Stop Bugging Me:

Challenging the spectre of antibiotic resistance

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Cancer scientist George Preston glances up at the clock. It's just gone 12:30. It doesn't feel like he's got time for lunch today, but he knows he has to eat and he's mindful that you need breaks from screen use to preserve the health of your eyes. He leaves his office in the University biomedical research facility.

As it his habit, George heads over to the cafeteria in the adjoining hospital. There is a small coffee shop in his building, but their selection of food is so limited he prefers to make the slightly longer trip to the more substantial eatery across the road. His plan is to grab a sandwich and take it back to graze on while he finishes the draft of the paper he's writing. Once he gets to the café, however, he notices Peter at the checkout, about to pay, with a full tray on his hands.

Suddenly the tyranny of the urgent is put to one side. Seeing his friend gives him the perfect excuse to procrastinate. He's going to regret it later, but the prospect of a break from work wins out.

'Hey Peter! So, you are around! You didn't answer the email I sent you Monday about having lunch this week, so I assumed you were on holiday'

'I wish! No, we've had a bit of a family crisis. Are you staying here for lunch?'

'Sure, why not?', replies George with a shrug.

'OK, I'll grab a table, then I'll fill you in with the gory details.'

As he waits for a panini to warm and takes furtive sips of his not-yet-paid-for coffee, George starts to worry about what might have occurred. Maybe something's happened to one of Peter's kids? When the panini is ready, he shifts over to the cashier. He takes his phone out of pocket and wafts it in the direction a contactless payment terminal, which offers a beep of grateful acknowledgement.

George picks up his purchases from the counter and sets off towards their usual place, but can't see Peter. Eventually he spots his friend towards the back of the seating area. By the time he gets over to the table, where Peter is already tucking into his own sandwich, George is fearing the worst.

'So Peter, what's up?', he asks, even before he's sat down.

'It's my aunt Ruth', Peter replies. 'She went into hospital a couple of weeks ago for a scheduled hip replacement operation but there were some complications. I didn't want to say over at the queue, in case I was overheard by one of our patients, but it looks like she's got an antibiotic-resistant infection, probably MRSA[1]'.

'Oh no, is she ok?', George offers as the obvious immediate question.

In some senses George is relieved to hear the issue is not with one of Peter's own children, but he knows that infections of this kind can be hard to shift. He understands that talking about these things in the cafeteria queue at a hospital is not the smartest move, especially if you're one of the local medics, and can see why Peter has chosen this more discreet table.

However, despite the personal nature of the situation, George's academic interest is piqued and he wants to know more details. But he holds back whilst he gives Peter a chance to respond to his initial query.

'Well, she's been running a fever, and there's inflammation around the wound, but they've switched her onto intravenous Vancomycin and think they've caught it early enough to avoid having to redo the surgery, which is a relief.

'Vancomycin's nasty stuff though, they wouldn't have put her onto that if they thought something else would work.'

'Yeah, she's in an isolation ward over at St Thomas'. They reckon she might be there for a few weeks.'

'So why wasn't your cousin Tony looking after his mum?', George asks eventually.

'He is now, but he's been away acting as a consultant on some big construction project in Dubai. It was him who rang me and asked if I could check up on her as the project was at a crucial stage and he couldn't just drop it and run. Actually, this will

[1] MRSA: Methicillin-resistant *Staphylococcus aureus*. It's a dangerous bacterium because it is resistant to a few of the most common antibiotics. It's usually contracted in hospitals.

make you laugh... When he rang me, Tony told me his *mum* had become resistant to antibiotics'.

'Eh-uuh!', George makes the wrong answer noise from a popular TV quiz show. 'Classic mistake! But scary – if someone as well educated as Tony doesn't realise that it's the bacteria that develop resistance, not the patient themselves, then no wonder other people get confused about aspects of infection. I'm always amazed how many people don't know there's a difference between bacteria and viruses, or realise that antibiotics don't work on viruses.'

'Of course, you used to do research in that field before moving to cancer, right?

