HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: Antimicrobial resistance, HC 231

Wednesday 22 June 2022

Ordered by the House of Commons to be published on 22 June 2022.

Watch the meeting

Members present: Greg Clark (Chair); Aaron Bell; Tracey Crouch; Katherine Fletcher; Rebecca Long Bailey; Carol Monaghan; Graham Stringer.

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Witnesses

I: Professor Alison Holmes, Professor of Infectious Diseases, Imperial College London (appearing virtually); and Lord O'Neill of Gatley, Chair, Review on Antimicrobial Resistance (2014–16).

II: Dr Kitty Healey, Head of Antimicrobial Resistance Policy and Surveillance Team, Veterinary Medicines Directorate; and Professor Mark Woolhouse OBE, Professor of Infectious Disease Epidemiology, University of Edinburgh (appearing virtually).

III: Dr Seamus O'Brien, R&D Director, Global Antibiotic Research and Development Partnership (GADRP) (appearing virtually); Professor Robert Schooley, Professor, Division of Infectious Diseases, UC San Diego School of Medicine (appearing virtually); and Dr Peter Jackson, Executive Director, Infex Therapeutics (appearing virtually).

Examination of Witnesses

Witnesses: Professor Alison Holmes and Lord O'Neill of Gatley.

Q1 **Chair:** This morning we are conducting a one-off evidence session on antimicrobial resistance. This is an issue of long-standing interest to the Committee. Indeed, in 2014, our predecessor Committee issued a report with a recommendation that the Government set up a review of the UK's response to the threat of antimicrobial resistance.

The Government's response to that report was to announce the commissioning of the O'Neill Review on Antimicrobial Resistance, so we are very pleased to welcome this morning the chair of that review, which was published in 2016—Jim O'Neill, Lord O'Neill of Gatley, who joins us today. Thank you very much for joining us, Lord O'Neill.

We are also joined by Professor Alison Holmes. Professor Holmes is the professor of infectious diseases at Imperial College London. She is the current president of the International Society for Infectious Diseases. Thank you very much indeed, both of you, for joining us.

I will start off with a question to Professor Holmes. Can you describe the basics for us and for viewers tuning in? Is the problem of antimicrobial resistance a personal one, as it were, where, if someone takes too many antibiotics or other antimicrobials, future doses will be less likely to work on that person, or is it something that is about society taking more antimicrobials and having society-level resistance? Describe the basics of it for us, if you will.

Professor Holmes: It is both at the individual level and at the societal level. Antimicrobial resistance means that a microbe is resistant to a drug, so it generates drug-resistant infection. As you said, this can be at the individual level, but it is also at the societal level. I stress that our healthcare absolutely depends on our antimicrobials being able to work, so this is a massive threat to our being able to deliver healthcare safely—innovation in healthcare, as well as the basic healthcare that we are all used to.

You may recently have heard antimicrobial resistance, or AMR, being called a silent pandemic. I want to stress that there is absolutely nothing silent about it. The O'Neill report, which you referred to earlier, said that the number of deaths related to AMR was likely to be around 10 million by the time we get to 2050. A recent publication, led by Chris Murray, which came out in *The Lancet* in February, re-examined the data in a much more detailed way, although there is a challenge that there is still not good enough data out there. The latest estimate is 1.27 million deaths per year. To put that in context, the overall global burden for HIV and AIDS is about 863,000. For malaria, it is 643,000.

However, I want to stress that the implications are not through the numbers alone. The implications are that it is a complete threat to our being able to deliver healthcare, both at a societal level, as you framed it,

and at an individual level. The challenge is massive. It is real, and we really need to be doing something about this.

Q2 **Chair:** Thank you very much, Professor Holmes. That is a very good introduction.

I turn now to the author of the review, Lord O'Neill. Six years on from your report, can you summarise briefly, before we go into more detail, how you think the UK and the world are doing?

Lord O'Neill: It is a great pleasure to be with you guys again. Let me try to be as concise as I can. I am answering this question, hopefully, towards the end of the scale of Covid damage, at least for most of the western world. On the one hand, that realisation from the horrors of Covid demonstrates how serious these kinds of global health threats can be, as Alison has just eloquently described for AMR, so it gives a great big new window for global policymakers, as well as the UK, to be truly active on investments to prevent these things. In that sense, in the spirit of never letting a crisis go to waste, let us make sure the message for AMR does not.

Against that, and slightly contradictory to it, because so many resources have had to shift to Covid, it may be the case that it has taken immediate attention away from some initiatives. As I am sure Alison and some of the people coming later will know better than me, in some parts of the world—not the UK, I suspect—it has probably made the AMR fight even worse. I am thinking of India as a particularly good example in the emerging world. In that regard, as Alison highlighted with regard to Chris Murray's report, the actual evidence of how many people are dying from AMR-related illnesses today, from Chris's really detailed analysis, which took five years to do, is that the number is twice as big as we thought. Some people thought that our estimate of 10 million by 2050 might be a bit excitable. If anything, Chris's report suggests that it could be a lot more. In that context, I remain of the view that the health and economic damage from AMR could be much worse than that from Covid, if we do not treat aspects of it on a global basis much more seriously.

You made a point of asking about the UK. I thought that in some areas the UK response to our review had been pretty good. There was great success initially on reduction in agriculture, and we tried to be a pioneer for policy action on a global basis. Of course, in that regard I have to welcome the initiative that NICE announced recently about pioneering payments for two drugs in a very novel new way, but the truth of the matter is that the amounts of money on offer are not particularly substantive. I am sure we will come back to this, but what would be really important, in this very challenging era for global co-operation, would be if everybody else did their global GDP pro rata to the UK initiative. That could be significant, but from what I can see there is hugely stalled attention, despite endless talk on this, in most parts of the rest of the world.

Q3 **Chair:** We will come on to that in a bit more detail. I will put your observation on the impact of AMR, compared with Covid, which you mentioned, and other infectious diseases, to Professor Holmes. Professor Holmes, you are a professor of infectious diseases, in the plural. How would you assess antimicrobial resistance against other threats? How important is it as against other potential diseases that might transmit themselves around the world?

Professor Holmes: As I mentioned before, the impact on the individual and society is massive, but the impact on clinical outcomes and what we can do in healthcare is also a major challenge. Our ability to deliver safe surgery, appropriate immunosuppressant therapy and simple, regular clinical interventions will be completely threatened and undermined.

I would like to get back to something relating to Covid and what has happened with healthcare-associated infections. These are infections that people get when they are within healthcare. I want to flag that this is a really important issue, as this is where drug-resistant infection happens and, of course, where we use most antimicrobial agents. It is such an important indicator, which, unfortunately, we have stopped using. The estimate is that one in five antibiotics used in healthcare is to treat healthcare-associated infections, so we should be watching these really carefully. Not only would that give us an indicator of the amount of antimicrobials used in healthcare, but it would highlight how we have to reduce infections that need antibiotics. One in five prescriptions in healthcare is actually to treat infections that are acquired within healthcare.

As you said right at the beginning, exposure drives resistance. That is just Darwinian evolution. It helps to select for it. I want to push the importance of looking at infection prevention within healthcare and to flag something Lord O'Neill pointed out—that healthcare-associated infections have risen significantly within acute healthcare during Covid, for a variety of reasons. Healthcare-associated infections have certainly gone up. These really are a threat to our ability to deliver safe care in this country and around the world.

I stress the issue of being able to deliver surgery globally. When you think about how many infections arise because of surgery, particularly in low-resource settings, the impact of AMR is absolutely overwhelming.

Q4 **Chair:** Are you saying that you think an important proportion of the rise in hospital infections during Covid was due to antimicrobial resistance?

Professor Holmes: No. I am saying that many infections acquired in hospital are drug resistant because there is such a high concentration of antimicrobials used. If we prevented them from happening in the first place, we would not need to use the drugs to treat them, which, in effect, is driving resistance further. To go back to what you said, that is driving resistance not just at an individual level but at a population and societal level, meaning that the healthcare we deliver is at risk because of

antimicrobial resistance and healthcare-associated infection. It is really important that we look at infection prevention as part of our strategy to address antimicrobial resistance.

Q5 **Tracey Crouch:** Professor Holmes, you have answered in part my question about the effect of AMR on the medical system, with some very specific examples of where you have witnessed that. I want to ask you about the long-term management of diseases such as HIV and malaria. How concerning is AMR in relation to those?

Professor Holmes: I go back to your initial remarks about its impact. I was talking about its impact on acute care and how it has affected healthcare-associated infection, which has gone up. However, I would like to stress that the impact of Covid on how antimicrobials have been used in the community has been incredible. Their use has gone way down. The overall amount of prescribing of antimicrobials in the community went down a large amount, although things are changing now. This has been widely reported, not just in the UK but in Canada, the US and so on.

Some of that may be good news, but some of it may not be such great news. Hopefully, it was not anything to do with being able to access treatment when it was needed and was related more to the reduction in transmission because of social interventions.

I am focusing mainly on bacterial infection here, rather than malaria, which is a parasite, or HIV—or, in fact, something that we are not discussing, fungal infection. In malaria, HIV, any viral infection and fungal infections, the implication of resistance is also absolutely enormous. You may be picking this up later on the One Health side of things, but the use of antifungals in agriculture has an impact on resistance to fungal infections, particularly in our immunosuppressed patients. We have talked about the Chris Murray report and are bandying around the figures from it. I want to stress that those numbers do not include resistant fungal infections, resistant malaria and resistant HIV.

