Automated Voice [00:00:03] This podcast is brought to you by the University of Aberdeen.

Dr Barbara Gorgoni [00:00:11] Welcome to this new episode of Café Connect, where we bring you the latest research from the University of Aberdeen. My name is Barbara Gorgoni and I'm part of the Public Engagement with Research Unit here at the University. In this series, we meet different researchers who will talk about their projects and their relevance to our life. If you have any questions, we would really love to hear from you. Please email peru@abdn.ac.uk and we will put your questions and comments to our speakers. Keep in mind, however, that they won't be able to answer any personal or medical questions.

Dr Barbara Gorgoni [00:00:57] So, today I'm delighted to welcome Dr Karen Scott, Senior Research Fellow at the Rowett Institute at the University of Aberdeen, and Dr Soumya Palliyil, Head of Scottish Biologics Facility. We'll discuss the benefits and challenges that we face with antibiotics. So, welcome both. So firstly, I will hand over to you to tell us a little bit more about your work and interests.

Dr Karen Scott [00:01:24] I'm Dr Karen Scott and I'm a Gut Microbiologist at the University of Aberdeen, as Barbara said. And a lot of my research involves investigating which bugs normally live in the healthy human gut and how we can boost the numbers. For those who don't know there are more of these microbes known as the commensal microbiota and in us than there are human cells in our body. These microbes perform many important functions to keep us healthy, including digesting bits of our food that we can't digest, which releases important nutrients and chemicals that circulate around our body, and they also protect us from pathogens. While I was investigating these microbes, I realized that some of them contained antimicrobial resistance genes. These genes were very similar to each other, regardless of whether they were found in microbes that came from humans or animals. And this got me really interested in finding out how these genes spread and where they came from. So, nowadays I combine these two research areas together looking at the functions of different members of the commensal microbiota and also seeing how they contribute to the maintenance and spread of antimicrobial resistance genes.

Dr Barbara Gorgoni [00:02:38] Thank you, Karen. And Soumya, over to you.

Dr Soumya Palliyil [00:02:41] Thanks, Barbara, and hello, everybody. My name is Soumya Palliyil, and I am the Head of Scottish Biologics Facility. This is a research group part of the University of Aberdeen, where we develop antibodies and new therapies for various human infections and diseases. So, my research mainly focuses on developing innovative diagnostic tests and novel therapies for human diseases. These tests and drugs are based on a type of molecule which our body makes in fighting diseases. These molecules are called antibodies. In the Scottish Biologics Facility, we engineered these antibodies and made them super sensitive and highly potent so that these antibodies can be used to detect disease-causing agents and also can be used to remove this disease-causing agents or disease-causing cells from our body. There are two main disease areas where we are working at the moment in the Scottish Biologics Facility. One is developing ultrasensitive diagnostic tests and therapies for dementia, including Alzheimer's disease, and the second area of interest is developing new therapies and tests for detecting and treating life-threatening bacterial and fungal infections.

Dr Barbara Gorgoni [00:03:55] Thank you, Soumya. So, can I start by just asking what's the difference between antibiotics and antimicrobials because it seems that you're using these terms interchangeably?

Dr Karen Scott [00:04:09] That's very true, Barbara. I am very guilty of using them interchangeably. So, if you are being very specific about it, antimicrobials is a generic term that means any agent that's anti any microbe. So that is an all-encompassing term, whereas often we use antibiotics as if we are talking about an antimicrobial. So, they are used interchangeably and really what we should be is much more specific and we should really refer to antibacterials, which would be agents against bacteria or antivirals, which would be agents against viruses or antifungals, agents against fungi. So, we're really guilty of using antibiotics when we shouldn't because an antibiotic and an antimicrobial are very interchangeable and if you look at the word antibiotic that's really against any life and we don't really want to be against all life, we just want to be quite specific. So really, we should be specific, but I would have to say that in this podcast, I probably will use the terms interchangeably because I'm guilty of doing that. And also, if you go to the doctor to get a prescription, you're always prescribed an antibiotic. So medical doctors really use antibiotics to mean antibacterials often, I think they tend to be more specific efforts against fungus, fungi and viruses, but much less they use an antibiotic instead of an antibacterial. And most people are familiar with the term antibiotic as well.