'Yep, when I first went to SmartaPharma in the States, I was working on development of new antibiotics, but they decided to shut down the whole Anti-infectives Division[2]. A lot of my mates lost their jobs, but I was fortunate that the compound I'd been working on was related to an anti-cancer drug they were still interested in, so they kept me on. Actually, that was the point where I switched focus to oncology so, on a personal level, it was a lucky break for me.'

'I've never really understood why pharmaceutical companies aren't putting more effort into antibiotic discovery and development.'

'Oh. That's easy, Peter… "It's all about the money, money, money"', he sings to a tune vaguely reminiscent of Jessie J's song Price Tag[3]. 'No seriously, pharmaceutical companies are not charities. Rightly or wrongly, their primary responsibility is to make profits for their shareholders. Think of all that up-front investment; no-one is paying you through the R&D[4] phase or the clinical trials. Antimicrobial compounds simply don't offer enough scope for recovering that money, let alone turning in a profit. They may actually be the worst kind of drugs, from the point of view of a company wanting to make money out of them.'

Peter nods his head.

'You may be exaggerating a bit…'

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[2] As George has noted, antibiotics only work against bacteria. But there are plenty of infections caused by other organisms, such as viruses or parasites. People sometime talk collectively about the drug that work against these various organisms as antimicrobials or anti-infectives.

[3] The original lyric is "It's NOT about the money, money, money" – George knew this and was being witty, perhaps inappropriately under the circumstances

[4] Research and Development, the period during which a company goes from the first idea about a new drug through refinement, manufacture, animal testing and then moving into human trials

‘No, really. They have plenty of issues. We’ve already discussed one of them – bacteria develop resistance. If you spend ten or more years and millions of dollars producing an antibiotic but the bugs can become resistant to it in a matter of months, then it’s going to harm the usefulness of that treatment, and therefore your profits. Secondly, think about when and how often you take antibiotics. You only generally need them when you’ve got an infection, and only then for about a week. If you’re running a pharmaceutical company you want to be investing in something that people are going to be taking every day, for years of their life. Things like anti-cholesterol drugs, blood pressure medicine or asthma treatments. If you’re Director of a Pharma business you’re going to see what other people are doing and go after a “Me too”’.

Peter looks genuinely confused for a second.

‘The movement against sexual violence?’

‘No, are you being deliberately dense? A copycat drug! If you’re a Director at Company B and you see Company A are turning in a tasty profit on some wonder drug, then you’re going to look over and say “Me too, I want me some of that”. You try and develop a drug that’s as close as possible to theirs without infringing the other guy’s patent[5]. Take statins as an example. Until it fell out of patent in 2011, sales of Lipitor, the anti-cholesterol drug Atorvastatin, were worth about 13 billion US dollars a year to Pfizer[6]. Other companies see that and they think “Pfizer have done all the basic research, if we can develop something similar we are going to be able to get a slice of that cake in super-quick time because we’re not starting our research from scratch”. So the project managers over at Merck, for example, get their team working on something similar and come up with Simvastatin. And other firms do the same. Meanwhile interest in anti-infective fades into the background. Do you know how many new types of antibiotics, with novel modes of action have been launched in the last 50 years?’

‘I already knew it wasn’t loads, but the way you’re asking the question makes me suspect it’s very low. I’m gonna say ten, maybe?

[5] For more on Me too drugs, see https://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf
[6] https://www.the-scientist.com/the-nutshell/lipitor-patent-expires-41658

‘Lower! It depends a bit who you talk to, but it’s only, like, three or four new classes of drug[7] in the last half century. The fifteen years before that had been the golden age of discovery, when it seemed anyone could come up with a new antibiotic, many based on natural compounds produced by other microbes.’

‘So, the problem is lack of investment in antibiotic research?, Peter asks, ‘And here was me thinking resistance development was supposed to be caused by evil doctors like me giving out antibiotics to patients who didn’t need them, and the patients not finishing off their prescriptions!’, Peter has a glint in his eye, knowing very well that this is still a genuine issue.’