Q6 **Tracey Crouch:** Are these threats rectifiable?

Professor Holmes: I do not think we can rectify something that is fundamentally an evolutionary response, so I would not use the term "rectifiable." However, it is absolutely the case that they can be mitigated by addressing issues that reduce the drivers of resistance and reduce the occurrence of infection, its acquisition and its transmission—all of those things. It is not just about new agents, and it really cannot be about new agents. It is critical that in the research agenda we do not think it can be all about new agents. We have to look at how we can optimise the use of our existing agents and any future ones, and how we can personalise them. There is a lot of work that can be done in that area. It is not rectifiable, because it is Darwinian and it is evolution, but we can certainly mitigate it, particularly with societal and political engagement and massive raising of awareness.

Q7 **Tracey Crouch:** So far we have focused very much on the health threats to human health from AMR. Do you have any comments about animals?

Professor Holmes: I think you will be speaking to experts on that. I am not an expert in animal health. We talk about One Health, but one thing I would like to push is the absolute importance of global and integrated surveillance. I would like to make a plug for the most extraordinary global surveillance that my society delivers, through a programme called ProMED, which looks at emerging infectious diseases and is completely integrated, as it looks at human health, animal health, livestock, veterinary and environmental and brings it all together. We have to be able to look at signals across all these different sectors.

Q8 **Tracey Crouch:** Lord O'Neill, as somebody who has recently chaired a major review for the Government, I am always really interested in speaking to the forefathers of reviews to find out exactly what has happened to their reports and recommendations. In your view, which of your recommendations have been, dare I say, neglected and which require more attention?

Lord O'Neill: Gosh. I could spend the whole day talking about this, so it is quite a challenge. I will try to be really succinct, at the risk of not being as thorough.

I will pick up on the question you asked Alison. On agriculture, when we were making our recommendations, we found great protests from important Governments around the world to what we were going to recommend on reducing the use of antibiotics in farming, so we were surprised initially by the fact the UK specifically adopted our target and then, within a year, met it. Not long afterwards, the EU became tougher as well, and, to our real surprise, the US finally accepted, at least formally, banning antibiotics for growth promotion in farming. Even more surprising is the fact that, partly because of consumer choice and the next generation, probably, the evidence appears to show, notwithstanding data issues, that the use of antibiotics in farming in the US has declined quite a bit, despite there not being the same scale of attention on that policy-wise as there is here.

As Alison said, you have real experts coming up, and you should quiz them. I say all of that because, without getting into the politics of Brexit, I suspect that in the search for new trade deals, particularly with the US, at the margin we are vulnerable to not being as tough on policies in agriculture as we should remain. We should be a world leader on that.

I would say that is the biggest surprise, positively, from the review. All our recommendations came under 10 areas. I used to call them the ten commandments. There were two where there seemed to be quite a bit of progress. Alison is living proof of one of them. The growth of new academic research centres, especially in the UK, on AMR, was speedier than we thought, which was good. Secondly, the support from

Governments for early-stage money to try to begin the search for new antibiotics was also quite impressive.

Where it has been woeful—here Covid is important as a learning thing—is on diagnostics. I have talked to this Committee and the Health Committee about that before. It is still alarming to me that, especially after having gone through Covid, we are not embedding state-of-the-art technology right in the middle of our health systems. Alison has people in her centre, and there are others elsewhere, working on this, which can make a huge difference in deciding whether or not an antibiotic is needed and which is the right kind of antibiotic. Our most aggressive recommendation was that we should ban the use of subjective prescriptions in secondary settings, at least, in western countries until they have gone through a state-of-the-art diagnostic. Nobody has done it, because it is a vicious circle and the technology is not there.

We have to give incentives to get this embedded, because it would make a permanent difference. I think about it as an economist. What you really need to do is to reduce the permanent demand for antibiotics—particularly their inappropriate use, which Alison touched on—at the same time as trying to boost supplies of existing treatments and alternatives. Without using diagnostics, you cannot do it.

Q9 **Chair:** Can you unpack a bit what you mean by subjective prescriptions? That is where there is no test that says there is an infection. It is just suspicion.

Lord O'Neill: Yes. Basically, doctors have to make a very educated guess.

The other big thing relates to what I said about learning from Covid. I was involved in the UK Government's taskforce for Carbis Bay. In all of this really admirable desire for vaccines, with 100 days from design to implementation, a rational thing to do, in my view, to keep pharma companies focused on vaccines would be to encourage them to support vaccine usage for disease prevention in animals, so that there would be no theoretical case for antibiotics that so many people in the farming world claim there is. They always argue that we need these antibiotics just in case there is a major disease outbreak. Obviously, that is true, but if you had much better usage of vaccines the risk of outbreaks would be considerably less. I still get together three or four times a year with all my old review team. We are still baffled about why there is not greater progress on this issue, especially post Covid.

Q10 **Tracey Crouch:** Have you had any follow-up meetings with Ministers with regard to your report and its recommendations?

Lord O'Neill: A little. The other thing I would say as it relates to the UK, at the risk of provoking broader things, is that they get attracted to whatever is hot in the news and focus on that. I suppose that is the wont of a democratic Government—not just this one. That seems to apply to

various health issues, as well as anything else. Given the scale of AMR—particularly with the Chris Murray report, which both Alison and I have touched on—people should not kid themselves. The actual influence of AMR on people dying now, based on more real evidence, is twice as bad as we assumed in 2015-16, when we published our report. From what I can see, there are very few other infectious diseases that warrant the kind of attention that AMR warrants.

Q11 **Carol Monaghan:** Lord O'Neill, you talked about the limits from your report being accepted. Were they actually implemented?

Lord O'Neill: We made 29 specific recommendations, so we were rather pleased that some of them were implemented. In the UK, as I said, the very precise recommendation we made on agriculture was implemented. The fact the Government achieved it so quickly made us think we had not been tough enough. They also followed in spirit a number of the recommendations we had about trying to find approaches to reduce the usage—at least, the inappropriate usage—in humans.

I would say that in the UK the role of diagnostics has been the area that has been the most persistently disappointing. I do not really quite understand it, but the whole NHS system and its thought leaders, never mind Ministers, do not seem to grasp the scale of the power of the appropriate use of technology to reduce this issue permanently. When I get involved in forums on AMR, there is still always so much focus on the search for new drugs for pharmaceutical companies to invest in—much more than any other topic. Obviously, that is important, but eventually, as Alison could explain way better than me, the bugs will be resistant to whatever new ones we come up with. What we really have to do is to reduce permanently the inappropriate demand and to stop treating these things like sweets.

Q12 **Carol Monaghan:** I know Professor Holmes would like to make a point there. Lord O'Neill, have we seen any impact in terms of increased infections or outbreaks as a result of reducing the use?

Lord O'Neill: There are some interesting anecdotes, and I know of a couple of published pieces that suggest that in some areas. I am glad you asked me this question, because it is an important one to highlight. If you apply some nominal target for reducing antibiotics and impose that on the system, so that the whole system has to follow that goal, without diagnostics, in some areas people who really need them may end up not getting them. I am sure Alison will know about those cases. I know there are some specialists who claim that may have happened to some degree. To be honest, my own view would be that, in a way, while that is really bothersome, we must have a general framework of trying to reduce the overall use of antibiotics.

Professor Holmes: One of my colleagues, Paul Aylin, has done some work looking at the impact of antimicrobial stewardship policies in wanting to avoid harm, addressing exactly what you say, which is that we

have to make sure any reduction does not interfere with access to effective therapy. Globally, the issue is access to effective therapy. By and large, the data is very comforting, apart from some specific areas of prescribing and delayed prescribing, particularly among the elderly.

I want to go back to the diagnostic points. Testing is not just for making a therapeutic decision about whether or not to treat a patient. We have shown in Covid how incredibly important it is for surveillance and knowing what is going on. Can I just flag the importance of integrated testing along patient pathways, not to make decisions about whether, how and which drugs to give, but to know what is out there and how to protect patients coming into hospital and so on? Testing and diagnostics is more than making a therapeutic choice; it is also about surveillance and letting us understand what the problems are and how we can target them.

Lord O'Neill said how important it is to look at how we optimise the use of our agents and not just think about new agents. I cannot stress enough that we can get much more bang for our buck in how we use our existing agents with minimal application of technology and much better data. This was a challenge with the NICE committees. There was not enough real-world data. We have to do much better on real-world data and how we use drugs to enable us to personalise treatment for different population groups and infections, and use them much more effectively. It is not a one size fits all. We can do much better in getting that data, and the NIHR is certainly trying to do that.

Q13 **Graham Stringer:** Professor Holmes, on that last point, it is obviously common sense in most cases to know what you are treating before you start treating it, but if I were a patient going into accident and emergency and the clinician suspected I had sepsis, I would want antibiotics banged into my arm as quickly as possible, so obviously there is a limit to diagnostics in that area. Would you agree?

Professor Holmes: No, not entirely. I do not completely agree with Lord O'Neill. Your point is well made. However, the issue is that the diagnostic does not necessarily need to be at that first point of contact when you are really worried about your patient and it is undifferentiated, but at 24 hours or 72 hours. If you know the patient has a specific infection that can use a very selective targeted drug, change to it, or, if it is completely clear that there is not an infection, stop the drug. You may not critically need the diagnostic to shape your choice at that first point, but you certainly could use it 24 hours or 72 hours later. Some beautiful work has been done by a colleague, Martin Llewelyn, on how to implement that across the UK and safely review it and stop at 72 hours. This could be a useful intervention that reassures people who are considering exactly what you raise, which is that on first contact you do not want to delay if somebody is extremely sick, but, my goodness me, you absolutely need to target your therapy or stop it if, within 48 or 72 hours, you know it is not an infection. It needs to stop.