Dr Barbara Gorgoni [00:05:57] OK, excellent. Thank you. That's very helpful.

Dr Karen Scott [00:06:00] Can I just add to that, Barbara as well? So, there are different classes. So, when we talk about the antibacterials, particularly, there's four different classes of antibacterials, so you can get what we call broad spectrum antibacterials that are active against many different types of bacteria and narrow spectrum ones which are much more targeted activity. And then again, they're split again to those that actually kill the bacteria, so they're bactericidal drugs and those that just prevent the bacteria from reproducing, so they are bacteriostatic. And the differences in the types of antibacterials that are prescribed are actually quite important in terms of how effective they are or what the best type to prescribe is.

Dr Barbara Gorgoni [00:06:48] Thank you. That's really helpful and interesting because we hear these terms over the news as well quite often so that is very helpful. So, why is overuse of antibiotics such a problem?

Dr Karen Scott [00:07:02] OK, so overuse is really a problem, because what you do then is sometimes, you're having a constant exposure to the antimicrobial agent. And if you have that constant exposure, there is a mix of what we call a selective pressure on the bacteria. So, the bacteria constantly experience the pressure to become resistant to that antimicrobial and that can cause them to change so they evolve to become resistant to that antimicrobial, so that they can still grow and reproduce in the presence of their antimicrobial agent. So, the more we use antimicrobial agents or antibiotics, then the more we have that problem of resistance evolving in different microbes against those antimicrobial agents. And what we need to recognise as well is that when you when you talk about exposure to antimicrobials, if I say to you, when are you exposed to an antimicrobial agent, your automatic response would be when I go to my GP and get a prescription. But that's not true. We're exposed to them in many more different ways than that because antimicrobials are not just used to treat humans, they're also used to treat livestock and they're even used to spray onto crops, which is something I did not really know until quite recently. And of course, as soon as you introduce them into the environment like that, then they start to contaminate the water and then that water goes into rivers and reservoirs, and we drink it again. So, we're exposed to antimicrobial agents, not just when we get a prescription from the doctor. And that low level of constant exposure is actually worse than a big, massive dose that you get when you take a prescription drug.

Dr Soumya Palliyil [00:08:50] And I think Karen based on your area of expertise, this exposure is not only contributing to the bad bacteria, but also to the to the friendly bacteria in our body, isn't it? So that's also something that we need to really think about, especially in situations where we are unnecessarily taking antibiotics for infections, which doesn't need antibiotics to clear off that infection. So, that would be quite an interesting point to hear a little bit more about, Karen.

Dr Karen Scott [00:09:32] Yes, sorry Soumya. Thank you for reasoning that, that's a great point, because what happens when we take any antibiotics or if, for example, you go to the doctor because you've got an ear infection, so clearly the doctor needs to clear that up. If it's caused by a bacterial infection, then they'll give you an antibacterial or an antibiotic. But of course, because they don't know exactly which bacteria is causing the infection, they want to give you one of those antibiotics I mentioned before, that's a broad-spectrum antibiotic. So, they want to kill lots of different bacteria to be sure that they kill the bacteria that they need to kill, that's causing the infection in your ear. But because you don't apply the antibiotic to your ear, you take it orally, so then it goes into your body through your digestive tract and that affects all the bacteria that are in there as well. And that's where we have this problem because those bacteria are not necessarily resistant, we hope they're not resistant to the antibiotics, so it has that effect, and it kills off a lot of bacteria in our body that we don't necessarily want to kill. And some of those killed bacteria that are doing beneficial things normally. And what happens then, is that if you if you take antibiotics too often and some people do have to take antibiotics a lot, we can't avoid it all the time. You do have to take them to cure infections. But then if you have that constant exposure and your commensal gut microbiota, they become resistant and they then form a reservoir of resistance, and those genes can then be transferred to pathogens that come in there. So, the effect that has on the commensal microbiota, as well as having a very bad effect and killing it, if you want, they also have a less obvious effect in increasing the sort of level of resistance that's there all the time that can then be transferred into other bacteria that come into that system. So, yes, there's the two factors are both very important, and it's really important then that we make sure that when we do go to the doctor to get; see, we have an infection, we go to the doctor, if it's a viral infection, we really do not need to get an antibacterial because it's not going to help at all in curing the viral infection, and it can cause all this collateral damage. So, we really want to have enough knowledge that we don't try to persuade our doctors to give us antibiotics when we don't need them.