‘Don’t get me wrong, physicians giving into pester power and handing out antibiotics like sweeties just to get patients out of their door has definitely contributed to the problem… as you well know! But antibiotic overuse or misuse in medicine is only part the whole story; there’s a myriad of factors involved.’

‘Misuse in farming is also a big issue, right?’, Peter asks.

‘Yep, that too. It’s been far too easy to let casual use of antibiotics cover up for sloppy animal husbandry. So people wanting to pack extra chickens into their barns have put antibiotic in the water or animal feed to reduce the risk of an infection spreading through the flock. Then there’s also a culture of using antibiotics as growth promoters on the basis that energy the animals don’t spend fighting infection is energy they can turn into muscle development instead. That kind of usage has been banned in the EU since 2006, but it’s still widespread elsewhere in the world.’

‘In some sense we’ve all contributed to the problem by buying into the hype about antibiotics being miracle drugs that made bacterial infection a thing we could basically ignore. What’s that famous quote from the American Surgeon General in the 1960s?’

‘Sorry, I’ve no idea’, George admits.

[7] Linezolid (an oxazolidinone), Daptomycin (a lipopeptide), Bedaquiline (a diarylquinoline), and Retapamulin (a pleuromutilin) were all first licensed for human use during that period. However, some of these had actually been discovered before 1970, a point we will come back to in a moment. None of these drugs could be described as being household names in the way that penicillin, tetracycline or erythromycin might be. Their usage is also fairly limited. Teixobactin, a member of a new class of compounds, was first reported in 2015 but has not been used in the clinic yet.

‘It’s something like “infectious diseases are a thing of the past, the war against pestilence is won”[8].

‘Well I think it’s fair to say history has proven him wrong, hasn’t it! There’s definitely a problem with increases in antibiotic-resistant bacteria. This may be too close to home, given that your aunt Ruth is still undergoing treatment, but did you hear about that American woman who’d had several leg operations in India and came home with an infection that was resistant to 26 antibiotics[9]?

‘Twenty-six, wow! Thanks for that cheery anecdote. Hopefully Ruth won’t have anything like that...’

‘I’m sure she’ll be fine, Peter, don’t worry. But the story of that poor woman does highlight one of the other issues, which is the impact of travel in spreading infection. People, animals or even plants can be transported from one place to the other side of the world in a matter of hours, taking all sorts of infectious agents with them. That’s why this really is a global problem. People are especially worried about India because there’s a perfect storm of circumstances there right now, making it a real hotbed for antibiotic resistance development.’

‘What circumstances are you talking about?’

‘India has a large population with relatively poor healthcare infrastructure and a high burden of disease. Cheap antibiotics are easily available from chemists without prescription and they’re also used extensively and indiscriminately in farming[10]. All of which makes India the largest consumer of antibiotics in the world. Having said that, though, there are worries associated with antibiotic use in *lots* of developing

[8] The actual quote is “*It is time to close the book on infectious diseases, and declare the war against pestilence won*”. It is usually attributed to the US Surgeon General Dr William H Stewart. However, it is fitting that George couldn’t remember the exact quote or who said it, since careful investigation has found no record of Stewart actually making this pronouncement. However, research does confirm that this view was certainly prevalent amongst other scientist at that time. For more details see Spellberg and Taylor-Blake (2013) On the exoneration of Dr. William H. Stewart: debunking an urban legend *Infectious Disease of Poverty* 2:3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3707092.

[9] The woman, a 70 year old from Nevada, sadly died. The problem was caused by a multi-resistant strain of the bacterium *Klebsiella pneumoniae.* The case was reported in the journal Morbidity and Mortality Weekly https://www.cdc.gov/mmwr/volumes/66/wr/mm6601a7.htm.