Q14 **Graham Stringer:** That is a really interesting answer. If I may go back to your previous answer, you went through all the problems in the four areas: fungal and parasitic infections, viruses and bacteria. It is probably my fault, but I tend to think of AMR being about bacteria and antibiotics. Is there any sense in which our response to these problems is distorted strongly towards antibiotics and we are ignoring or not doing as much as we should about fungal or viral infections?

Professor Holmes: I do not think so. There has been a lot of attention on TB, HIV and malarial resistance. Fungal resistance does need more attention, but the impact of resistant bacterial infection is so much greater. Clearly, they all need attention, but the antibacterial side needs a huge amount of attention. The one that may need to be looked at in quite a bit more detail is fungal infection.

Q15 **Graham Stringer:** Turning to Jim, and incidentally I like the photo you have on your wall—

Lord O'Neill: There are two more there.

Graham Stringer: Anybody who produces a piece of work—this certainly applies to me—after a little while thinks it could have been better, or wishes they had done something different. Are there any further recommendations, six years on, that you wish you had made in your review?

Lord O'Neill: Thank you for that question, and I am glad you ask. The answer is yes, and hopefully that would be the case for all of us as time passes. One recommendation that Sally Davies and I still chat about quite a bit is on this topic. We come together quite often. I wish we had considered making a recommendation that AMR could be cited as a cause of death on death certificates because, going back to the silent pandemic, it is partly why it is so hard to get it into people's heads without getting on the "Ten O'Clock News" every night. That would be one.

I am becoming more and more focused on the second one, which relates to global economic policy. I touched on it in an earlier answer. I think about this as a macro-economist or as somebody from the world of investing. We have to find a way of truly investing in disease prevention in terms of surveillance, diagnostics and having a stock of treatments, in the same way that perhaps one thinks about preparing for war. I wish I had thought about recommending that the IMF, as part of its so-called Article IV series in which it analyses every member country and states what is right or wrong about its economy, should opine on countries' health systems and how much they are committed to health, as opposed to just leaving it to the WHO. Credit rating agencies and financial markets listen only to that from the IMF, not its forecasts in general, and countries therefore do it because they think it can be done. We need to find a way of allowing countries to genuinely invest more in health. That applies all over the world, including in the UK. As some members of the Committee will know, partly because of Sally Davies's bold efforts when she first

came into the role of chief medical officer, AMR prevention was on the UK risk register along with other things, but, as we saw with Covid, it is a classic example of action being more powerful than words. Unless you really invest in preventive things, words end up being meaningless. I regret that.

With it, there could be some kind of adaptation and a much more sophisticated version of fiscal rules which allow us truly to invest, so you separate out, certainly in the Department of Health, investments from maintenance spending. By the way, you might want to do it in other Departments. I think financial markets would be perfectly happy with that, as long as it is done in a transparent and credible way. What happens—no doubt, given the mess we currently have cyclically, it will end up happening again—is that investment areas always end up getting cut because it is tomorrow rather than today. It is very hard for democratic Governments to do that, but we cannot really solve these things unless we invest in them properly.

Q16 **Graham Stringer:** You mentioned international comparisons and how the EU, UK and the United States have improved. Is there any particular country from which we could learn lessons? Is there an exemplar out there that is doing better than anybody else?

Lord O'Neill: Gosh. My honest answer, Graham, is that, because I am not following it with the same intensity around the world as I was, it would be a bit presumptuous of me to state a confident view. I would hope there might be. I think the UK does a pretty good job on this compared with most countries. As with most things in life, the Scandinavians—hence why their productivity and living standards are typically better—seem to me to do a pretty good job, but I would not want to comment further than that. I am sure there must be. In the areas that I think are really vital, like the role of diagnostics and a much bigger role for investment in health and vaccines as an alternative to the use of antibiotics, I am not aware of any great example-setters around the world.

Q17 **Graham Stringer:** You express pleasure and surprise at the reduction in the use of antibiotics in farm animals. Do you trust the statistics that are coming out of farms?

Lord O'Neill: I would take up that question with the panel to come. Not entirely. In particular, those with a self-interest are eager to present statistics in a certain way.

Q18 **Graham Stringer:** There is a definite benefit to using antibiotics, is there not, in the short term?

Lord O'Neill: So they think, sadly. Another slight positive surprise is that both China and India, at least officially, announced a bit of time ago that they are banning the use of so-called last-in-line antibiotics in agriculture, particularly colistin. I do not understand why things like colistin can't just be banned, full stop, which is still not the case here in the UK.

Chair: We will need to keep answers a bit shorter if we are to have time for our next witnesses, which we are very keen to do.

Q19 **Rebecca Long Bailey:** Professor Holmes, in the report of the Academy of Medical Sciences, which you chaired, on the effect of Covid-19 on AMR, you concluded that AMR had not captured public and political attention in the way that Covid-19 did. Is AMR as significantly risky to warrant the same level of attention and, if so, how can this level of attention be achieved?

Professor Holmes: That is a really important question. That workshop and output from the Academy of Medical Sciences, with my colleague Sharon Peacock, produced some other interesting areas that we could develop from how the UK responded to Covid and how we could apply that to AMR. As for societal engagement, it also needs to be captured in the way that climate change is captured, particularly with the younger generation. We are not only saving the planet but we are saving and delivering healthcare. We have had a real problem with engagement, and it absolutely has to be done with society and people being completely involved in this.

For a lot of us in the field of infectious diseases, nobody was nearly as effective until an economist came along and talked about it and engaged much more effectively with the world. We need to think about how we can capture the interest of society in AMR, because we will not be able to provide any useful healthcare and it will be a problem for us and the next generation. Also, conceptually, this is not happening as rapidly as Covid. Absolutely, of course it is not. However, in absolute numbers, it is really overwhelming.

I think the efforts to work and engage with the public and the young will be a critical feature. Public awareness was one of Lord O'Neill's ten commandments, and it is still the case. I think we need to reframe the language we use on the level of threat so that people can understand it in the healthcare we can provide.

The other issue is that we are all connected. It has to be global and collaborative; we need to work across this. The UK is really strong in vaccine development because of the deep roots of investment. They could be world leaders. We need the same in other aspects of AMR, such as diagnostics, as Jim says.

Q20 **Rebecca Long Bailey:** My next question is for both of you. You mentioned Government support for academic research centres and surveillance, but what do we need to see next from Government? If you could make any specific requests today on the support you need from Government to support research and surveillance, in a nutshell, what would you be asking for?

Professor Holmes: One of Lord O'Neill's ten commandments that has not done so well is human capital. I am afraid that I do not think the human capital is adequate at all, and not just in terms of supporting

excellent research. We need to be offering fellowships, keeping people with expertise in this realm and providing jobs and support to keep them within public health, academia and direct clinical care. We need to be able to do that and support people in this area.

The other area of need in that loose spectrum of people is at the frontline. We do not have enough people working in clinical microbiology and in those absolutely critical posts within the NHS that support applied research, get the data, inform what we do and inform public health. We need people in this area both in research and on the frontline.

Lord O'Neill: Ban the use of last-in-line antibiotics for feeding animals and, with that, make sure the post-Brexit trade deal search does not water down the stance we had.

As I touched on—I do not have time to go into how you might do it—embed diagnostics in the centre of all this, which is an important area of our recommendations. The UK does not seem to be excited by that idea. I do not fully get why.

Then, as I have already said, help the broader growth of focus in pharmaceutical companies on being in the vaccine business. It is great that they all came to the rescue on Covid, but in another couple of years most of them will disappear again because they will not see any need to be in the business. So, one area is to have more vaccines to prevent the illnesses that antibiotics are useful for, especially in farming.

Q21 **Rebecca Long Bailey:** Lord O'Neill, you mentioned the use of the IMF economic health check, which I thought was an interesting concept. Do you think the UK would do well in an Article IV health review in relation to AMR?

Lord O'Neill: It would do better than many others—that's for sure—but in how it approaches the whole stance of investing in health more broadly, not really, no.

Q22 **Tracey Crouch:** I have some quick questions on Covid. Resource was redirected from AMR to tackle Covid-19. Research in non-Covid fields, including AMR, was deprioritised, delayed and even halted. Now that the Government are no longer financing public Covid testing and demand has dropped, have you seen any commitment towards facilities being repurposed back to AMR, as it were?

Professor Holmes: A lot of people flipped or completely changed direction to support everything in terms of Covid, both clinically and in research. A lot of that is going back. However, some of the learnings from the Academy of Medical Sciences workshop with Sharon Peacock highlighted the importance of not losing some of those really important features of Covid.

On diagnostics, for goodness' sake, everybody is happy with taking tests. Women have been happy doing pregnancy tests for a long, long time. We

could be integrating tests into patient pathways in the community and in care to be able to know much more about AMR. We could harness some of that around diagnostics and surveillance, and bring it to AMR. We could use the amazing work on therapeutics, vaccines, collaborations and methods to get rapid evidence in how we use antibiotics and get real-world data. We could use the work on vaccines to think about how we could do much more not only to address bacterial infection. If you use vaccines on any infection, the drive to prescribe antibiotics will go down, so it is a win-win situation with vaccines. We should now be harnessing a lot of the work that was done on Covid as it could certainly apply to addressing AMR.