Dr Soumya Palliyil [00:12:18] Yes. And also, important that we complete the course of antibiotics, that particular course, because otherwise, if you stop in-between then the bacteria is exposed to that antimicrobial that or that antibiotic but won't be completely cleared off. So, that means there will be more chance of resistance development because of that kind of short-term exposure to that particular antibiotic. So, that's also important that we complete the course of that.

Dr Karen Scott [00:12:50] Yes, that's a great point to add on because you end up being having repeated courses as well if you don't take all of the first one exactly right and the resistance just exacerbates,

Dr Barbara Gorgoni [00:13:00] OK. And so, what do we mean when we hear the global antimicrobial resistance problem? What does that actually mean?

Dr Soumya Palliyil [00:13:11] So, Karen explained how bacteria or microorganisms in general, are constantly developing changes in their genome or they're constantly evolving. And what happens with this when they are growing in a hostile environment, i.e., in the presence of an antibiotic or an antimicrobial agent, they will make changes to their genome which will be then reflected on the

structure of the bacteria or the fungi, and they can withstand that particular antibiotic or antimicrobial agent. So, in simple terms, what happens, this microorganism stops responding to the drug that you are using to treat that infection. And this is quite serious because then it takes much longer and harder to treat an infection and it causes severe illness in people and eventually death in certain patient population. Again, this resistance can spread between microorganisms, it can spread between humans, animals and, you know, from the environment we can get these resistant microbes into our system. So, this is all very much interconnected with the way the world works nowadays, which is constant movement of people and goods. And this is not just confined to one geographical location, this will spread all over the world and we have seen effects of that spread with the ongoing pandemic, sadly, it started in one part of the world, but then really quickly spread to the rest of the world. So, although this might start in a in a small patient group, in a particular part, this can easily become a global problem. So, that is why we call antimicrobial resistance a global problem. And these bacteria and fungi develop resistance, they start with developing resistance to probably one drug, which is it's being treated with, but it can then develop resistance to multiple drugs, and we call that multidrug resistant bacteria or fungi. It doesn't stop there, what happens is then they keep developing resistance, and at one point, some of these bacteria and fungi will become resistant to the whole group of antimicrobial agents with which you can treat those bacterial fungi and these organisms are called pan-drug resistant microbes. This is again a really serious problem because we have people who are immunocompromised. So, when I say immunocompromised people or patients, these are patients with a low level of immune system. This could be patients undergoing chemotherapy so that with the chemotherapy drugs, that they have a lowered immune system. This could be people who have had organ transplant and are on immunosuppressive drugs, so their immune system doesn't have the ability to naturally defend invading bacterial fungi like healthy people have. So, they are constantly dependent on antimicrobial drugs even for the simplest of the infection. So, we call these prophylactic drugs, which means we are giving them before an infection starts because that's the only way these people could stop an infection developing in their body. But this kind of long-term dependence on antibiotics again results in resistance development. So, when these people are confronted with multi-drug resistant or pan-drug resistant microbes, bacteria or fungi, sadly, this will develop into a very serious illness and in some cases, we see death of these people not from the initial disease, like cancer or kidney failure but unfortunately, the death happens due to the presence of multi-drug resistant or pan-drug resistant bacteria and fungi in their system. So, it's a real problem, and it is important that we should avoid the development of this drug resistance in bacteria and fungi.

Dr Barbara Gorgoni [00:17:42] OK, and how have we traditionally then discovered antimicrobials?

