think until recently it really was not considered to be needed. It really wasn't. I can see that with my clinical relationship between myself and my microbiology colleagues and clinical colleagues. It was, "Why would you do this complicated thing when the antibiotics work?" I think it is only just now that we are realising that the antibiotics really are stopping working. We have to do something, and that has motivated and reincentivised that dialogue. So now you have doctors who want the phages now that we need to do the trials. Certainly, if we had had better production facilities, there would, I know, have been more trials in the UK.

Chair: That is probably a perfect point to turn to some clinical witnesses. I am very grateful for that kick-off session, which has briefed us very well as a starting point to the inquiry. Thank you to our three professors.

Examination of witnesses

Witnesses: Dr Jones and Dr Soothill.

Q36 **Chair:** I will introduce our next witnesses as they take their seats. Dr Josh Jones is a clinical phage specialist at NHS Tayside. He is the UK's first NHS clinical phage specialist and oversaw the provision of phage therapy to diabetic foot infection clinics at major NHS hospitals in Edinburgh and Glasgow. Thank you for joining us, Dr Jones.

Dr James Soothill is consultant microbiologist at Great Ormond Street Hospital—GOSH, as it has been referred to—and is part of a team that has treated several patients with phage. Thank you very much indeed for joining us.

You obviously heard the first session. Dr Soothill, will you address the point that has been evident already about why progress on wider clinical use of phages has been relatively slow, compared with other countries in eastern Europe, we understand, and compared with antibiotics?

Dr Soothill: Antibiotics are much easier to use, in that they kill a wide range of things. In clinical circumstances, if you are trying to keep alive a patient who has very poor immunity, which we do a lot of, you need very broad-spectrum things that you know will work against a range of things, so it is no use with phages. You have to know what your diagnosis is and what the infecting organism is before you do it, if you are trying to treat an infection. Antibiotics are a lot handier to use. The fact is that we will need them, and phages will not replace them. We have to think very hard about how we are going to keep antibiotics going in the country.

Phages have suffered from the problem that big pharma has not wanted to get involved. I tried to involve Pfizer in work on calf diarrhoea, where phages seem to work very well. They had various problems. You would have to make a cocktail; you would have to produce each one to high standards and make sure it was producing the same stuff each time. They looked at the profit margins and thought it probably was not a runner. There are all those problems.

If you try to do it to a high standard, it is expensive. Intellectual property has been a problem, which people have mentioned. Without big pharma, there has not been the interest in vending. The fact is that drugs companies do most of the trials of things that work.

Therefore, the small people have largely been kept out in recent years. I treated one patient with phage back in the 1990s. I wrote a letter to the chair of the committee and said, "Can I use this sewage-derived virus on this patient's burn?" The chair wrote back to say yes, so next week we went ahead. The patient was very sick and was likely to die. The patient did come through, but we gave them a lot of antibiotics, too. It was the first demonstration of multiplication on a patient that I have seen recorded.

The difficulty is that either you have to make it reasonably easy to do trials for small people, or big companies need to be involved. For small people to want to be involved, you have this good manufacturing practice. None of us is advocating bad manufacturing practice, but the thing about good manufacturing practice is that it means you want to use a phage in a patient—and nowadays the genetics are fantastic. I have been working with Ben Temperton at the University of Exeter, who is actually here now. You send them a strain, they know that the genetics are okay and they can make the phage and about a week later you have it, but if you want to do good manufacturing practice it will take nine months and cost £1 million.

First, if the patient is horribly sick, the patient will be dead before that happens. I am keen to work on colonisation. What we are trying to do in this case is to get rid of gut bacteria, which you do not have to do so

urgently; you can put in a small dose to start with and then work out whether it works. What is important here is that we work out that it works. You can put in a low dose and show that it has multiplied, which means it has worked, and work out whether it works in that situation. Even if you are trying to do that, nine months is way too slow.

What are we gaining from GMP if you are using a low dose, which I think people should do in the first instance? It is all very well to say, "We think this works," but doctors like to do proper trials to show that things work. With phage, you can do a fairly proper trial without doing a complete one. You can look and see whether the phage multiplies and the bacteria goes away.

You can do that, and that should be made easy. If you are using oral phage it could be classed as a food and not a drug—that is, where you are not treating a medical condition; you are just trying to clear gut carriage. In that way, you would get the probiotic companies involved.

Q37 **Chair:** As to the extent of clinical use—you described some barriers to that—in our written evidence we heard that failures of phage treatment are common, so presumably for any patient, when you have antibiotics and an uncertain application of phage, if you want to save the patient you will go for antibiotics. Is that a barrier?

Dr Soothill: When I started working on phage back in the 1990s, I thought, "Where is anyone actually going to use this?" That is where the resistant pathogens are. I refer particularly to the E. coli-like bacteria and something called pseudomonas, but let us talk about E. coli because people have heard of that.

The E. coli-like bacteria are the real worry. I had three yesterday; I was trying to sort out patients with very nasty resistance. Some of them had got infections; some were merely going for bone marrow transplants and were colonised with very nasty things. You have to try to work out how you will treat them if they get sick.

Where I see this coming in is when you want to use it for those very resistant bacteria, which I think is what a lot of people are working on here.

In bone marrow transplants, if the patient has got very sick you do not have time to work out which phage to use. It is a good idea to pre-empt it and try to get rid of the thing, so you can use antibiotics, which will be the mainstay.

Q38 **Stephen Metcalfe:** Dr Jones, please correct me if I am wrong, but you are the UK's first NHS clinical phage specialist.

Dr Jones: Yes.

Q39 **Stephen Metcalfe:** Marvellous. Can you tell us what role you are playing in the advancement of phage therapy within the NHS at the moment?

Dr Jones: For my previous post at the University of Edinburgh, I had a Medical Research Council grant to oversee the provision of phage therapy to diabetic foot infection clinics at the Royal Infirmary of Edinburgh and Queen Elizabeth University Hospital in Glasgow. My current post in NHS Tayside is funded by the Tayside Health Fund. I should add that I am not here speaking on behalf of NHS Tayside. That is a charitable grant that runs until the end of 2023, so it is not core NHS funding and it is not part of a sustainable plan but provides a platform by which we can provide phage therapy for patients within NHS Tayside and stimulate further interest thereafter.

Q40 **Stephen Metcalfe:** Is the work you are doing confined to Tayside at the moment?

Dr Jones: It is currently confined to NHS Tayside.

Q41 **Stephen Metcalfe:** It is not rolled out across the whole service.

Dr Jones: No.

Q42 **Stephen Metcalfe:** What key issues have you identified in being able to roll it out on the more national basis?

Dr Jones: We have heard a lot about GMP manufacturing and access to GMP. That is a really key issue. At the end of this 12 months, this stops because we do not have a supply of phages any more. It is quite right, as we have heard, that phages manufactured in the UK for use as a special or unlicensed medicine are required to be made to GMP at the moment. There is not anybody doing that and we have heard some of the reasons why.