Tracey Crouch: I am pleased you said that, because I was going to use the phrase "harnessing the momentum from Covid."

Professor Holmes: Absolutely.

Q23 **Tracey Crouch:** Has there been any progress in reforming the regulatory environment around new treatments for AMR?

Professor Holmes: The regulatory environments are a challenge. I think there is a major challenge around diagnostics, and this is increasingly recognised. We need to understand the map. What does industry need and what do we need to be able to develop diagnostics rapidly to understand the regulatory requirements and the economics? The other thing is to be much more intelligent about diagnostics and how we regulate them, because they need to be all-encompassing. A single diagnostic is great, but in decision making a lot of things are often integrated. We can be much smarter in applying technologies in this space.

Q24 **Chair:** I have a couple of quick questions for Professor Holmes. Obviously, the more people are exposed to antimicrobials the more resistance builds up, so it is a question of slowing down that exposure. One aspect of this is the standard advice to complete the course of antibiotics.

Professor Holmes: Yes.

Q25 **Chair:** I understand there is some dispute around this. Taking the entirety of a prescribed course may increase exposure beyond what is necessary. Where are you on that?

Professor Holmes: It is becoming increasingly apparent that the courses of antibiotics can be made shorter and shorter. What is important is that we have the data so we can absolutely say that a course is far too long. Courses are getting shorter and shorter.

If I can go back to diagnostics, we should not be talking about diagnostics just in terms of the infection; we should be looking at diagnostics in terms of the host response—that is, how people respond to the infections and how we can stop the antibiotics as soon as possible.

How can we get data on drug levels to maximise their effectiveness and give the shortest possible course? Carrying on to the end of a course is important for things that require long treatment, but we will be able to go shorter and shorter with courses of antibiotics. We have moved on from that.

Q26 **Chair:** Is there an action point for the NHS to review its prescribing guidelines?

Professor Holmes: Absolutely, looking particularly at duration, but getting the data to make safe recommendations about duration, and looking at trials and how we can get that real-world data.

Q27 **Chair:** To extend it slightly—obviously, this has been prominent during Covid—we have been talking about drugs, but take antibacterial gels and the protections and increased use of them. Are they subject to the same build-up of resistance over time?

Professor Holmes: I am not an expert on topical therapy, but we have to be very careful because they can exert pressure as well. We need to think carefully about how we use topical agents.

Q28 **Chair:** The same logic would apply, presumably.

Professor Holmes: Absolutely.

Q29 **Chair:** Post Covid, many places are still disinfecting surfaces far more than in the past and using a lot of chemicals. Should that be reviewed?

Professor Holmes: Certainly. Particularly within healthcare, how those are used needs to be looked at. I was referring more to topical treatments that you put on a person.

Q30 **Chair:** I have one final, unrelated question. The Committee takes an interest in a breadth of subjects. You are the president of the International Society for Infectious Diseases. The monkeypox virus—although I understand it might be renamed imminently—is obviously of current concern. Professor Heymann of the London School of Hygiene and Tropical Medicine said that the overall risk of monkeypox appears to be small. Do you agree with that assessment, and what risk is there of monkeypox escalating to a pandemic level?

Professor Holmes: Of course I defer to David Heymann. In terms of the whole population, it is potentially small, but this depends on having very strong infection prevention activity. What this illustrates is how critically important it is to have surveillance, rapid diagnosis, sharing of data, public engagement, vaccines, infectious disease expertise and genito-urinary medicine expertise. Colleagues are working extremely hard on this in the UK. Prevention is also critically important.

Monkeypox has illustrated how we need to be completely vigilant and have expertise, joined-up thinking, surveillance, infection prevention and the use of vaccines, and the other thing referred to earlier, which is

complete engagement with patients and the public in their activity in preventing this.

Q31 **Chair:** Based on what we know so far, how worried are you about monkeypox in the UK and around the world?

Professor Holmes: I am worried about a pox virus. I do not think I can say much more than that at the moment. We will see how things go, but, hopefully, with very active infection prevention, surveillance, altered behaviours, engagement with the public and patients and the use of vaccines, we should have all the tools to be able to contain it.

Chair: Thank you very much indeed, Professor Holmes and Lord O'Neill, for giving evidence today. We are very grateful for your appearance and for the work you have done for many years now. It is encouraging to see what an impact it has had. You have given us some strong steers for our recommendations as to how we can ensure progress continues and might even be accelerated. Thank you for your time this morning.

Examination of Witnesses

Witnesses: Dr Kitty Healey and Professor Mark Woolhouse.

Q32 **Chair:** I will now introduce our next pair of witnesses, who I am pleased to see online. We have Dr Kitty Healey, head of antimicrobial resistance policy and surveillance at the Veterinary Medicines Directorate of DEFRA. If you caught some of the previous discussions, you will know that we have been talking about animals already, so we are very keen to hear from you.

I am very pleased to welcome back to the Committee Professor Mark Woolhouse, professor of infectious disease epidemiology at the University of Edinburgh. Professor Woolhouse has been very generous with his time and advice in advising the Committee on Covid, and it is very good to see him in another part of his expertise. Thank you for being here today.

Perhaps I can start with Professor Woolhouse. Could you give a brief overview of where we are in antimicrobial resistance in this country and around the world, and whether you think we are doing enough? What are the key points where you think we should be doing more, if that is required?

Professor Woolhouse: I think we are in the quite advanced stages of a global public health emergency. The issue is that this emergency, unlike Covid-19, is a slow burner. It is one that accumulates over decades, so the 1 million deaths a year globally that you heard about earlier will go on year after year. Lord O'Neill's report says quite clearly that, if anything, we expect that global number to increase. You can see the numbers adding up. At the moment we are not in a position where we can confidently say that we are on top of the problem and that the

trajectory is down. There are some encouraging signs in the UK and Europe, but in most of the world there are not.

One of the key lessons from Covid-19, even if we are learning it in slow motion, is that early action can be less drastic action. If we see an incipient and growing problem, possibly an exponentially growing one, we need to get on top of it early. If we do that, we will save ourselves an awful lot of misery and public health problems down the line.

Q33 **Chair:** As for getting on top of it, is it fair to say that any public policy and set of medical interventions is about slowing down the spread of antimicrobial resistance? Legitimate and well-indicated exposure to antimicrobials will build up resistance, so it is a question of eking out that window for as long as possible; it is not something for which we can find a cure, but a question of extending for as long as we can the benefits that we currently enjoy. Is that the right way to think about it?

Professor Woolhouse: That might be a little pessimistic. Antimicrobial resistance was around even before humans. This is part of the natural world. Bacteria and other micro-organisms produce antimicrobials, and other ones evolve resistance to them. They have been doing this all the time, so there is a background level of antimicrobial resistance on the planet, if you like, to which humans have significantly added. I would hope that, in the very long term, there is a level of antimicrobial usage that we could sustain, but clearly we are well above that at the moment. We are not treating this sustainably. That is the issue.

Q34 **Graham Stringer:** Professor Woolhouse, my notes say that in a talk in 2018 you even questioned whether our legitimate use of antimicrobial drugs is sustainable. That seems to be at odds with the answer you just gave.

Professor Woolhouse: No, it is not. There are two parts to that. First, it is very important that we minimise as best we can the rate at which we are using antibiotics, for all the reasons you heard in the first session. One of the ways to do that is to clamp down on what is widely described as inappropriate use. The problem to which you are alluding, and which you say sounds contradictory, is that bacteria do not distinguish. Whether we badge it as appropriate use, misuse or absolutely essential use, the bacteria do not care; they will evolve in response to that use.

The question then becomes: what level is sustainable in the long term? The bottom line is that we do not know the answer. Current levels, which involve a lot of inappropriate use, are clearly too high and we have to bring them down.

In answering the Chair's question just now, I raised only one issue about how you manage this global health emergency, which is to reduce the use of antibiotics. The other, which was alluded to very clearly in the evidence you just heard, is that you manage the demand and the amount of bacterial infection of all kinds. Many bacterial infections are not

antimicrobial resistant. They are still a public health problem and require the use of antimicrobials to treat them.

The two key things—Professor Alison Holmes rightly emphasised this—are, nationally, infection prevention and control in hospitals and healthcare settings, reducing demand, and, globally, it is sanitation, safe water and public hygiene, or what are called the WASH programmes. That will also reduce demand for these drugs. I am optimistic that there is a sustainable level, but we are not at that point at the moment.

Q35 **Graham Stringer:** Do you think that NHS advice to patients on the use of antibiotics is scientifically based and sound, in particular the advice that patients should finish a course of antibiotics?

Professor Woolhouse: The history is interesting, and there has been quite a lot of writing and discussion of that. Basically, it goes all the way back to Alexander Fleming, who, as you well know, anticipated the evolution of resistance. That comes partly from his advice. As I understand it, it was not questioned for many decades.

However, I think Professor Holmes gave you a very good answer. There are clearly clinical possibilities to reduce the course of some treatments. I would add a caveat. She said very clearly that we need the data to support that, and I agree, but do not expect that all treatments for all bacterial infections can be reduced. One of the things that makes this a very different problem from Covid-19 is that, there, we were focused on a single threat or kind of virus. Here, it is a much more complex problem. There are many kinds of bacteria, many drug-bug combinations and many clinical conditions that we are concerned about. It is far more complex. There is no single answer. A contribution like reducing the length of treatment will help, but nothing is a single solution; we need an integrated approach right across the board.