Dr Soumya Palliyil [00:17:48] So, it was pretty much a lucky accident the way antibiotics were initially discovered. But we have used antibiotics throughout several centuries. So, if you look back to ancient Egyptian civilisation, for example, they have used extracts from plant and molds to treat infections in people. So, although they didn't really know the proper antibiotics, people have been using this in in various civilisations. But a proper antibiotic discovery is when Alexander Fleming discovered penicillin, which is an antibiotic which stopped the growth of bacteria when he was conducting microbiology experiments. So, this penicillin is a compound, which was produced by a fungi called penicillium notatum and this compound produced by this fungus stops the growth of bacteria. So, this is how the first antibiotic was discovered, and since then several new antibiotics were discovered from natural products. So, when I say natural products, these are the secondary compounds metabolic compounds made by bacteria or fungi, which will stop the growth of other bacteria or fungi. So, because there is always this kind of fight going on for resources when bacteria and fungi coexist. So initially, the way of discovering new antibiotics was by a method called empirical screening. You would screen for natural compounds,

fermentation products, microbial extracts and look for activity where these compounds are stopping the growth of bacteria. So, several antibiotic compounds were discovered that way, but this became quite a long process and a tedious process. and what was happening was most of the new compounds discovered later on were replicates of original compounds, so there were no new compounds being developed. Then scientists started moving away from that empirical way of developing antibiotics to more target-based discovering antibiotics. So, they would look at a particular pathway like cellular synthesis pathway or protein synthesis pathway, so these are quite essential for a bacteria or fungi to grow and survive in an environment. So, they would look at those targets or enzymes, which are crucial for the function of those pathways and then started looking for chemical compounds which inhibit these cellular pathways. So, this type of finding new antibiotics is called target screening, and this was a much easier way of finding new antibiotics because you are moving away from this natural product screening, which was just taking long time and tedious. So, these are the ways with which they started empirical screening and then moved on to target screening for developing or discovering new antibiotics.

Dr Karen Scott [00:20:58] So, can I ask a question about that Soumya as well? Because clearly the original way, the empirical screening where you're looking at existing microbes and trying to identify those that have activities against other microbes, because the reason, as you said, that they have these activities against each other is because they live in this competitive environment. So that also meant the other microbes had resistance to those activities that were being designed to compete against them. So that is the resistance to antimicrobials almost coexisted with the production of antimicrobials in different microbes living in the same environments. And this was being part of the problem. So as soon as we identified and started to develop a new antimicrobial using that empirical method, there was already resistance out there that could then be transferred into new bacteria. And that's why if you look at the timelines of antimicrobial development using that empirical method and the recognition of resistance, they're like two, three, four years apart. So, they're very quickly, almost as soon as we started introducing a new antimicrobial agent in medicine, we were starting to see resistance coming through. So, I just wonder if this new method, if you think that it's less likely for that resistance to come along so quickly because they are chemically synthesised molecules rather than existing molecules from the environment?

Dr Soumya Palliyil [00:22:39] Not really, so the target screening has its own limitations. And so, we have so many drugs in the market which came out of targeted screening, and again, that resistance built up quite quickly with the target screening. A lot of this is because we have to really consider the type of targets that we are looking for because sometimes if the target is really something which is crucial for the cell survival, the cell, the bacteria or fungi will start developing mutations to kind of circumvent that so that they can live in that environment. It's quite natural, this evolution is something which is a natural process, and it's something that you can't really put a stop to it. So even with the target screening, it certainly reduced the time period required for finding new inhibitors, but the problem of resistance never went away because these were targeting certain cellular pathways or, like I said, protein synthesis machinery. So, if you inhibit one pathway or one particular part of that pathway, they would there will be always mutations and the development of resistance as a result of targeting that pathway. So, it never solved that problem, the target screening. There were also a lot of other factors to consider because if you look at target screening, you're just looking at one particular enzyme, for example, in bacteria. So, if it needs to work in other species, you need to have the same enzyme present in other bacterial species. But at the same time, you should not have that enzyme as part of a mammalian cell or a human cell. Otherwise, what will happen is the same drug will have toxicity when you use it to clear infections. And there's quite a lot of things to think about or consider when you select a target. But like you mentioned,

the resistance development was something that we couldn't remove even with the target screening approach.

Dr Karen Scott [00:25:11] It's probably worth pointing out as well about the resistance development, because you mentioned to me before when we spoke about this, that when humans evolve, we evolve very, very slowly because our reproduction time is 20 years or something and microbes are quite different, aren't they?