At the end of this 12 months, we will have no phages. Access to GMP and GMP manufacturing will allow us to move forward clinical trials. We have heard that because clinical trials require GMP phages. As soon as we have a GMP facility, we can respond to unsolicited requests for phages from across the NHS because we can meet the criteria, but it will also help to catalyse business.

We have heard a bit about GMP manufacturing and it being prohibitive, but in a sense we could think of it as being a little bit like generic drug manufacturing. The paracetamol we buy over the counter is made to GMP, but the patent has expired and it is relatively cheap. This is a similar model. However, we will not have a lot of GMP manufacturing centres because there isn't a huge market there, because when you are making phage you are making very small volumes of highly concentrated stock. I worked out that about 160,000 doses, or patients, could come out of an 8-litre fermenter, and that is pretty small.

Q43 **Stephen Metcalfe:** To be clear, you said you had run out of the supply of phages at the moment.

Dr Jones: We will at the end of 12 months. We are reliant on the good will of international laboratories that are supporting us at the moment.

Q44 **Stephen Metcalfe:** And then the work you are doing would stop?

Dr Jones: The grant stops at the end of February 2023.

Q45 **Stephen Metcalfe:** In terms of the timeline for getting a GMP facility in the UK to make phages, when do you think that might happen?

Dr Jones: From the discussions I have had about this, at speed it could take a couple of years to build a GMP facility, but we are probably talking of two to three years. There will be a gap, and in that gap it is a question of what we do. We could be reliant upon and try the good will of other international collaborators again, but that is finite; and the more interest we have in the UK, the quicker that will evaporate, because they cannot answer requests from everybody. It is possible to get GMP phages contract- manufactured. That would be an option. It could cost probably £500,000 to get a batch of GMP phage contract-manufactured in the EU and brought in to supply the NHS.

The other issue is who is supplying. I have to be careful what I say here. At the moment, health trusts are cautious about supplying other trusts because of issues or concerns about whether they want to take on liability for that, so it needs to be either some sort of central supplier or something not tied to a certain geographical area.

Q46 **Stephen Metcalfe:** First, who will build that facility over the next two to three years? Secondly, do phages travel well? Is it necessary to have it in the UK, or can it be scaled up and moved around the world easily?

Dr Jones: Phages travel pretty well. It depends on how they are stored. At the moment, we are using a cold chain. I did a few pilot experiments in the lab for the phage we are using. That might not need a cold chain, but for reassurance we are importing it from the continent by a cold chain.

Q47 **Stephen Metcalfe:** When you say "cold", what do you mean?

Dr Jones: Four degrees, so it is like a fridge. That is expensive, and costs have gone up a lot in the past few years. When I started this in Edinburgh and Glasgow, it was about £500 per import; now we are talking about £1,500, but if we do it on a per-patient basis that becomes very costly. Importation in a cold chain is prohibitive.

As to the other part of your question about who will build it here, that is an open question. I think this would work well as a public service. However, I do not think that will meet the timescale. We will be working a while potentially.

Q48 **Stephen Metcalfe:** If I throw open my wallet, do you think—

Dr Jones: In my other role in UK phage therapy, I am working with a company called Fixed Phage and the Centre for Process Innovation, which has an excellent track record in receiving Government and Innovate funding. We are looking at developing GMP manufacturing in the UK, beginning small scale, which would initially, we hope, act as a bridge to

the creation of a larger centre. We put something out recently about that, and I think it was in an appendix to Fixed Phage's evidence.

Q49 **Stephen Metcalfe:** You have a very sick patient with a bacterial infection. You have identified which bacteria it is and you can target your phage, as I understand it. Can you just do that, or do you need to seek permission from someone to treat them with phage, and what is that process?

Dr Jones: Phages are unlicensed medicines. All NHS trusts have unlicensed medicines policies, so we can follow those existing policies and they provide governance for the use of phages.

Q50 **Stephen Metcalfe:** There is no restriction; you can just treat.

Dr Jones: You can go ahead and treat providing you follow local guidance.

Q51 **Stephen Metcalfe:** Because it is not a novel manufacturing process; it is naturally occurring?

Dr Jones: It is broadly classified as an unlicensed medicine in the same way as other unlicensed medicines. Therefore, it is not to do with whether or not it is biological; just because it is not licensed, it follows that policy.

Q52 **Chair:** How much variation is there between local policies in this? You are in Scotland. What about in Great Ormond Street? Do you happen to know whether the policies are similar? Do they look at each other?

Dr Soothill: I can tell you what we did. We were using genetically modified phages. It went through our ethics committee and drug and therapeutics committee. People did talk about genetic modification, but in a way it is not proper genetic modification; it is the kind of genetic modification that could have happened naturally, so that was regarded as not a very big deal.

That was what happened at Great Ormond Street. We were importing from America, where they did not manufacture by GMP. That is what happens. You can import phages that have not been made by GMP, but you cannot make them in the UK if they are not manufactured by GMP, which is strange. The Americans do not insist on GMP, the Australians do not insist on GMP and the Belgians are sending people phages here which are not made by GMP.

There are different ways of handling this. You can be doing what they are doing in Scotland, which is presumably using off-the-peg phages, of which you have a whole set and you pull them out of the collection, but there will also be cases where you want to find a new one, which was what I was talking about. If you are faced with nine months, it is a complete joke. The great thing is that finding the phages is very quick. Even the Americans with their genetically modified phages were pretty quick. It was quick enough for a microbacterial infection.

Q53 **Stephen Metcalfe:** You are saying it is quick to find a new phage to treat a bacterial infection, but it would take nine months to get approval.

Dr Soothill: No. Nine months is the figure Ben Temperton gave. That is how long it would take him to get some GMP phages, or for it to be made by GMP. What I am arguing against is that I think the GMP is crippling the ability for fast reaction.

Q54 **Stephen Metcalfe:** For clarity, who has determined that it has to be GMP?

Dr Soothill: I think the European Union said that trials had to be GMP.

Q55 **Stephen Metcalfe:** Unless you import it from outside the UK.

Dr Soothill: No. I am not the world's expert on this, but I think clinical trials on GMP were by the European Union. The Australians are doing a whole-country clinical trial without GMP. They do not insist on GMP for clinical trials.

As to the bit about the individual patient, I think that is Britain. The trial they were talking about as being positive was one that I was involved in initiating. I did not put my name on the paper at the end. That trial was done immediately before GMP came in.

Stephen Metcalfe: I suspect we will look at that further.

Q56 **Chair:** Why did you not put your name on the paper in the end, Dr Soothill?