Q36 **Graham Stringer:** The last time Sally Davies was before the Committee she surprised me, as witnesses often do, with one of her answers. She said she had changed her view about the use of antibiotics, particularly in developing countries, because she had witnessed or had seen evidence that a very poor person in India using one tablet or one antibiotic was helpful to them in some way. She had changed her view, which would have been against allowing that at one time, to believing it is a humane and, if not satisfactory, clinically sensible thing to do. What is your view on that?

Professor Woolhouse: I absolutely agree with the difficult question of how we best balance access versus excess. It is quite correct that, in large parts of the world, the bigger problem is access. That is a bigger public health problem than antimicrobial resistance per se. We have to find that balance.

How do you reduce the need? You can bring down demand as well as increasing the supply of drugs. In many settings, such as India and many

parts of Africa, where I have worked for many years, a large part of reducing demand comes back to what I said earlier. It is better sanitation; it is safer water supplies; it is WASH. That is also a more available public health tool than increasing the supply of antibiotics. In those settings—India, Africa and many parts of the world—we need to do both.

Q37 **Graham Stringer:** Dr Healey, I put the same question to you. Is the veterinary advice on the use of antibiotics scientifically sound?

Dr Healey: In general, on the veterinary side there is a lot less evidence to go on than there is in human medicine. The available advice is also not structured in the same way as on the human health side, so you do not have the equivalent of NICE guidelines, for example, although species-specific vets come together to provide prescribing guidance. That is done on a regular basis. I suppose the advantage here is that it is much more flexible and can be updated much more readily. It is evidence-based in that it reflects the data we have. I am referring mainly to the surveillance data on antimicrobial resistance and antimicrobial use. It also reflects what is practical in the field and, as I say, what can be discussed and changed.

Is it being followed? That is a difficult question to answer accurately. A few people have alluded to some of the reductions we have seen on the agricultural side, of which I think everybody is rightly proud. We definitely see that not just veterinary prescribing advice but the ambitions that the different agricultural species sectors have set themselves, initially in response to Lord O'Neill's report, have been ongoing and self-perpetuating. These have turned to targets, such as looking at specific disease challenges that might be a greater cause of the use of antibiotics in some sectors. Where there are vaccines, should we be trying to increase the uptake of those vaccines? That is monitored by a particular taskforce established for that purpose.

Q38 **Graham Stringer:** Can you give us some idea of the scale? How routinely are antibiotics used preventively in farmed animals and fish? Is there much evidence of an overlapping misuse of antibiotics, so not just for preventive purposes?

Dr Healey: That is a very good question. One of the things we lack in our surveillance data is the reason for use—the metadata behind why the antibiotic is prescribed and getting to that level of detail.

Professor Woolhouse talked about the reason for treatment. I absolutely agree that exposure to the antibiotic causes the resistance rather than the specific reason for use. Therefore, we in the policy team, but also more collectively as the veterinary profession and the wider agricultural sector, focus very much on reducing unnecessary use, which includes reducing the need to use. Without being able to quantify it, I can say there is definitely still group prophylaxis going on in the agricultural sector, and in certain sectors it is likely to be more common than in

others. That is definitely where we need to work to bring it down. The urgency with which we do that is dependent on the sector and what we see in overall reductions. We are seeing reductions in almost all sectors. In one sector in particular—I cannot recall whether this is one you brought up—in the pig sector, where we see the highest overall antibiotic use, that is also where we have been seeing very substantial reductions.

Q39 **Chair:** On the question of use in agriculture and fish, what is the relative amount—what is the quantum of use—in agriculture versus human use?

Dr Healey: Could I clarify whether you are asking about animals overall compared with humans or fish specifically?

Chair: Non-human use. It is obviously prescribed for humans and non-humans. What is the balance? Is it mostly humans or not?

Dr Healey: In the UK it is mostly humans. To put some quantification around that, there are different ways that we can look at this. We can look at the total tonnage of the active ingredient prescribed for humans and prescribed for animals. That is a bit more problematic than it might look at first glance, because the weight of animals varies from a couple of kilos to several hundred kilos. So we adjust for the population size and the anticipated weight at the time of treatment. We come out with a milligrams per kilogram value. I should clarify that that has no bearing on dose rates, but it is a better way of comparing it. When you look at the milligrams per kilogram value, the most recent data we have published—it dates from 2017 and lags a little behind the data we have in individual reports—for humans the figure is 118 mg per kilogram, and in food-producing animals it is 32.5 mg.

Q40 **Chair:** That is per kilogram of the animal or human. In global terms, are we pumping out more antibiotics and antimicrobials into the animal population than the medical profession? Behind that question is: where should most of our effort be? Is the progress we are making on humans simply swamped by the contribution to microbial resistance that comes from animals?

Dr Healey: In the UK, no, that is not the case. To clarify a little better what the two figures mean, they can be taken as being as close as we can get to a direct comparison. It means we are looking at approximately one third of the use of antibiotics in animals compared with two thirds in humans, if you look at all antibiotic use in the UK in humans and animals.

Q41 **Chair:** You said that is the UK, but I detect a sense that it might not be the same around the world.

Dr Healey: It is not the same all around the world. The data do not exist in all countries. One issue we have when it comes to surveillance data and looking at something that involves a lot of different sectors, species and datasets is getting data that can be compared. That is a challenge. We do not have that available worldwide. It is available regionally within Europe. I do not have the absolute figures, but I can find them for you

because they exist in a published report. As for the trends within Europe, a decrease of 32% was observed in animals between 2014 and 2018, and in humans antimicrobial use increased slightly.

I am saying that animals appear to be doing better than people. That is not the case straightforwardly. The figure I just gave of 32.5 mg per kilogram relates to food-producing animals. They do not get old; they do not have hip replacements; they do not have chemotherapy. When we say that the use of antibiotics in food-producing animals is lower than in humans that is absolutely correct and is how it should be. We are also on a journey. We are still decreasing the use of antimicrobials in animals, and there is further to go before we reach the point where it is sustainably the lowest we can get.

Q42 **Chair:** Professor Woolhouse, do you have any comment on the overall balance of the contribution to antimicrobial resistance that comes from agriculture versus human medical use?

Professor Woolhouse: Dr Healey described it very accurately. The trends in humans are a little more subtle because there is some evidence of decrease in community use, basically by GPs in the UK, particularly over the Covid years, which might be unusual, but there is much less evidence of any kind of reduction in hospitals. If anything, prescriptions are going up. The reason is the one that Professor Holmes gave earlier, in that we have a problem with hospital-acquired infections, so we need antibiotics. As Dr Healey said, those are not caused, certainly not directly, by animal use. This is all about the use in hospitals, particularly in ICU-type environments. While you can certainly link some antibiotic usage overlaps in animals and humans, some of it you cannot. There are things like carbapenems which we do not really use in animals but we use as last-resort drugs in hospitals. The usage of those and the resistance to them is going up. That is not about farm animals.

Q43 **Carol Monaghan:** We understand there are reservoirs of AMR within the human population, the animal population and the wider environment. What are the biggest risks for cross-reservoir transfer of drug-resistant microbes? I am not sure who is better placed to answer that. Perhaps I can start with Professor Woolhouse.

Professor Woolhouse: It is a big issue. We can trace the movement of bacteria these days through whole-genome sequencing. There have been quite a few studies of that around the world. When you do it on a large scale, basically looking at bacteria found on farms and in humans, it is very difficult to find much overlap in the bacteria. When you do it on a much more focused scale—for example, people like farm workers—you can see some signs of that overlap. For most of us, the way bacteria might get from animals to humans is via the food chain, so food safety is very important.

None the less, the movement of the whole bacteria is probably not the main mechanism of the movement of antimicrobial resistance. That

comes from features called mobile genetic elements, possibly in commensal bacteria. Often you can find them in the environment as well, and it comes from those. That has proved much harder to quantify. There is quite a lot of research going on around the world on how to get an accurate picture of how many of these mobile genetic elements that are prevalent in animal populations subsequently appear in humans. But while we are using the same antibiotics—most of the antibiotic classes are used in both humans and animals—the selection processes are in both populations anyway. They are not just in food animals, which then pass it to humans; they are happening in humans too, so all the same processes that we are worried about in food animals will be going on in the human population. It is very difficult to separate this.

Q44 **Carol Monaghan:** You talked about a focused group—for example, farm workers. In your opinion, where humans and animals are in such close contact, is that where there is most likely to be a transfer of drug-resistant microbes from one to the other?

Professor Woolhouse: For the whole microbe—the whole bacteria of the micro-organism—yes, but for the mobile genetic elements that cause antimicrobial resistance, no, that will not be the major route. As I say, these are present in our food. They are also present widely in our environment in our drinking water. The entire human population is exposed to these all the time from multiple sources. We live in a sea of bacteria. If you magically made all other life forms disappear except for the bacteria, we would all be there as ghosts painted by our bacteria. All our animals and crops—everything—would be there. This is a bacterial world; the rest of us are just a veneer on top of it. All of these things are in the environment and they reach us by multiple routes.