[10] The list of problems in India is adapted from Antimicrobial Resistance: Is the world UNprepared? PLOS Medicine (September 2016) https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002130

countries[11]. There are plenty of places where people can buy antibiotics at shops or market stalls without any need for a prescription. People know enough about antibiotics to understand they are something that you can take when you're ill, but they are ignorant about dosage and pretty indiscriminate about the types of illnesses they take them for. Someone might take a couple of antibiotics if they had an infection, which won't be enough to clear that properly if it was a bacterium causing the problem, or they might equally take some for a headache or stomach pain whose cause is entirely unrelated to infection. I read in a recent survey that in some West African country[12], participants admitted to taking a medicine offered by a neighbour or friend without even asking what it was. And alongside that – as we were just discussing – you've also got the fact that the pipeline for new drugs *has* really dried up. I've got to admit though, I do find the rising awareness of antibiotic resistance a bit bizarre.'

'How do you mean?', asks Peter with his mouth full. While George is excitedly talking about a topic that he clearly still follows closely, Peter has been taking the opportunity to get on with his lunch.

'Well, as someone who's had an interest in this field for a while', George replies, 'what surprises me is that this really isn't new news. I remember writing to the Agriculture Minister back when I was a student to raise concerns about the use of antibiotics in farming[13]. So we've known about the risks for decades.'

'So what do you think has changed now, then?'

'Well I guess that the scale of the problem has reached the ear of the right people! I thought it was interesting that when the UK commissioned a big report on the impact of the antibiotic crisis they put an economist in charge, not a scientist[14]. It was an acknowledgment that antibiotic resistance is about more than a few individuals taking longer to get over an infection. There are financial implications and wider human

[11] George probably feels he's been politically correct by referring to India as a "developing country" rather than a "third world country", like many still do. Whilst that would have been a worse choice of phrase, it is generally considered better to talk about Low and Middle-Income Countries (or LMICs for short).

[12] The survey was actually conducted in Ghana https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0210716

[13] One of the current authors actually did write to the Chief Veterinary Officer during his PhD to raise exactly this concern. He wishes he could find the original reply, but the summary translated to "there, there dear, we know what we are doing".

[14] In July 2014, the economist Jim O'Neill was commissioned by British Prime Minister David Cameron to lead a Review on Antimicrobial Resistance. His team published their final recommendations in May 2016. See https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

costs that result from the problem. I don't know whether the UK's actions were the trigger, or whether they were just early players in a wider movement, but there was definitely a breakthrough moment in 2016 when the United Nations General Assembly flagged up antimicrobial resistance as a significant threat to achievement of their broader Sustainable Development Goals[15] and put out a major declaration on their commitment to tackling the problem.

'I didn't know there was an SDG on antibiotics.' Peter observes.

'Oh, for sure – It's a big issue. I don't remember the exact details, I can send you a link to the report online later if you like. But I know there are four or five main strands. Firstly, there's the whole matter of ringing the warning bell and getting the world to wake up and take note of the seriousness of the situation. Secondly', George counts on his fingers as he starts to summarise the key points, 'there's a recognition that prevention is better than cure – steps like improved hygiene and infection control, coupled with vaccine development, have a big part to play. Simple interventions like provision of clean water and encouraging handwashing can be disproportionately beneficial. Reducing the need for antibiotics reduces the chances of resistance developing.'

'But lots of places still don't have access to running water', Peter points out. 'This is one of the big unresolved things, and not only for the infections.'

'No doubt. There's lots to be done still in that area. Tied in with that, thirdly, there's the fact that we actually need solid data rather than gut feeling to monitor what's really happening. So there needs to be better surveillance and research, including the development of rapid and accurate tests to diagnose what's actually causing somebody's illness; is it viral or is it bacterial? And if it is bacterial, which organism is the problem, and is it resistant to specific drugs?'[16].

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[15] The UN set up Millennium Development Goals in the year 2000. They included eight basic points, from eradicating extreme poverty to reducing child mortality. The plan was to ensure that every country would reach them by 2015. Since this didn't happen, they were morphed into the Sustainable Development Goals in 2017, something that George doesn't seem to be aware of, which now include 17 objectives to be reached by 2030.

[16] Technically, the five action points he summarises are actually from the Global Action Plan on Antimicrobial Resistance, published jointly by the World Health Organization (WHO), the Food and Agriculture Organisation (FAO) and the World Organization for Animal Health (OIE) in 2015. That report can be found at https://www.who.int/antimicrobial-resistance/global-action-plan/en/ . However, the first statement in the report published by the UN in September 2016 was to reaffirm the five strategic aims of the WHO's plan. The development of new diagnostic tools is actually tied in the report with the discovery of new medicines, but fitted better to the flow of our story when linked to the collection of data.