Dr Soothill: I did not like the way it had been reported. I wanted it to be reported differently and I said, "I don't want to do this if it is not going to be reported in the way I want it to be."

Q57 **Chair:** To reflect on the exchange that you had with Stephen, at the moment you can import phages for clinical use that are not manufactured through GMP and are imported from other countries, but you cannot use them if they are manufactured here.

Dr Jones: If they are made here, it has to be manufactured to GMP.

Chair: But you are free to import them from other countries that do not practise GMP. That is very helpful.

Q58 **Rebecca Long Bailey:** Dr Soothill, you said GMP was crippling the production of phage here in the UK. We are not experts on GMP. What elements of GMP are in addition to what happens in places like Australia and countries where they do not operate on a GMP basis?

Dr Soothill: GMP is very exacting, and you need to know exactly what you are doing with everything and how everything is being done. I have never been involved in this, but it is very exacting.

It is a process that is designed to ensure big companies are doing a good job and they are exactly sure what stuff they are making and that it is as safe as it can be. I am not against GMP, but there is a balance and we

are facing a really serious crisis. I am looking at the resistance we have at each three-month interval and thinking it is a bit worse than three months ago. Whoever is trying to balance the books on the health service needs to take a very careful look at what is going on with resistance, because it will be a big problem unless we do some things to fix it. There are some things to fix it, and this could be one of them, and we need to get on and do that.

Dr Jones: Can I speak briefly in defence of GMP? That may not be very popular in this room. A GMP is an internationally recognised standard for the quality of medicines. My view is that with phage we should be working to meet that standard, not necessarily adapting the standards specifically for phages. That is not to say there will not be refinements as we go forward.

The other issue is that, if we have an internationally recognised standard, it will allow us to export the phages we produce in the UK. We have heard reference to the period of nine months. If we have GMP phages and a utility that is manufacturing phages to GMP, we can start to lay down stocks and bank them; we can freeze dry them so that when we have to be responsive we can pull them out of the freezer relatively quickly and provide it to patients, but it will take time to build that resource.

Q59 **Rebecca Long Bailey:** On clinical trials, we heard from the previous witnesses that one trial in 2009 was thought to be relatively successful, but we have heard of the difficulties caused to further clinical trials in not having a GMP facility in the UK. More broadly, in the absence of this clinical trial framework, how confident are both of you that phages are both safe and effective, and what specific areas do you think require more clinical evidence?

Dr Jones: I am very confident. There have been 13 clinical safety trials since 2000, all of which have shown phage to be safe. That is by a variety of routes of administration. There was an excellent systematic review published by our colleagues in Belgium last year. That reviewed 2,241 clinical cases since the year 2000. Again, the safety results were very promising.

That review also showed excellent efficacy, with about 80% of those patients having clinical improvement. Those were mostly patients who had antibiotic-resistant or antibiotic-tolerant infections. The subtlety there is that whereas pure resistance may be relatively rare, a lot of the infections in the NHS that cost a lot of money are antibiotic-tolerant. These are infections that on paper are susceptible, but clinically we cannot clear those bacteria with antibiotics.

There is a discrepancy when we come to efficacy between observational and clinical trial data. Seven trials have looked at safety and efficacy. Of those, just two have shown some evidence of efficacy. The issue there is that phage is a little more complicated to use than just giving a tablet. You have to get the right phages because they are very specific to the

right place; they have to get to the bacteria at the right time, and there have to be enough bacterial cells in that infection to allow for replication.

If you get something in that constellation wrong you will not get efficacy. Some of those trials—I have recently written a review—have, by their own admission, got some of those bits not quite right.

As to the evidence we need to see, it is reassuring that the American Antibiotic Resistance Leadership Group published last year considerations for the use of phage therapy, which suggested that the therapy was appropriate to consider in difficult-to-treat infections. Health Improvement Scotland is currently reviewing a similar question and its report is due out soon.

It is reassuring that there is a sufficient evidence base to consider phage for unlicensed use. We have heard a lot about compassionate use. We do not have compassionate use in the UK; we have named-patient use or early access medicines. "Compassionate use" is more a colloquial term.

Before we move from unlicensed use to licensed use where we are imagining that we have an off-the-shelf cocktail of phages that you can buy, or that might be used in hospitals, we will want a larger clinical trial to prove efficacy once and for all through a clinical trial before we get to that licensed product stage.

Dr Soothill: When talking about phages, we are talking about a very wide range of things; some of them I would definitely not want to put in sewage, but happily they have DNA in them, which can create a variety of things, some of which are not pleasant.

We are now in a very happy position in that we can analyse DNA in a very short time and people will have very good banks and will know what is going on very well. I am very confident now that most of the applications with phage will be pretty safe from the point of view of that problem. They do not seem to have caused a lot of toxic or allergic problems in use.

One problem that could occur would be very rapid lysis of bacteria causing a problem. In the first case I told you about in the '90s, the patient's temperature did rise alarmingly after we gave the treatment. That gave me a lot of concern, but they were fine after that. That could have been bacteria breaking up.

Do they work? Personally, I am completely convinced that in certain cases it has worked completely brilliantly. A sick dog had had ear infections for years and years. We put a low dosage into one ear. The next day, we got masses of phage out and the ear was transformed, and the dog never needed treating again. We then did it to the other ear and the same thing happened. That dog never needed treatment for the rest of its life for its pseudomonas ear infection. That was very good.

We did a clinical trial in dogs as well, but unfortunately the company removed all the controls, so it did not turn into a clinical trial. Again,

these were pet dogs that were sick. We did not know much more at the end of the clinical trial than we did before, but in certain cases it worked very well.

Personally, I am convinced from that evidence that it works. There have been animal experiments in large numbers of calves. They were given E. coli phages and that worked completely brilliantly, so it can work, including in the gut, very well.

What more needs to be done? A lot. People need to get away from giving vast doses of phages straight away, which is what is happening, and it means we are not getting very much data from anywhere in the world at the moment. Whenever possible, give a low dose and major multiplication, which means you need sites where you can measure multiplication, by people who know how to do that.

Then, we will get evidence as we go along, rather than saying, "We are desperate, so we will give them something." That needs to happen. For those individual cases, yes.

When we hear about phage banks and the cocktails of stuff being sorted out, that obviously needs to happen and the clinical trials need to happen, but getting these other studies done with multiplication is good.

Another thing that needs looking at is that phage and probiotics have been modified cleverly. It gets complicated because it can be different organisms modified by a system called CRISPR, which is a gene-editing system. This is a very powerful-sounding technique that can cause bacteria to remove their resistance, or do other things to them to clear it out.

If I was looking at this and was responsible for the health budget, I would be thinking, "Can we have some way of getting this stuff out of the gut?" Phages might be one. Probiotics need freeing up a bit, too, and the CRISPR system, whether it is phage or not phage, could be a great way of clearing things out of the gut. That needs specific funding for getting rid of antimicrobial resistance.