Dr Soumya Palliyil [00:25:34] Yes. So, again that's a really good point. So, the mutations are constantly happening in bacterial cells, and they reproduce every 20 minutes. So, these mutations can be quite rare and let's say if it is one in a million chance of one mutation happening and, you know, as a microbiologist, Karen, how many bacterial cells cities are in a human body, you know, it's in trillions. So even with a one in a million chance of a mutation happening, this is a million mutation that could be happening in our human body. Plus, if you consider the replication time, which is 20 minutes within a day, you could have billions of cells with that particular mutation kind of getting reproduced and dominating a particular microbiological environment. So that fast rate of reproduction of bacteria is also one of the factors which contributes to antimicrobial resistance in such a vast speed.

Dr Barbara Gorgoni [00:26:50] OK, so having outlined all these issues, are there new ways then to develop new therapies for an effective and targeted treatment of infection?

Dr Soumya Palliyil [00:27:01] Yes, there are. So, we did discuss the limitations of targeted screening or the traditional of making or discovering new antibiotics. So, scientists are now looking into alternative therapies for infectious diseases, and much of these are specifically targeting the pathogenic bacteria or fungi and not kind of disturbing the rest of the good bacteria within the body. So, these types of drugs are called narrow spectrum antimicrobials, one such example is bacteriophage or bacteriophage therapy. So, this bacteriophage, in simple words, phage are viruses that infect bacteria, and they are quite specific in the sense that they do not infect human cells. So, we have human-invading virus, but this phage viruses are the ones which are specific for bacterial cells. So, there's quite a lot of traction gaining in this field that a lot of companies coming up with various ways of phage therapy and looking at specific pathogenic bacteria and treating them with these phages. Another way is making monoclonal antibodies for treating infectious diseases. So, I mentioned antibodies briefly in my introduction, the antibodies are soldiers of the immune system, and they are made by a particular type of immune cell called the B-cell. Antibodies have the ability to bind and either neutralise or kill invading bacteria or fungus. And so, what scientists have discovered over the years is you could make antibodies by immunising animals with the bacteria or fungi you are interested in. So, this method has been successfully used in treating wound infections during World War II, people used to immunise animals like sheep and horse with diphtheria toxin and then generate serum, which is a component of blood which contains these anti-diphtheria antibodies, and these were used to treat soldiers with wound infections. And this worked to some extent, but the problem was the kind of animal origin of these antibodies because they were produced in sheep or horse. Nowadays, with the advancements in molecular biology and biotechnology, we can make fully human monoclonal and monoclonal antibodies, and this type of treatments have been quite successfully used in treating cancer and autoimmune disorders. So monoclonal antibodies are highly promising therapeutic modalities for treating infectious diseases. We have shown it in a in a slightly different way in the last century, but now there are more ways of developing antibodies and making them much more potent for treating these infections.

Dr Barbara Gorgoni [00:30:14] And so what is stopping these new antimicrobials being used?

Dr Soumya Palliyil [00:30:19] So this is a complex problem, Barbara. It's certainly not science or innovation. As you can imagine, drug discovery takes a huge effort in terms of funding, and it takes several years to discover a drug and test it through various clinical stages and get it into the market. So, if you want to know in terms of cost, a company needs to invest something around the region of $1.5 billion to develop a drug. Okay, so that's a huge undertaking and with the resistance problem being discussed and how Karen was mentioning the speed at which microbes are developing resistance to existing antibiotics and there is much less chance of recouping the investment back. So, this put off Big Pharma's interest in developing new antimicrobials. The other issue is, again, I don't know whether you've heard about a terminology called antibiotic stewardship. So, what is happening is any of these new high-end antibiotics that's being developed will be kept in reserve as a drug of last resort, so it won't be straight away used in any infection, it would be only used in multi-drug resistant or pan-drug resistant situations. So, what is happening is companies spend so much money developing these drugs, but then that's not getting used, so that means they're not getting any revenue back. So that kind of stopped the development of new antimicrobials and it's purely because of lack of funding. Yes, that's something that we need to address, or government organisations need to address.

Dr Barbara Gorgoni [00:32:16] And so are there any of this closest to marketing them?