Peter has finished his meal already and looks at George's food, mostly untouched. He's so caught up with the topic that he seems to have forgotten his lunch.

'You should pay more attention to your panini', Peter says. 'It's bound to be cold now!'

George looks at his sandwich like it just had appeared out of nowhere.

'Ah, yes.' He takes a quick bite but continues with his enumeration before he's finished chewing, in a way that he would never have done in the company of anyone except his old friend. 'Fourthly, we need to take good care of the drugs we've already got. So this is where the arguments about antibiotic stewardship and reducing the inappropriate use of drugs comes in. That includes restricting the use of antibiotics in farming and for pets as well as in human medicine. A lot of importance is being placed on what they're calling a One Health policy, with joined-up thinking and closer coordination across agencies promoting human health, animal health and care for the environment[17]. And finally, there is the importance of rebooting the programmes to find and develop new medicines. Boom, remembered them all!'

'Well done!', Peter claps briefly. 'All these years doing cancer research don't seem to have erased everything you knew about infectious diseases. But I thought you just said that there was no money to be made in antibiotic development… In which case, how's all that going to work? The existing financial models are not suitable, so this calls for a fundamental rethink of the way we go about incentivising research.'

'I don't know how that would happen, Peter. The pattern that works for most pharmaceuticals, where companies look to maximise profit by increasing volume of sales, isn't appropriate for antibiotics because we know that more exposure to these drugs leads to more resistance development.'

'But surely this is a wider problem. Becoming resistant or tolerant to a treatment, and needing to crank up the dosage over time, is a common experience with lots of medicines. Cancer treatments are the best example, and companies still make tons of money out of them.'

'Oh yeah, you can definitely develop resistance to all sorts of medicine. But in those cases it *is* cells in the individual patient that have become resistant. It is "contained", that's the main difference. That insensitivity isn't going to spread to the

[17] This was the motivation behind the joint report by the WHO, the FAO and the OIE mentioned above.

person in the hospital bed next to them. With infections it's the bug that develops resistance and they *can* get passed to somebody else, exacerbating the problem. Potentially making it global in the end.

'Yes, I see what you mean', Peter nods. 'Maybe this is how humanity ends, after all! Are our kids going to grow up in some post-antibiotic apocalyptic world, in which people die when they get some routine infection and doctors won't even attempt the kinds of surgery my aunt's had because the risks of complications are simply too high?'

George laughs at the way Peter has described this scenario, although it's not that far away from one of the potential futures.

'Well, I hope not', he answers, 'but the situation certainly is pretty serious, Peter, even if we joke about it.'

'I wasn't joking about it!', Peter protests. But then he quickly admits it: 'OK, yes, maybe a bit.'

'All right, laugh all you want, but I've seen experts quoting 700,000 deaths per year already due to antibiotic resistant infections and bandying around figures of 10 million extra deaths per year by 2050[18] unless we get on top of the problem. Obviously projecting that far into the future is always going to be more than a little speculative, but I've got no reason to believe that the figures are being hyped up. The point is that those are the kind of death rates there may be unless we start to act now.'

'I know, I know', Peter apologises. 'I'm aware there's reason for concern. There's been for quite a while, in fact. I can't help thinking there are echoes here of the whole climate change debate.'

'Yeah, the parallels to climate change are actually pretty strong – the experts have been offering warnings for years, as you said, but governments and the wider community, haven't been listening'.

'For one thing, it's proven tricky to get people to take the issue seriously because we're talking about future problems that people don't implicitly feel are real right now, even though the seeds of disaster were sown years ago. In that sense it is

[18] To the best of our knowledge this figure first appeared in the O'Neill Report in 2014 https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf, but has been widely re-stated since then

quite similar to global warming. Now it's five minutes to midnight, some people are suddenly in panic mode, but others are still only bothered about what's happening today or tomorrow. And, like climate change again, it's also going to need a combination of individuals taking more responsibility, whilst governments and other bodies also act at a more global level.'