Q60 **Rebecca Long Bailey:** There is very limited clinical use at the moment, but to what extent do you think the NHS is equipped to understand phages and monitor their safety and effectiveness and to share the knowledge they find in particular hospitals with the wider phage community?

Dr Soothill: I think the NHS is pretty good at looking for what problems are going on in the patient. I have dealt with the NHS, anyway. Was the rest of the question about whether they can monitor safety?

Q61 **Rebecca Long Bailey:** Whether they understand phages, and to what extent they can—

Dr Soothill: No, I do not think the NHS understands phages well. Most people do not know much about them. I think a bit of education would

certainly be helpful, and educating clinical labs in how to count them, and maybe having some funding available so that that process can be flexible, possibly with the University of Exeter, which has a service to provide phages. Perhaps you could have people who go out from there or the centre in Scotland to do the counting on site. That might be good.

Dr Jones: I would agree that the NHS does not really understand phages particularly well at the moment, but I would hope that changed. The vision for this that is achievable, notwithstanding the absence of GMP manufacturing within five to 10 years, is that we have off-the-shelf phage cocktails, much like they have in the eastern bloc, Georgia and Russia. Those are used in hospitals as we would see antibiotics being used. Therefore, a local NHS department should be doing that testing. Effectively, they are counting and screening those. We will need to equip those NHS clinical microbiology facilities to do that, but we will also need to educate other people involved in the system, such as pharmacists and so on.

Ideally, that should be backed by that personalised medicine service. Ninety per cent. of clinical demand should be off the shelf and done in local NHS trusts. The few patients whose needs are not covered by that would then be backed by that personalised phage service.

I do not think there is any issue about NHS monitoring. Is this specifically in relation to clinical trials or in general?

Rebecca Long Bailey: Generally.

Dr Jones: Certainly, in terms of unlicensed use, if it is part of routine clinical care I do not see any obstacle. I am not involved in clinical trials and I am not able to comment on how strenuous that monitoring would be, but I imagine that the clinical parameters being looked at would not be too onerous from a trial perspective.

On data sharing, I think clinicians are well aware of the issues that can be encountered in unlicensed cases that may be individual and perhaps could be more identifiable even without identifiable information. There are procedures in place for sharing information, such as Caldicott Guardian Approval, and those are available.

Generally, I think the publication of data on unlicensed use in case reports is acceptable, and that will be an important contribution going forward.

Q62 **Carol Monaghan:** Dr Jones, we have heard about treating ear infections in dogs. Can you give us an example of the type of infections for which you might use phages? I am assuming it is long-standing resistant infections where phages are a last resort to try to tackle it. Maybe you could give us some examples.

Dr Jones: Phage can be used when licensed alternatives are not meeting the patient's clinical needs. That may be antibiotic-resistant but, as I said, it might be antibiotic tolerance. As you said, typically these are

patients with chronic infections. We expect the major specialty that would be interested in this to be diabetic foot. Diabetic foot infections are a vast problem. The NHS spends about £1.2 billion a year on diabetic foot care—not all to do with infection.

Q63 **Carol Monaghan:** The spend is £1.2 billion per year.

Dr Jones: For every £140 spent by the NHS, £1 is spent on diabetic foot care. Not all of that is due to infection.

Q64 **Carol Monaghan:** It is not quite 1% of the budget; it is probably 0.6% of the NHS budget.

Dr Jones: For example, if phage therapy could save 5% of outpatient care for diabetic feet, it would save £10.5 million a year. If it cost you £30 million to establish your GMP facility, you would get that back in three years. It is really a no-brainer from a financial point of view, and that is just diabetic foot.

Q65 **Carol Monaghan:** I take it that diabetic foot is an infection to do with circulation.

Dr Jones: Exactly. Patients with diabetes tend to have poor peripheral circulation. They get ulcers, which become infected and sometimes they are very difficult to treat with antibiotics.

Chronic bone and joint infection is another issue. There are about 3,000 hip or knee revisions due to infection across the country every year. I know that about 1% to 2% of the total revisions get infected. Where they do get infected they can be catastrophic in those patients who come back for multiple revisions. That is very costly, particularly in theatre time.

There are chronic respiratory infections. James has been involved in treating a patient with mycobacterial infection. That is particularly tricky, but we have also heard about pseudomonas and so on.

There are also urinary tract infections, which in some respects are perhaps a little more complicated, but there is a large burden of chronic urinary tract infections where phage has the potential to be very useful.

Q66 **Carol Monaghan:** That tends to be in more elderly patients, does it not?

Dr Jones: Elderly patients and women get more urinary tract infections, but James may wish to add some indications to the list.

Dr Soothill: I have to say that at the moment I am obsessed with trying to get rid of gut carriage.

Q67 **Carol Monaghan:** For different reasons.

Dr Soothill: Yes. I am very worried about where things are going. I am very focused on the idea that we have to do something to stop this because resistance is getting worse in E. coli-like bacteria. The beauty of working on that, too, is that you are not in a hurry; you do not need to

put high doses of phages in; you can count what is going on and see what is happening.

CRISPR does have some worries in that effectively it is the release of GM organisms. One of the questions around that kind of thing is whether anybody is ever going to use them. Those conversations need to start now because we should be beginning to use something to control these gut carriages. Phages are one possibility; probiotics are another. This is another thing. Perhaps trying to set up some kind of body between the MRC and BBSRC to discuss with scientists whether you are going to do this and what you are and are not going to do would be good. If it was funded more by MRC and less by BBSRC it would be more medically oriented.

Obviously, farm animals have guts full of resistant bacteria, too. There is a problem about people with guts full of resistant bacteria arriving in large numbers in planes from countries all over the world. With the best will in the world, if you try to control antibiotic use in hospitals and the resistance is already there, you will use some antibiotics and there is going to be a problem that is going to get into the environment. Therefore, sorting out the environment of hospitals and having better, faster and cheaper screening for this carriage is important, too.

Q68 **Tracey Crouch:** I, too, am totally obsessed with gut health at the moment, for all the right reasons.

I want to ask about the lessons the UK can learn from other countries, particularly the US, Australia and Belgium, and their wider use of phage treatments and therapies. Dr Jones, in answer to my colleague you highlighted specific conditions for which this could be used. We are aware that Georgia and Poland are using phage therapy in broad, general terms. Is there any data we can get from their standard use of phage therapy for those particular patients you highlighted and use it as an example of how it is better, cheaper, etc?

Dr Jones: They have been doing it for a very long time and they have an awful lot of historical data. A lot of that is not accessible to us as a western audience. There are a few review articles out there, but they tend not to cover what I imagine would be the scope of the data that is there.