Dr Healey: Following on from Professor Woolhouse's last comment, I want to bring up two points. We tend to think of animals as being the reservoir from which resistant bugs and genetic elements can pass to humans, but it is a whole ecosystem. We see incursions of resistant bugs or genetic elements in animals from other sources. Some of those may well have originated in people. It is very suggestive that that is indeed the case. In the literature, I believe there is a paper from Finland showing that carbapenem resistance was detected in a household. It was detected in bacteria isolated from humans and also from their dog. We have also seen carbapenem resistance in bacteria isolated from a seal that was known to be in an area where there was a sewage outflow into the sea. Those are simply two examples.

As Professor Woolhouse said, wherever resistance ends up, whether it ends up in a farm animal or a person—by whatever route it arrives there—it is likely to get amplified if antibiotics are given.

Q45 **Carol Monaghan:** Is there going to be greater risk of transfer as humans and animals start living in much closer proximity?

Dr Healey: That is a difficult question. I do not have the answer to that. We can often identify transmission routes, but as to quantification of hotspots—in other words, which routes are responsible for most traffic—we have some of that information, but we have a lot more blanks than have been filled in.

Q46 **Carol Monaghan:** A paper in the journal *Microorganisms* in 2019 concluded that "the importance and risk posed by vectors of transmission between environments has not been systematically studied." Is that still the case and, if so, where are the biggest knowledge gaps in the transmission of AMR?

Professor Woolhouse: I can speak to that because we have been doing some research ourselves on it in a particular setting in Nairobi, Kenya.

The broader answer to your question is that this is an active area of research. I think we have a pretty good understanding of the ecosystem, as Dr Healey described it, and the way in which the bacteria, and more particularly the antimicrobial-resistant genes, move around this complex network of environments. What we are still working on for most of this is how to put numbers on each of those links and how strong the links are.

In our work in Nairobi, we were able to pick up—this is what you mentioned earlier—direct sharing of bacteria, basically the same bacteria, in humans and animals, most commonly where they exist in the same household. In the Nairobi setting it would often be food-producing animals. In the UK, where similar studies have been done, it works with pets too, but again—Dr Healey emphasised this—I do not think we should go away from this part of the discussion thinking that animals are the reservoir from which human antimicrobial resistance arises. That is only partly true.

My analogy is to imagine you are dealing with a completely different problem. You walk into your bathroom one day; you find both taps are on and the bath is overflowing on to the floor. How do you solve that problem? You do not solve it by turning off one of the taps; you turn off both.

Q47 **Aaron Bell:** Thank you both for your time. The paper that Carol Monaghan just referenced also refers to the way in which antibiotic-resistant genes and bacteria can get released into the environment via what is called pollution either by human waste water or run-off from agricultural uses. To what extent do you think pollution in the environment is a real risk threatening human and animal wellbeing and health?

Professor Woolhouse: The UN environment programme has just produced a report on this, and it highlights that particularly important issue. There are a number of routes. They basically end up in the system through the sanitation system where we excrete bacteria, mobile genetic elements and antibiotics. They can end up in the water system. There is a

concern about pollution from pharmaceutical companies when they are producing it. There are obvious concerns about run-off from farms where antibiotics are being used, including fish farms—aquaculture. All of those are seen as increasing the level, not just of antibiotic resistance genes directly, although they do do that, but also contamination with antibiotics and thus changing the selective environment. We even see some evidence of that in the sewerage system, for example. It also has an impact on the bacterial flora there. It is the full network. Yes, that is widely seen as a major concern.

Q48 **Aaron Bell:** Are there any specific things we should be doing? I am thinking particularly about hospitals, which only contribute about 1% of total waste water but have a disproportionate effect on resistance because the excretions from patients will mostly have antibiotics in them. Should we perhaps be doing something specific about sewage from hospitals to try to ameliorate this, or is it not so important a risk factor that we need to think about that?

Professor Woolhouse: That is something we have studied explicitly in Edinburgh, using, if I may advertise this briefly, a rather clever technique called metagenomics, where you take a sewage sample and do genome sequencing of everything in the sample, every single gene of every kind, and very simply, with a computer, you can pick out the genes that we know confer antimicrobial resistance. You can do very good surveys of this.

There is absolutely no question but that the sewage coming out of hospitals contains more, and also different, antibiotic resistance genes than sewage coming from a regular community. However, by the time you get down to the sewage treatment plants, it has pretty much been diluted away and we cannot see that. Yes, there is definitely an issue, but it seems to be dwarfed by what is coming out of regular communities. Do not forget that, in terms of volume, 10 times as many antibiotics are prescribed in the community through our GPs than in hospitals, so our regular sewage is also very important.

Q49 **Aaron Bell:** That bring me neatly on to surveillance more generally. I am not sure whether we used sewage to track Covid as well. How advanced is our surveillance capability for monitoring these sorts of transfers? Is it a one-off project that you have done in Edinburgh, or is it something we are looking to roll out more widely?

Professor Woolhouse: It is something we and our collaborators in Denmark, who initiated this scheme, want to roll out widely on a global scale. As you heard in the first session, there is a real issue with getting high-quality data on levels of antimicrobial resistance simply because, as I said before, it is such a complex problem. Which drug-bug combination do you look at? Which population do you sample? Everybody answers those questions in different ways, so the data is very heterogeneous. The sewage sampling is a very easily standardisable way of doing a routine

survey. When we do that, we can compare levels around the world and we can compare levels over time in a very easy-to-use format.

Covid-19 was helpful because, when my colleague Frank Aarestrup and I were promoting this just before the pandemic, it was seen as a little bit off the wall—a bit of a wacky idea. Now, because it has been used successfully for picking up Covid-19, it is much more accepted as a surveillance tool that would be valuable in public health, and it will be going forward. As a general rule, there is never a single solution. This is one helpful element to the surveillance programme. There are many others that we need to focus on as well.

Q50 **Aaron Bell:** You are hoping to roll it out. Are you looking for funding in the UK or internationally?

Professor Woolhouse: We have been. That was slightly interrupted by Covid-19. We are in discussions with GLASS, the World Health Organisation's surveillance system, about rolling it out further.

Q51 **Aaron Bell:** Dr Healey, can I ask you about the pollution element that comes from agriculture? What surveillance are we doing there? How much of a risk factor do you think the run-off from agricultural use is?

Dr Healey: If I may, before I turn to agriculture, I am absolutely not the Government expert in looking at surveillance in sewage, but I know there are colleagues in the Department of Health and Social Care and in the core DEFRA department who are working on this. In fact, it is part of a programme that secured funding recently under the PATH-SAFE programme, so the importance is recognised.

Turning to agricultural run-off, this area does not have the same kind of focus as human sewage. It is also not having the same kind of focus at the moment as the surveillance programmes on antimicrobial use and antimicrobial resistance on the animal health side. It is part of a very large to-do list on AMR, and it is a function of the fact you have to prioritise now. It will be interesting to see where we go with this in future.

The agricultural run-off issue is local, so it will be the animal equivalent of sewage. The manure is on the farm and sometimes it is spread on farms, but it is local. Sometimes it degrades locally in the landscape and sometimes there will be run-off into watercourses, but there is nothing of the scale of storm overflows and that kind of thing when it comes to the agricultural sector.

You touched on a pharmaceutical company manufacturing effluent. This is not something my team is leading on, but it is one of the things being looked at by the Department of Health and Social Care, as part of the UK's G7 presidency last year, and indeed is one of the things that continues to be a topic of discussion and dialogue internationally in policy circles.

Q52 **Aaron Bell:** Finally, there is some evidence that cross-reservoir transfer can occur through other key interactions, which would fall under DEFRA, such as close contact between people and animals, whether on farms or in petting zoos or whatever, bathing in coastal waters, wild birds acquiring resistant bacteria, and the preparation and consumption of animal products. To what extent are those on DEFRA's radar as risk factors, and what surveillance is taking place to try to track its prevalence?

Dr Healey: I would say they are all on DEFRA's radar. I will try to work backwards. Forgive me if I do not recall all the individuals when I come back to you, if that is okay.

Aaron Bell: Of course.

Dr Healey: On the wildlife side, there is not a systematic surveillance programme as far as AMR and wildlife goes. We have sporadic reports that come through, and sometimes they get followed up, but this is an area we have identified as a gap. It is a tricky one because the value of a lot of the surveillance we do is partly in monitoring trends but also in evaluating the success of the interventions we make. One of the challenges with wildlife is what interventions are possible. That is definitely on the radar.

When it comes to food and the preparation of food, that is more a Food Standards Agency area than DEFRA, but we work very closely together across all of AMR and surveillance, and the FSA leads on some ongoing programmes. Also, as part of one of our regular antimicrobial resistance monitoring programmes, we have structured surveillance of animals at the point of slaughter in abattoirs, so, effectively, we are sampling healthy animals at the point where they are in the process of turning into food. We have a very good system in place for evaluating that.

In terms of companion animals, we will be looking predominantly at dogs and cats, but there are other companion animals. Perhaps in some of the more exotic animals such as reptiles, which can carry salmonella, there are many risks—the harder you look the more you find—and also in horses. We have been stepping up our work with stakeholders in these areas. While we do not have comprehensive programmes in place for monitoring resistance, on the resistance side we are working—it is at the pilot stage; we would like to work further on it—to develop our relationships with private labs in order to see if there is scope for accessing data beyond what we have in our Government programmes. At the moment, that is not covering companion animals, but, looking to the future, there is absolutely no reason why it could not.

On antimicrobial usage, at the prescribing level, we are working with two sets of stakeholders to look at doing the target-setting process in cats and dogs; the data collection that we are already seeing is at a slightly more advanced stage in the food-producing animals. There is a focus on

veterinary prescribing software systems. I think you mentioned something else.