Dr Soumya Palliyil [00:32:20] So, there are around 40 to 50 new drugs in clinical development, but although that seems a lot that's nowhere near enough to keep up with the speed in which antimicrobial resistance is developing. So, we really need to have more effort and more funding in this area to develop new antimicrobial drugs. Currently, there's only a very small handful number of pharma companies that are interested in developing new antimicrobials. They've all exited from the space and they're more concentrating in much more economically beneficial disease areas, if you want to put it that way, like cancer and autoimmune disorders, which are much more chronic. So, you will be dependent, or you'll be using that drug for a longer time. And you can imagine a bacterial infection, or a fungal infection is for a short period of time, so would be using it for a shorter period and the returns are quite low. There are quite a lot of innovation and scientific discoveries happening in small and medium biotech companies. But clearly, this is not something you know, early stage of drug development is one thing, but to actually take a drug and take it through various stages of clinical trials, it's much more expensive. And at this stage, you need to have a big pharma taking on this drug and developing it through the trial stages and marketing it. So, there we have a real problem, a real gap that we need to fix. Some of these gaps are being fixed by the government organisations and philanthropic organisations coming into the picture, like the Wellcome Trust and Gates Foundation. So, they are all funding the early-stage discovery, but we really need much more, new models of initiatives from the government to attract more pharma companies back into the space and help with the later stages of drug discovery or drug development, which is the most expensive stage.

Dr Barbara Gorgoni [00:34:41] OK, so I really need to ask at this point, is it all doom and gloom?

Dr Soumya Palliyil [00:34:46] I'm sorry if we kind of painted that picture. It is a serious issue, it is something that we all should be looking at much more seriously and start to come up with solutions to it. Like we mentioned there are government organizations coming up with different economical models to fund antimicrobial drug discovery. So, the latest one announced by the UK Government was a subscription type payment. So, usually what happens is the companies get paid based on the volume of sales how much antibiotics has been used and then they get paid for that for that. But what the UK Government is proposing or introducing is a subscription type payment where there would be upfront

payment for companies developing drugs, which can be of use in the NHS. So that is a really good initiative and I'm sure that will encourage a lot more of pharma companies to come back into the space and develop new drugs. It's mainly in the clinical trial stages we need pharma input and in the space.
Also, it's quite encouraging to see government organisations, public sector academic groups and companies all coming together, forming consortiums for the early-stage development of new therapies, novel therapies like the ones that I mentioned previously, the phage therapy or antibody therapy, which is really exciting to see new science coming out. The science here is very strong again, the emphasis is all on new ways of funding this expensive drug discovery pathway so that we can get more antimicrobials in the market, which can withstand this resistance development problem.

Dr Karen Scott [00:36:53] I think that as well, I agree with Soumya. It's not all doom and gloom. I think we've recognised that the problem is out there, and I think that a big step was recognising the problem. And there's a global action plan that came out in 2015 and is updated on an annual basis and all countries in the world are joining together to try to get around this problem. And the important point to make is that any new drugs come out will be stewarded in a much better way than we have in the past. So, although we can't take back the resistance that's already out there, we can prevent that same resistance arising to such an extent with the new drugs that are being developed because we can really use them when we need to use them and not use them as indiscriminately as they've been used in the past. So, I think recognising all of that's been really important. And then there's also the World Antimicrobial Awareness Week that runs every year and that brings events out to schools and educates people right from a very young age, right through their lives. You'll see things when you go to your GP surgery. There are things about 'don't ask for antibiotics unless you really need them' and everything. So, I think public awareness of the issue is going to be a huge step forward to getting around this problem as well. So, the new inventions that Soumya has mentioned, combined with the increased awareness of the issue, I think together mean that we will survive, and it's not going to be the huge problem that it could have been. I mean, if we had sat back and done nothing, we would have been in the situation where we were no longer able to treat infectious diseases because they were resistant to everything, we could throw at them and that was a terrible problem that we were facing. But I think that we are not facing that anymore. So, yes, it's not all doom and gloom.

Dr Barbara Gorgoni [00:38:55] Excellent. And I think on this positive note, we should end. And of course, activities like this podcast having researchers like yourselves coming on and talking about the issue also helps towards the education and increased understanding for everyone. So, I'd like to thank you both very much, Karen and Soumya, for a fascinating insight into this very complex issue. And so, to our audience, thank you very much for listening. And remember that if you have any questions for our speakers, please email peru@abdn.ac.uk. And keep your ears open for our next Cafe Connect podcast. Goodbye!

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