The short answer in terms of modern evidence is: not really. I cannot think of a huge amount of modern evidence, not that it would match what I would have in my head as being what I perceive to be the amount of use being made of it in that context. There has been a lot of historical evidence. In the UK in 2009 a defence threat reduction project translated a vast quantity of historical data from Russia and Georgia, which was very interesting. I think a lot of people would look at that. It probably would not be evidence that would come up to our standards today, but it certainly paints a historical picture. In terms of modern evidence, I cannot put my hand on a lot.

Q69 **Tracey Crouch:** I can understand why one would not have access to

Russian data, but what about Poland?

Dr Jones: There are some reviews from Poland. There is quite a lot of literature about work done in the '80s, '90s and early 2000s. Off the top of my head, I cannot think of a particularly recent review from Poland, but, as to the data they have there and the paper I am thinking of, they published in the region of 1,500 patients that they treated over, I think, 10 years or so. How much of a snapshot of data that is I do not know.

Q70 **Tracey Crouch:** I appreciate that we have an obesity crisis here in the UK and diabetes is very much linked to that. It may not be the same levels of diabetes and obesity that exist in Poland, but presumably there is diabetic foot in Poland and it is treated by phage therapy. You are saying you have no access to any kind of phage therapy data that would show how it is treated in Poland.

Dr Jones: There is some clinical data there, but it is not to the extent that matches what I believe is probably the reality on the ground. They have published about 1,500 in the paper I can think of, but they have been doing it for so long that those 1,500 patients will not be representative of the broader context.

If we think about that in our context and imagine we have antibiotics and somewhere in the eastern bloc has not, and we are looking at others, would we publish our routine uses of antibiotics? Probably not. Where it is routinely used, I am not sure there would necessarily be the same motivation to publish that we would have here for using phage, for example.

Q71 **Dawn Butler:** Dr Jones, do you have a breakdown of how much money can be saved and where? It would interest the Committee to see that.

Dr Jones: I can produce one for you.

Q72 **Chair:** That would be very helpful.

On sourcing and manufacturing phages, you said in answer to an earlier question that they can be transported easily. Why do we simply not fill our boots with whatever we need from those people who do manufacture them, perhaps in Poland, and, therefore, enable your work to continue beyond the end of this year?

Dr Jones: We are getting our phages mainly from the Belgians. They have limited time and limited capacity. They would rightly say it is not their job to supply phages to the NHS.

Q73 **Chair:** But commercially, is there not a price you pay for it?

Dr Jones: We could pay for it to be contract-manufactured. That would not need to be to GMP, but contract manufacturers would effectively do it to a GMP-like standard. We could then import that as a non-GMP product. That would cost about £500,000 for phage that might treat somewhere between 100 and 200 patients.

Q74 **Chair:** Even if we had a GMP facility here, is it always going to be

expensive?

Dr Jones: No. The reason that is expensive is that we are doing it on a per-contract basis. If we had the GMP facility here and we could get 160,000 doses out of an 8-litre fermenter, the beauty is that the price drops the more we use it. I had some consultancy done at the University of Edinburgh and the summary is publicly available. In our numbers, provided you were recovering your initial investment, we got it down to £125 per dose initially with 500 patients, which is comparable with a dose of intravenous antibiotics. If we extended that to 8,000 patients, the price per dose would fall to a couple of pounds. The more patients we treat, the cheaper it gets.

Q75 **Chair:** Six years ago, we made an observation that we did not have adequate capacity for vaccine manufacturing, so the late lamented industrial strategy set up a vaccine manufacturing innovation centre. Do we need the same thing for phage manufacturing?

Dr Jones: I am very pleased you mentioned that. Yes, we do. One of the issues with phage therapy is that, when you manufacture it, you have small quantities of very highly concentrated stock that has an awful lot of phage particles in it and then you dilute that to make your doses. Therefore, you are doing very pulsatile manufacturing of small quantities in order to build your library.

At the start, when we are building a library and laying down our reserves of phage, we will be manufacturing relatively frequently. As we go on, that will become more pulsatile because we will have a good stock and will not need to manufacture as much. That creates a lot of downtime. Downtime in a GMP facility is very expensive.

What we are hoping to do at the Centre for Process Innovation is to marry that with microbiome. We would bring together microbiome and phage so that where there is downtime, a GMP facility has resources that are shared and, therefore, that makes phage more viable. That has been a problem before with phage manufacturing. It is difficult to make phage manufacturing alone financially viable.

Chair: May I thank Dr Jones and Dr Soothill for their evidence today? It is very helpful to have that clinical perspective.

Examination of witnesses

Witnesses: Stephanie Lesage and David Browning.

Q76 **Chair:** We turn to our final panel of witnesses for this morning. They are going to talk about some of the commercial applications.

As they take their seats, I am going to introduce Mr David Browning, the chief executive officer of Fixed Phage Ltd, which specialises in applications, including securing efficient wound care, possibly for diabetic foot, and effective treatment of skin conditions and safer vascular grafts; and Stephanie Lesage, chief executive officer of Oxford Silk Phage Technologies. She founded the company in 2020 and is pioneering an

antimicrobial biomaterial technology that combines bacteriophages and silk, which is very intriguing.

Perhaps I may start with a question to Ms Lesage. Describe what your product does and what it is used for.

Stephanie Lesage: We are integrating bacteriophages into materials, and, in fact, we are looking at wider materials than silk. We started with silk because it is a sustainable material, but the idea is to produce medical devices and medical implants that will reduce the risk of surgical site infections. Surgical site infections are devastating for patients undergoing surgery, and we want to make sure that that can be prevented.

Q77 **Chair:** I see. So, is the silk impregnated with a phage? How is it combined?

Stephanie Lesage: We bind the phages to the material that we then use to produce devices. It is a tight binding of cocktails of phages, in fact, into our materials.

Q78 **Chair:** Was the idea for that your own? Did you it take it from a research programme? What is the origin of it?

Stephanie Lesage: I co-founded the company with a vascular access surgeon. When I spoke to the patients of my co-founder, one of the common issues that came back was the infections that they had had, and the one clear message was that they wanted anything other than an infection again, so we thought we really need to find a way of preventing the infections in the first place.

Q79 **Chair:** I see. You did it with a clinician. Tell me a bit about your background. How did you come to be in this space?

Stephanie Lesage: I have a very broad background of biological sciences, textile engineering and medical devices. When I got into the field, I became fascinated with vascular medical devices and met my co-founder, and then ended up focusing on preventing infections.

Q80 **Chair:** Thank you. Mr Browning, describe your product—what it does and what its origins are.

David Browning: Absolutely. We are very much focused on translation. That is something that other panellists have brought up today. Fixed Phage is a spin-out from the University of Strathclyde and has been working on phages for over 12 years now and has demonstrated the potential in many applications from improving food safety—extending the shelf life of foods; we have just concluded a successful trial in that field—through to aquaculture, animal health and now human health.