'We don't learn from our mistakes… What could we do differently?'

'Well, that's the 64,000 dollar question[19] – no pun intended! There certainly does needs to be more money invested in this, but that in itself isn't sufficient, because profit is not an appropriate driving factor here. Having said that, I do think the last few years have seen us turning a corner, I certainly hope so.'

'Really?', asks Peter, surprised. 'From what you said so far, I thought we were already going down the drain... What's giving you cause for optimism?'

'Well, all of a sudden there's a whole bundle of new initiatives. With my background, I've got to be pleased that governments are finally taking the issue seriously, but there's also a sense of irony. As I said, work on bacterial infections was a poor cousin for so many years, compared to investment in sexier areas of research. Now suddenly controlling antibiotic resistance has become something you need to write into every grant application, whatever your field of research. I know sociologists who have shifted to working on patients' attitudes to antibiotic prescribing, and there's even been money given to architects to work on making ventilation in new homes better at cutting down the spread of bacteria[20]. For all I know there are people getting paid to write poems about antibiotics…'

'You're demonstrating your bias against Sci-Art projects again George! '

'Yes, you know how much I love them', he said ironically. 'I can't stand those schemes that seem to only serve as an excuse to tick a box confirming you've taken part in public engagement activities or, worse, look very like a scam to get some part-time work for the under-employed artist married to someone else in your department. But you're right, I was being flippant. There's definitely room for some significant public information being passed on in an entertaining way'.

[19] The expression "That's the $64,000 question" comes from an American TV gameshow that ran in the 1950s. The top prize was that amount of money. See https://en.wikipedia.org/wiki/The_$64,000_Question
[20] https://www.bbc.co.uk/news/uk-scotland-glasgow-west-40593962

‘See? It was not so difficult to admit it, was it?’, Peter jokes.

‘Well-conceived public engagement can certainly be useful, for sure. I’ll be the first to admit it. I read about a project in Ghana that was challenging exactly the types of issues I mentioned earlier. Apparently, dance is a really important way of story-telling in Ghanaian culture. The government there commissioned the country’s National Dance Company to create a musical to tour around rural communities sharing the importance of not buying antibiotics from markets or taking medicines passed on to you by a friend, and for chemists not to sell them unless the customer brings a prescription[21]. I can see the value of that kind of arts project, but not just another bloody way to represent the DNA helix.’

‘Sounds really cool! Well, it’s good to hear you’re not a complete cultural philistine, George. But that dance approach will only work in Ghana and similar cultures. We are still stuck elsewhere in the world.’

‘Yes, that’s probably true. But there are some other approaches being launched as well. For example, there are “thinking outside the box” incentives for pharmaceutical companies to find new products. There’s serious talk about the World Health Organisation, or whoever, rewarding companies with a substantial cash bonus, maybe a billion dollars, if they develop an entirely new class of antibiotic. That would compensate them if a collective decision is taken to park the new drug until it’s really needed, rather than introduce it into the market before the patent runs out’.

‘Much more effective than dancing, at least in the Western world… But I’m not sure I see the point.’

‘It’s very simple, George. Companies pay for research that will earn them lots of money in a short time. That’s market logic, it makes all the sense from their point of view. That’s why they invest so much on cancer research. Because they are allowed to ask for absurd sums or money for every new drug that has a marginal benefit’.

‘Business distorts priorities,’ Peter continues, You’re not going to see them put as much effort into developing a malaria vaccine, which is actually what the world really needs the most, because the returns on that are much less impressive. That should change, because it’s plain dangerous.’

[21] This project is discussed in a video The Power of Dance produced by the Wellcome Trust https://youtu.be/H1mE6evAEb8

Of course, Peter is right. George is aware that letting big pharma follow money's call can be dangerous, given the fact that they are an essential piece of the healthcare puzzle. Nevertheless, he truly believes that companies should be allowed to make their own decisions. He knows he won't convince Peter, but at least he will try to find a middle ground.