Aaron Bell: Bathing water was the last one.

Dr Healey: Bathing water, yes, thank you. That is more the remit of my colleagues in the water quality area of DEFRA. I know it is on their radar, and I believe they are working on it.

Aaron Bell: They are not just looking for pollution; they are looking potentially at antimicrobial resistance. That is excellent. That is very comprehensive and very helpful. Thank you both.

Q53 **Chair:** I have a couple of questions for Professor Woolhouse, to which I would like brief answers. We have talked about the deaths from antimicrobial resistance. In previous meetings of the Committee we have talked a lot about deaths from Covid and some of the challenges in measuring that. Are you confident that we can robustly measure deaths from antimicrobial resistance, and how is it done?

Professor Woolhouse: You are exactly right that the same problem applies to any cause of death. It is called the attributable fraction. It is the difference between dying with some agent or something and dying of that agent. The Murray report in *The Lancet*, which you heard referred to in your first session, does the best possible job—these people are very good at what they do and they put a lot of care into it—at making that estimate. Even on their estimate, there is uncertainty—plus or minus 50% either way, or more—but it is the best we can do at the moment. I certainly think it is sufficiently good to drive policy.

Q54 **Chair:** There are two sides of the equation. One is suppressing the use, especially inappropriate use, of antimicrobials, yet the other side is developing new antimicrobials that can replace the ones to which resistance has been derived. Do you think the UK Government's balance of attention is right between those two tasks—those two challenges?

Professor Woolhouse: Sorry, the balance between developing novel antimicrobials and?

Chair: We have talked a lot about suppressing the inappropriate use, or suppressing the use, of antimicrobials, but we would not need to do that. Even when we are suppressing it, it is at the expense of some prophylactic use to prevent disease. If we could have a reliable stream of new antimicrobials that could allow prescriptions to continue, that would be the best of all worlds, would it not? Do we have enough focus on that?

Professor Woolhouse: Very briefly, with novel antimicrobials, in the short and medium term, that is an absolute priority. I completely endorse all the emphasis that the O'Neill report and others have put on that. If we can make the UK a powerhouse for developing those technologies, it would be to everyone's benefit. I would not want to diminish the importance of that at all, but I think there has been less attention paid to the other side—what Jim O'Neill has called the demand side rather than

the supply side, when I have spoken to him about that. You focused on reducing usage, which we have done, and it is a way of reducing demand.

I would also like to see a big reduction in the demand for essential usage, the appropriate usage. The way we do that is by better infection control, particularly in our hospitals, and globally by better sanitation and safer water supplies. We should reduce the demand in that way. Then there is less demand for appropriate use. That is the route where we began. It is how you make a sustainable response to what is, as I characterised earlier, a global health emergency.

Chair: Thank you very much indeed, Professor Woolhouse. That is characteristically clear. We are grateful for your help to the Committee today and also that of Dr Healey.

Examination of Witnesses

Witnesses: Dr Seamus O'Brien, Professor Robert Schooley and Dr Peter Jackson.

Q55 **Chair:** The talk of innovation takes us very neatly and appropriately to our final panel of witnesses this morning. I see them on the screen. I am very pleased to welcome and introduce Dr Seamus O'Brien, R&D director of the Global Antibiotic Research and Development Partnership; Professor Robert Schooley, professor in the division of infectious diseases at the University of San Diego—we are very grateful to you for joining us at an ungodly hour on the west coast; and Dr Peter Jackson, executive director of Infex Therapeutics whom the Committee met when we visited the University of Manchester. It is very good to see you again, Dr Jackson.

Perhaps I can start with a question to Dr Jackson. You may have heard some of our proceedings this morning. We are looking back at the O'Neill report of six years ago. What is your assessment of how the UK is doing, particularly on the development of new technologies?

Dr Jackson: Thank you, Chair, for the invitation to talk to you this morning. As well as running Infex, I have also had the privilege of being on a small group that reviewed BBSRC's investment in AMR over the past few years. We have great science—you have heard from some of the great scientists who are out there—but we are failing to convert that science into industry. Over the past 10 years, only nine companies have come out of the BBSRC investments. In total, right now, they employ 16 people and have less than £1 million on their combined balance sheets.

I also did a report that fed into the five-year AMR strategy four years ago. Then we had just 23 small to medium-sized enterprises in the UK working in the field of AMR. One of my teams reviewed that in preparation for this hearing, and that 23 is now 19. Those 19 have less than £35 million on their balance sheets.

My company, Infex, is one of those SMEs. We stepped into this, very much encouraged by Jim O'Neill five or six years ago. In that time, we have developed seven programmes. The first two of those are just about

to enter clinical trials, and, importantly, neither of them is conventional antibiotics. One of them is an immune infection antibody and the other is a resistance bypass drug that switches off one of the most critical resistance mechanisms in serious priority drugs.

Overall, we have great science and we understand the opportunity extremely well, but there are still structural factors within the UK that prevent the full potential being exploited; and, as the WHO reported globally, there is still an inadequate supply of new drugs coming through the pre-clinical and clinical pipeline.

Q56 **Chair:** Thank you very much, Dr Jackson. I will ask Professor Schooley for an international perspective. I am sorry, I should have introduced you as coming from the University of California San Diego School of Medicine. Looking globally at the innovations, how do you feel the world is progressing to contributing new technologies to deal with this global programme?

Professor Schooley: Dr Jackson hit the nail on the head. We have great science, but we are having trouble translating it into clinical applications. There are two major reasons for that. The first is a lack of investment on the part of pharma in this area. They see acute interventions with drugs that reverse a process and that you need to take for two weeks as a much riskier intervention than a drug that you take for the rest of your life for depression, say, or some other issue.

The other challenge is clinical and translational research mechanisms and trial programmes that allow us to unequivocally learn how to use these new products. It is complicated to come in with a new antibiotic in a critically ill patient with a multidrug-resistant organism and show that that antibiotic or that antimicrobial has a clinical impact. It takes large clinical trials done by sophisticated clinical trial units, who struggle to launch the clinical trials that are needed to provide the evidence physicians need to know how to use these drugs.

Q57 **Tracey Crouch:** We have heard from other witnesses about how reducing the unnecessary use of antibiotics could help to address the problem of AMR. How hopeful are you that we can effectively innovate our way out of the AMR problem with new treatments?

Dr O'Brien: Thank you for the question, and thank you for the opportunity to speak today. It is not just about new treatments. New treatments are very important. The word "treatment" is an important word to use here. We talk about developing new drugs and new interventions, but we need to know and understand how to use them. Regardless of the type of intervention, we need to demonstrate the evidence of how they will be used in the clinic, building on the point Professor Schooley made.

Where we have greater innovation at the moment is in the pre-clinical pipeline. The UK has had a key role in supporting initiatives such as

CARB-X. You can see the innovation coming through there. Where we are lacking innovation at the moment is in the clinical pipeline. We need to address that first, and we need to understand how to develop these new innovative approaches, be they antibiotics with new targets or what we call non-traditional antibacterials.

We also need to think about innovation in how we demonstrate the evidence on using the drugs in the clinic. This was a point made very early on in the session this morning by Professor Holmes. We need to make sure that we invest in understanding, first, how we are using our current treatments. We have heard a lot of very important comments today about reducing the use of antibiotics, which is absolutely true, but we need to use the antibiotics we have optimally and more appropriately to get the best use out of them. Until we do that, we are going to have challenges both in the UK and globally in how we use new interventions.

We need to build the evidence of how we use the drugs in clinical development and translate that better into how to use them post licence in hospitals. I would include the UK in that. The UK is very well set up to do it because of the NHS and because of the National Institute for Health and Care Research. They could look to set up programmes to assess how to optimally use new antibiotics and look for innovative ways to do that. I will stop there. I probably could say a lot more, but I will pause there in the interests of time.

Q58 **Tracey Crouch:** Dr Schooley, I have been reading a little about phage therapy. Could you give us a little bit of background on that? Do you think it is the answer to the problem of AMR?

Professor Schooley: Bacteriophages, or phages for short, are viruses that infect bacteria. Just as Professor Woolhouse gave the analogy of us living in a sea of bacteria, bacteria live in a sea of phages. There are 10^{31} unique phages in the world. They are the most common living agent in the world, and they have been interacting with bacteria for 300 million years. Phages and bacteria have this dance in which phages infect bacteria, grow in bacteria, lyse them, and then go on to infect nearby identical bacteria. Those bacteria are selected by the phages so that they become resistant, and this evolution has continued so that at this point in time there are multiple phages for any given bacteria on the planet that are able to kill it in good order.

Phages are not going to be a substitute for antibiotics, in my view. They are going to be another piece of the armamentarium to treat multidrug-resistant bacteria. We need to learn to use them in a rigorous way, just like we have learned to use antibiotics, and in combination with antibiotics to optimise the use of both. They have unique advantages that we need to take into consideration as we develop them, but I think there is great potential for them to have a much bigger and more radical impact than they have had so far.

Q59 **Tracey Crouch:** With that potential, do you think the Government could

do more to support the roll-out of phage therapy to patients in need? I am interested in whether you have any comparative insight into how the British Government and the US Government are thinking about this therapy.