My background is very much in the translation and innovation side. I started in the health service back in the ’80s as a biochemist. I have worked in large organisations—most notably Philips and Johnson & Johnson—and I have also led start-ups in oncology and the fields of life science in the UK and in the States.

I joined the company just over three years ago. We have been bringing in additional talent alongside phage expertise that very much focuses on the quality of the end product. We have colleagues from big pharma like GSK and so forth who are looking at the quality standards.

We also leverage a proprietary technology that overcomes some of the challenges that we see with phage around stability. We can use a special plasma technology and a vacuum to apply phages very tightly to a whole range of substrates. That could be from, as you mentioned, wound dressings right through to cellulose for oral ingestion and so forth.

To conclude on what we are doing, we have trials ongoing at the moment. We are just starting in canines in the field of periodontal disease and skin disease. Picking up on Dr Soothill's point, we also have one starting on canine otitis, which is ear infection, and that is a good target. The plan is to translate the learning and capability from those animal studies—we have a partner who will fund the scale-up and regulatory submissions in animal health—into human application.

Chair: Good. Thank you very much. We will turn to my colleagues. The business in the Chamber will start soon, so we will need to be a bit brisk in this session with both questions and answers.

Aaron Bell: Thank you both for coming in. Given the evidence we have heard from the first two panels—you both listened to it—you were both quite brave to set up phage companies in the UK, in view of the difficulties.

What do you see as the primary market for your product when your businesses are mature? Is it going to be mostly domestic, or are you hoping to export as well? What are the barriers that you find in trying to get to that point?

David Browning: Very much international. The other applications—food and veterinary—are stepping-stones. They are viable businesses in their own right with international potential, but, ultimately, it is about human health.

Diabetic foot infection was mentioned. That is a very significant cost not just in the NHS but in the American market, where the incidence of diabetes and complications is, by virtue of lifestyle and population, very much an even greater problem. We very much see this as an international opportunity.

Q81 **Aaron Bell:** What are the obstacles?

David Browning: Challenges have already been discussed. One is access to finance. It is relatively easy in the UK to secure seed funding. We have burned about £8 million so far. We need another £27 million this year to scale up into human health, so it is quite a step.

Then we start to see the resistance from investors who want a certain amount of evidence before they will continue on that journey. It is around access to funding and the right regulatory frameworks that support the

translation of rapid innovation. We look to the great example from covid. Greg, you mentioned the covid vaccines. There is a lot that can be learned and applied there. We would welcome the opportunity to have further dialogue about that.

Q82 **Aaron Bell:** Ms Lesage, your company is a bit newer, but you are facing the same considerations.

Stephanie Lesage: Very much so, yes. I completely agree on the international impact and scale and export potential. We are not looking at phage as compassionate use; we are expanding on to a product using a phage. It is very much an innovation that we can patent, that we can protect, and that we can protect internationally, so our markets are going to be not just the UK for our patients but internationally in Europe, the US and everywhere else. We do not have that limitation of patents because we are using naturally occurring entities, but we are combining them with products.

David has a much broader view on the different fields, but it is very much international. We have the same obstacles. There are two obstacles: the GMP manufacturing requirement for early clinical trials and, interestingly, for compassionate use. If we are not building up the case for compassionate use, we are not informing the early clinical trials—

Q83 **Chair:** Describe what compassionate use is for those watching who may not know.

Stephanie Lesage: Compassionate use is for all the individual cases that essentially come to a dead end because antibiotics do not work. There are no other ways of treating their infections, and they need to use medicines that might not be formally approved yet. There are many patients as I speak now who desperately need to use phages as an alternative, and that would be compassionate use—using a very specific cocktail of phages against particular bacterial infection.

Q84 **Aaron Bell:** How have you found the investment environment in attracting investment?

Stephanie Lesage: Challenging, because of the GMP requirements and because of the lack of a clear regulatory framework. If we go to grant funding, we are in the same mix as other, more traditional technologies with very clear regulatory frameworks and with easy GMP production. When we go to investors, these questions always come up: how will you deal with the regulatory requirements? What is going to happen with phages? Our pool of investors is much more limited than it should be.

Q85 **Aaron Bell:** From a science perspective, what UK strengths can SMEs like yours draw on when developing your products? I am thinking of universities, from which you are a spin-out, and the NHS. What strengths are you able to draw on that are specific to the UK that make us a good place to develop phages?

Stephanie Lesage: The academic research in the UK is brilliant and it is internationally recognised, but, as was mentioned earlier, there is not yet

enough collaboration or visibility of the different groups that are doing that really great job. We have existing biobanks such as the Citizen Phage Library. Leicester is building a biobank. We could definitely draw on these existing capacities for our work as well.

Q86 **Aaron Bell:** Has your company been working with the NHS yet, or are you not at that stage?

Stephanie Lesage: We are talking to the NHS, but we are not actively working with the NHS yet.

Q87 **Aaron Bell:** The same questions to you, Mr Browning.

David Browning: I agree. There is a significant opportunity for first-class science here, and you heard about that earlier from Cath, Martha Clokie and so forth.

NHS access should be a great strength. In my previous company, we had some similar challenges bringing new oncology products to market. My experience goes back several decades, and I have to say it is a lot more difficult now than it was some years ago.

Back when I worked for Amersham International—some of you may remember it was a very successful British company—we could work with university hospitals in the UK. They would publish data and that would be shared in international journals. We were the first to do that in the UK. The NHS would enjoy rapid and immediate access to new technologies. If one hospital adopted it, others would take that evidence and make their own decisions based on it. We found that the bureaucracy in the NHS, I have to say, limits that significantly today.

It is a shame because the model we had in Amersham was to do that early-stage clinical trial work with the NHS and with leading hospitals that had an international reputation, and still do, and then we could use that as evidence to submit our regulatory pathways to the States, Japan and so forth. It would be great to get back to that, but some of the bureaucracy we see in the NHS is a limiter for us.

Q88 **Aaron Bell:** Why do you think that has changed? Is it because of risk aversion, or is it just simply that bureaucracy has multiplied over the years?

David Browning: I think it is a little bit of risk aversion. I would hope to see some change following the successes we have seen with covid. There is also a bit of parochialism. There is a lack of communication between different trusts and that higher-level decision making that can encourage adoption across the country. We are finding—Josh spoke about it a bit—that we are able to potentially develop more traction in Scotland. There is more of a joined-up scenario there with Scottish Enterprise, which has been one of the funders of Fixed Phage, and with other aspects of the community, and we would like to see that extended across the UK.

Q89 **Aaron Bell:** Regarding good manufacturing practice and the barrier that that is potentially creating for you to be able to manufacture things to

that standard here, what is your view on whether that is the right route for us to go down in the long run? You heard Dr Jones in the previous panel saying he did not think that we should dilute the standard and that we should find a way to get to that standard. Is that your view, Mr Browning?

David Browning: Ultimately, we need to get there, but we can work in parallel. With the named-patient basis, there is enough to go for to start developing evidence. While our investors want long-term return on investment, they want to see evidence of economic outcomes. Doing both is actually the answer. We have invested in our facilities in Scotland to bring them to a level where we can transfer to GMP.

It would be very difficult, given the nature of the facilities we have and the age of the buildings, to bring them up to GMP, but we can bring them to a standard where we can make that transfer. We are already doing that in animal health, and we would envisage doing the same in human health. In the meantime, we are starting to develop evidence, as I know Ms Lesage is, in other fields with compassionate use.

Q90 **Aaron Bell:** Ms Lesage, does GMP apply in the same way for devices as it would for the phage product itself?

Stephanie Lesage: It does in the sense that all the phages that we use will have to be produced to GMP standards. It is, in fact, a big development barrier for us because before we get to early clinical trials we will have to produce our phages to GMP standards. It means that we will have to start the set-up of that much earlier, and that makes the cost of our development very high very early on. It is a bigger risk for investors before they know whether the technology will be effective in humans.

Professor Clokie said it takes 20 minutes to produce a phage. For every single phage that we will have to have produced to GMP, it is going to take probably nine to 12 months to set up, and every individual phage has to be produced that way. It is going to cost about £150,000 from abroad at the moment for every phage. If you have a cocktail of 20 phages, you multiply that by 20.

With phages, the big advantage is the diversity. We will need to produce a cocktail of phages and then make sure we can evolve it. Every time we want to target new bacteria from a particular region, we are going to have to spend £150,000 for the set-up. The costs down the line are much lower once you start producing, but the upfront costs are really a big barrier for us.

Q91 **Aaron Bell:** Is there an alternative, or are those just costs you are going to have to absorb on the journey?

Stephanie Lesage: To me, the alternative would be to not require GMP standards for compassionate use and not require them for early-stage clinical trials simply because the compassionate use cases in the UK to date have used non-GMP standards, so we know that it is safe. That

entails having very clear entry criteria and very clear exit criteria for the production of phage instead of focusing on the steps in the middle. That would enable us to start building that traction generating successful data, as well as to initiate more clinical trials and reassure the investors that this is a technology worth investing in.

Q92 **Aaron Bell:** It is trials that the investors want to see, presumably. They want to see proof of concept.

Stephanie Lesage: Yes, definitely. They want to see successful data generated across any indications—and this is compassionate use—and they want to see successful initial trials.

Q93 **Carol Monaghan:** Can I continue with what Aaron was asking? I am interested in GMP and the particular aspects that make development tricky. Why is it nine months, for example?

Stephanie Lesage: As was detailed a bit before, every phage is different and every phage has to be put through a very detailed process. Every step of the process has to be tracked and has to be traceable. The first stage of the process is to produce the bacteria to GMP standards. Once the bacteria are produced to GMP standards, the phage can be amplified using the bacteria. There are already two steps to the process. Because of the different natures of—

Q94 **Carol Monaghan:** Would there be certification and inspection of every stage of that? Is that what slows everything down?

Stephanie Lesage: I believe so, because GMP is very traceable. If you put a label on a bottle, you have to write it down. That is the big problem. It is not particularly suited to phages as a result.

David Browning: There is an opportunity to learn and apply from other examples. If we take the flu vaccines where we have been very successful in the UK, again, it is necessary to modify that vaccine combination for new strains of flu. We believe that, if the regulatory processes for phage in the UK could accommodate a similar approach, it would not completely mitigate the challenges we see with GMP and so forth, but it would make the whole thing a lot easier, so that would be a good first step, and there is a good comparator there that we could draw on.

Q95 **Carol Monaghan:** David, will you say a bit more about this? We have had some evidence about regulatory frameworks in different countries that are different and could be helpful. Fixed Phage has said it is not necessarily going to be helpful if we change our regulatory frameworks: "Any licensed medicine needs to be able to be sold and used in multiple countries to secure adequate return on investment."

David Browning: That can be a challenge. I have seen that in previous examples in my career. Harmonisation of regulatory protocols is advantageous to industry because we can do one set of trials that is applicable and develops the relevant data for markets.

In practice, that is not usually the case. Often, regulators will default to the most stringent set of protocols that might be set by another country. Often, Europe might follow the States, and then Asia might follow that. Ultimately, harmonisation is important.

In terms of the UK being on the front foot, and going back to the examples that I mentioned from earlier in my career when we were able to work with university hospitals in a way that developed the good evidence, it is very important to say that all the regulators regard phage as safe as long as they are manufactured to the right protocols. That is taken as a certainty. There is an opportunity for us to be on the front foot here and start setting the regulatory standards and making sure that companies have the right framework to work to those.

Q96 **Carol Monaghan:** Thank you. In terms of research that has to still be done, where are the gaps in order to make these products commercially viable? Are we looking at dosage levels, storage conditions or shelf life? What are we missing?

David Browning: On the last two, that has a been predominant focus for Fixed Phage over the last three years. We have applied significant investment—millions actually—into ensuring the stability, purity and quality of the phage. That has been a big focus for us.

Going forward, it will be access to a bigger library, so, with Martha, developing a phage library. A limiting factor now is having ready access to the libraries.

Another one that we are starting to work on is the artificial intelligence that will be required to match the vast plethora of phages that can be available and select the best ones to a particular indication, or indeed a particular patient. To that end, we are advancing our positioning with investors to be viewed as a precision medicine company because phages are a perfect example of that.

We heard a little bit of evidence earlier about the diagnostic aspect. It is about bringing down the cost of sequencing so we can accurately understand not only what bacteria are present but what resistance genes are present, and being able to work more closely with the antibiotics industry, because phage and antibiotics are not mutually exclusive, and that was mentioned before. It is around more research about understanding the specific interventions and, ultimately, preventive therapies for the vast range of conditions that phages are applicable for.

Q97 **Carol Monaghan:** Thank you. Stephanie, do you have any additions to that list?

Stephanie Lesage: Continuing to develop phage libraries and the last point on AI are really critical.

We need to understand dosage. We can only understand it from treating more patients. We need to generate data from compassionate use because we cannot get that from healthy patients.

There is the development of cell-free production methods for phages. Instead of having to use bacteria to produce the phages, essentially, not amplifying with bacteria will be a great step forward that will make GMP or GMP-like—

Q98 **Carol Monaghan:** How would that work? I understand the phage tackles or eats, or however we want to describe it, the bacteria and is able to reproduce from that, so how can you reproduce without the bacteria?

Stephanie Lesage: I would not be able to give you accurate details on that, so I would prefer not to explain.

Carol Monaghan: I should have asked the first panel.