Professor Schooley: There are two ways in which a Government can enhance understanding of how to use phages clinically. One is the same sorts of clinical trials that we have been talking about. Phages should be one of the antimicrobials that enter the pipeline, because we need to learn how to use them using the same metrics we use to understand antibiotics. We need to understand their pharmacology, we need to understand their pharmacodynamics and we need to understand the emergence of resistance—all the same things that antibiotics need.

The other issue has to do with the regulatory environment. The regulatory environments in the US and Europe are quite different. In the US, the Food and Drug Administration plays a major role in the regulation of phages. When we either do a clinical trial or treat an individual patient, we interact with the Food and Drug Administration and provide it with information about that patient and those phages, and it provides an emergency IND to use the phages in that patient based on what we tell it.

In Europe, what has happened in many places is that this has been devolved to hospitals. Hospitals have a magistral process in which someone in an academic lab will tell someone in a formulary, "I would like to use this phage in a patient." It does not go through a rigorous process that leads to homogeneity in how the phages are produced, and it can actually be much slower than the Food and Drug Administration. I can pick up the phone now and talk to someone at the FDA about a patient who is critical and to whom I would like to give a phage cocktail and get approval to do it in literally 20 minutes. Contrary to what is believed in Europe, that the central regulatory agencies are a barrier, the FDA here has been quite permissive in promoting the use of phages.

The other thing about them—and this is my perception—is that there is a bit of reticence to use genetically engineered materials, in the UK in particular. Phages can be genetically engineered. We have, in fact, used one that a colleague of mine, Graham Hatfull, developed to treat a lung transplant patient in London who had an unusual mycobacterial infection. But it is very cumbersome to deal with phages that have had minor modifications in their genetics to make them suitable for use in clinical practice. I think that would be something to look at as a specific issue of phages, particularly as synthetic phages increasingly enter the clinic.

Q60 **Carol Monaghan:** We are hearing about lots of innovative developments in this area, but how conducive are current research and development conditions for the development of new antimicrobials? I am interested in both the UK and globally.

Dr Jackson: The first point to make is that there has been an impact from Covid. Our ability to attract new private investment into early-stage research and development over the past two years has gone down, and that is because of two things. First of all, many investors pivoted to Covid, quite naturally; secondly, with the exception of the UK, internationally, there has been very slow uptake of the changes to reimbursement for antibiotics. We have the dilemma that we need new drugs and we need the private investors to expend hundreds of millions of pounds or dollars in developing them, and then we want to preserve them and use them sparingly, as everyone who spoke earlier said.

Internationally, there is an accepted solution, and that is that we need to move to a subscription-based payment model. The UK has shown great leadership in putting that subscription model trial in place, which has resulted in two new drugs being selected into the programme, but we still have delay in the US and the EU. The UK reimbursement trial was a trial. That now needs to move forward into a permanent setting and to be rolled out across the UK because it was just with NHS England.

One of the reasons why investors are not backing the AMR mission as much as we would have hoped is because the clear reimbursement mechanism and the clear identification of the reward at the end of the investment process are not fully in place yet.

Q61 **Carol Monaghan:** Could you say a bit more about the subscription model?

Dr Jackson: I was pleased to be on the project advisory group for the UK trial. The idea is that once a successful drug makes it through all the clinical trials, it is proven to be successful and judged to be valuable, instead of the NHS paying so many pounds per dose or pounds per patient, the drug developer receives an annual subscription. In the UK trial, it is a maximum of £10 million a year for up to 10 years just to make that drug available to the supply chain and to have it on the shelf. Then the NHS can use the drug in only the patients for whom it is needed, so it avoids all the issues we have heard about of overprescribing and overuse. It gives a guaranteed reward to the drug developer to give a return on the risk capital that has been invested over the time to get there.

The UK is only 4% of the global market. To make an impact on this global problem, we really need the US Government and the EU to step up and introduce a similar scheme. The good news is that there are proposals on the table, but we need those to turn into law and action. If that happens, the reward could be amplified up to around $4 billion for a successful drug, which is the sort of level required to give us a healthier pipeline of new drugs.

Q62 **Carol Monaghan:** Professor Schooley, it is not necessarily your area of expertise, but do you have any sense of whether the legislation that Dr Jackson is talking about is likely to be implemented in the US?

Professor Schooley: I am the last person to defend the efficacy of our Congress in any area. This is something I would love to see happen. We are so obsessed with other things right now that it is hard to get their attention. There is no question but that the US reimbursement mechanism will not work in providing incentives for new antibiotics and antimicrobials. The approach that Dr Jackson talked about would be brilliant if we could push it forward here, but I really cannot predict what our network will do.

Dr Jackson: I do some work with the Milken Institute in DC lobbying Congress on this. The so-called PASTEUR provisions that would provide a similar subscription model have been incorporated into the 21st Century Cures Act 2.0, which has bipartisan and bicameral support, but, as Professor Schooley said, it is getting bogged down in making its way through government in the US because of local politics. However, it is in the legislation draft and it has both bipartisan and bicameral support. *[Interruption.]*

Carol Monaghan: Can I apologise for the bells? We live our life by bells in Parliament.

Dr O'Brien: To build on the point that my colleagues have made, the UK approach is fantastic. However, it will not prevent companies from becoming bankrupt if we do not have more initiatives in the same vein to address the value of antibiotics more than a volume-based prescription approach. This is a real challenge because most of the companies that are developing antibiotics and new therapies are biotechs. That is a problem for a number of reasons.

There are two problems. We are not going to address the priorities. I have not heard much talk about prioritisation here today, but it is key to understand the priority areas in terms of the impact of antibiotic resistance, as Professor Woolhouse mentioned earlier. We need to address those infections and those combinations of bugs and drugs where we are seeing the most impact in terms of mortality and morbidity in the UK and globally. It is a real risk if these companies are not able to bring those antibiotics through. Regulatory pathways do exist. They are flexible in the EU and the US now, but they are getting to the end of those pathways, and they do not have the funding to provide evidence for those priority infections, bloodstream infections and pneumonia infections, and for particular resistance mechanisms where they really add value from a public health perspective, particularly in countries outside the UK, Europe and the US.

One other key priority area that I want to call out is children. Children are seen as a post-approval population to address in antibiotic development. Because of the lack of a vibrant private sector supported by the reimbursement models that Peter talked about, development of antibiotics for serious infections in children, including newborn babies, is being delayed unacceptably. That is something we have to focus on in terms of a public health need.

Q63 **Carol Monaghan:** Dr O'Brien, you have talked about the UK situation. Do you know of any international examples of good practice in supporting development?

Dr O'Brien: My view is that the O'Neill report was very outward-focused. It was very important for the UK, but it was the first time there was a call to arms across all those elements that Lord O'Neill talked about. It is important that the UK continues to play this role internationally. Okay, in terms of Brexit, maybe not via Europe, but it has always focused on these issues for the UK and globally, particularly from an overseas development perspective, in terms of resistance.

There are a number of partnerships in which we are really seeing impact. I have mentioned CARB-X. The AMR Action Fund is very much an industry-driven investment. The organisation of which I am the R&D director has a number of Governments, including the UK Government, investing in our approach on a portfolio that really addresses the public health needs in terms of antibiotic resistance, which impacts LMICs and higher-income countries such as the UK. That is where I see the best practice.

In the future, because countries are really struggling to deal with AMR across the board given the complexity of the issue, we need to look at prioritisation. Governments such as the UK can play a key role globally in defining the priority areas for investment.

Q64 **Rebecca Long Bailey:** What progress has been made towards the development of effective diagnostic tools for AMR, starting with Dr O'Brien?

Dr O'Brien: I will be very quick. There has been a lot of progress in molecular techniques that have a real impact on surveillance of the infection, understanding particular resistance markers at the genetic level and rapid screening, which enables you to track them in a population and within a patient. We are still struggling with diagnostics that help you to determine whether the patient in front of you has a bacterial infection per se and whether that infection is susceptible to the antibiotics you have on your shelf.

That is particularly an issue for the serious and life-threatening infections Professor Holmes talked about this morning, where you have to treat within an hour of seeing a patient, a lot of the time without knowing the infection. You want to know rapidly whether it is a bacteria and whether it is susceptible to the antibiotics you have, and then you can change your decision making, including withdrawing the antibiotic or switching to something that covers the resistance mechanism you have in front of you.

Professor Schooley: I will just speak about phages. We are in a bit of a 1960s era in determining susceptibility to phages, essentially as we were with antibiotics when we were doing individual tube susceptibilities. We

need to do quite a bit of work to understand how best to select the phages for a given patient at scale and with the rigour that you would want to use for clinical medicine. A lot of effort is under way to get there, and I think that will come, but we are not where our colleagues are in traditional antibiotics because they have had a 40-year head start.

Dr Jackson: For the type of targeted antibiotics that Infex and others are developing, it relies on effective implementation of diagnostic strategies. The science is there. It is the translation of that science into the clinical utility, but, even more importantly in diagnostics, who is going to pay for it? It is going to require a significant investment by health authorities—the NHS in the UK—to establish those mechanisms and those diagnostic processes alongside the adoption of new, very targeted drugs.

Chair: I thank all three of our witnesses: Dr O'Brien, Dr Jackson and, perhaps particularly, Dr Schooley. Giving evidence at 3.45 am is quite a commitment, and we are deeply appreciative, as we are to all our witnesses this morning. It has been a fascinating update on a very important area.

The Committee will consider the evidence we have heard this morning and make some recommendations to the Government and other policymakers as to how we can move forward on antimicrobial resistance. Thank you to all.