Stephanie Lesage: I think you would have to send that back to somebody at the back, yes. It is something for which more and more research is needed.

Q99 **Carol Monaghan:** Dr Jones talked earlier about GMP. He is working in a hospital environment. Do you see a situation where your technology could actually be manufactured in much smaller doses in hospitals and in different settings rather than having a big, as we would imagine, drug-manufacturing facility?

David Browning: That is a good question. We are looking, as the next phase, at the potential to develop what we would call a kit, so the hospital would have access to the various phage cocktails and then they would be able to select and do a purification. It is something that we are doing already in veterinary, and it is a way that we can get product on to the market very quickly where we have a direct relationship with an expert vet.

Stephanie Lesage: That is also the way that it is done in Belgium at the moment. They have separate phages and the pharmacist produces the cocktail. As long as the individual phage preparations were available, they could be combined.

Q100 **Carol Monaghan:** How do they get round the GMP?

Stephanie Lesage: In the case of Belgium, they do not require GMP manufacturing, and neither does Australia. That makes it much easier, and, in fact, that is how we are getting our own phage preparations for the UK.

Q101 **Carol Monaghan:** If I could move on to funding of research, are there any specific changes to the UK funding landscape that could help companies like yours access and develop products more easily?

Stephanie Lesage: Having specific grants for phages would be very helpful because, at the moment, we are assessed among those other technologies that have much easier regulatory requirements; having funding to continue to build up biobanks because, ultimately, we will need those new phages; and having funding for facilities because, ultimately, we can produce to small scale non-GMP for compassionate use for early

clinical trials, but to commercialise we will need facilities with much more upscaled manufacturing.

Q102 **Carol Monaghan:** To take you back to that funding specifically for phages, do you feel as though Government have a good enough handle on the potential of phage technology in order to set up such a fund?

Stephanie Lesage: I do not know whether that is in place at the moment.

David Browning: There is certainly an opportunity there. We were delighted that Innovate UK recently sponsored the Phage Innovation Network. I am sure you will hear more about that in the coming weeks. We had the first meeting yesterday. It is a very important forum bringing together academia, industry and clinicians to really focus on the translation—

Q103 **Carol Monaghan:** That is a network rather than funding for—

David Browning: Yes, it is a network, but that network could be a conduit for funding as well. That is going to be important. We talk to investors who are very keen to leverage grants. In oncology, I have participated in examples where Innovate UK has worked with VCs and the VCs have done their diligence. The VCs have said, "We will look at this. If we feel this is a good case for investment, Innovate UK, will you make some grant funding available?" The two can work really well together.

I believe that there are opportunities there. I would suggest that maybe at a higher level looking at antimicrobial resistance as the big challenge to the NHS and as a global challenge, and then maybe constructing grants that open up avenues to phage within that wider AMR umbrella, would be a good way to go.

Q104 **Stephen Metcalfe:** We have touched on the international aspect quite a lot, particularly with a view to small and medium-sized enterprises. We have also heard quite a lot about Belgium. Who does it best when supporting SMEs? Who has the best framework? What can we learn here in the UK?

David Browning: We are doing early mouse model studies on diabetic foot in Australia. We would rather, to be honest, be doing them in the UK because of control and communication, but we have been able to secure not only funding from the Australian Government but access to first-class knowledge and capability in that area. From our experience, we can see a lot of positivity there.

Australia has been mentioned before. Belgium certainly leads, but others are starting to come forward. Even Germany and other European countries are starting to advance.

The other one I would say is Norway. I will just flash up a picture. The Norwegians have been investing in this rather splendid-looking phage production facility. That is not quite finished yet, but they are potentially

stealing a march on us by getting on with it. They have an ambition to be leaders in this field leveraging aquaculture into human.

Q105 **Chair:** Is that set up by the Norwegian state—by the Government?

David Browning: That has been set up initially by private enterprise, but with Government support.

Q106 **Stephen Metcalfe:** Going back to Australia, as you mentioned it first, what should we learn from them? Is that about the GMP?

David Browning: I think it is about a joined-up approach to the whole thing. I mentioned the Phage Innovation Network. Having forums like that and getting all the stakeholders together and working together is key.

Stephanie Lesage: I think the Australian STAMP protocol model is probably the best in the west. They have understood that, in order to gather information from all those indications and all those bacteria that cannot be collected from clinical trials because there would be too many otherwise, they have to make a compromise between compassionate use and clinical trials to generate the positive data that is needed in the area. I agree that they are the best models at the moment.

Q107 **Katherine Fletcher:** I have just a couple of quick ones to inform future evidence sessions. I do not think these need long answers.

Is there any difficulty with getting the appropriate volume of cases through with the current compassionate use? Are there thresholds of evidence bases that are required? I do not mean you would not get there eventually, but I mean in an acceptable timescale. I do not know who wants to take that one first. I have one more quickly. Is there any problem with the volume of available test cases?

David Browning: Yes, that is a challenge. To get to what we call phase 2a trials, we would need to be getting into hundreds of patients. That needs to be not so much a compassionate use trial but one where you have proper placebos and controls.

Katherine Fletcher: Which is not in place at the moment, so we need to cycle through that and framework and speed.

Q108 **Chair:** Ms Lesage, do you have any addition to that?

Stephanie Lesage: No, I agree with that.

Q109 **Katherine Fletcher:** In terms of localised manufacturing, it is almost personalised phage medicine. You mentioned pharmacies in Belgium. Do you have a perspective on who in the UK system would regulate that?

Stephanie Lesage: Who would regulate it?

Katherine Fletcher: Yes.

David Browning: I think it can come under the existing frameworks, albeit that they need to be evolved specifically for phage.

Q110 **Katherine Fletcher:** What I am getting at is: who is the clever lady in the white coat who goes to the local go-ahead pharmacy and makes sure that they have put the right reagents in the right hole in the phage manufacturing machine? If you do not quite know what I mean, it does not matter.

David Browning: I do. We would be looking at potential partners like Boots and pharmacy-led health and wellbeing. That would come under their existing pharmaceutical regulations. They and we would look to fit in with them.

Q111 **Katherine Fletcher:** Yes, but, as Carol pointed out, they are all done in really quite large sheds on industrial estates, not through diverse small-scale manufacturing.

David Browning: That is part of a bigger question around precision medicine. There will need to be the infrastructure not just for phage but for a whole range of therapies. It is an area I have been working in for some 20 years. Big pharma acknowledges the way to go, but they find it hard to move away from the blockbuster model. It is coming.

Katherine Fletcher: Understood. Thank you.

Chair: Thank you, Ms Lesage and Mr Browning, and thank you to all our witnesses today. In two hours, we have certainly progressed our understanding of the science, the regulation, the policy and the potential of phages. Our inquiry has got off to a flying start. I am very grateful for your evidence.