'I see your point', he says, 'but I think you are mixing too many concepts. Pharma companies are businesses, and they need to make a profit. That's a fact. If their goals don't align with what the world needs, that's why we have NGOs and big foundations, many receiving public money, that can fill the gaps[22]. They don't need to tell companies or anyone else what to do.

'It's not about *ordering* them what they need to spend the money on, of course. But little incentives can go a long way. For instance, there's this idea being floated that if your business develops an antimicrobial drug you could take the years of exclusivity that you'd have been owed via a patent on that new compound and transfer it to a different drug in your portfolio'.

'Sorry, you lost me there. What does that mean?'

'Let's say, after deduction of research time, you had maybe ten years of patent left to run on your new antibiotic. You could move that amount of time to the patent on you blockbuster arthritis medicine or asthma drug instead'.

'Genius idea!', Peter says. 'See, that's putting patent law to good use instead of just letting rich people get richer, I like that. It would probably net you a larger profit than you would have ever got from the antibiotic itself.'

'Yeah, but things are never that easy. I imagine that it would be a bone of contention with rival firms wanting to produce copies of your best-seller, especially the companies that specialise in making generics. However, if we are going to take this resistance challenge seriously, they may just need to suck it up.'

'These are all nice ideas, George, but is this all leading to any new antibiotics being produced or just wishful thinking?'

'Well, as you know, drug discovery is a long process. But I think there's genuine excitement about a few possible compounds. A drug called Zoliflodacin has just gone

[22] The Bill & Melinda Gates Foundation, for instance, have invested heavily in malaria research. So far, they have committed more than $2.9 billion to stop the disease.

into a Phase 3 clinical trial[23]. There's a lot of interest in that compound because it seems to be very effective against gonorrhoea. Rates of gonorrhoea in the USA have been labelled an "urgent threat" because they've shot up since about 2013[24] and there's an epidemic of strains resistant to many of the frontline drugs which is worrying people as it sweeps across the world. We're in desperate need of a new weapon in that battle, and it looks as though Zoliflodacin has an entirely new mode of action and no cross-resistance with any of the existing drugs[25].'

'OK, so the incentives are having some effect, then. That's good. Which trick did they use in this case to sweeten the deal to the company?'

'Zoliflodacin is actually a poster boy for one of those new funding models I mentioned. The trial is taking place in South Africa and Thailand as well as the USA, and is being part funded by the company that produced it, but in collaboration with a public-private partnership initiated by the World Health Organisation[26]. As part of the deal, assuming the trial is successful, the company gets exclusive rights to market the drug in high-income countries, but the WHO partner gets the rights in poorer countries[27]'.

'I love it', says Peter. 'So then Zolif-wotsit…'

'Zoliflodacin', George chips in.

'Yeah, that. Are there more examples of new antibiotics coming through? Because it sounds like we need a few more weapons in our arsenal, one new drug is not going to save the world…'

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[23] Clinical trials in humans involve three different phases. Roughly speaking, Phase 1 is checking for the safety of the medicine with a very small number of healthy volunteers (so this tells you nothing about whether it will be any good for patients). Assuming no problems emerge at this stage, the drug gets taken on to Phase 2 where it is offered to a slightly larger of patients, perhaps 200. Now you are looking at safety and efficacy. If it still looks promising, this is then scaled up to a Phase 3 trial with a larger and more diverse population of patients. Only after the drug has passed through all three stages and received formal approval can it be prescribed to patients beyond the trial cohort.

[24] Incidence of gonorrhoea increased 67% in the USA between 2013 and 2017 (Taylor et al, New England Journal of Medicine 2018 379:1835-1845)

[25] Basarab et al (2015) Responding to the challenge of untreatable gonorrhea: ETX0914, a first-in-class agent with a distinct mechanism-of-action against bacterial Type II topoisomerases. Scientific Reports 5:11827

[26] The trial of Zoliflodacin (also known as ETX0914) is being funded by Entasis Therapeutics and the Global Antibiotic Research and Development Partnership (GARDP).

[27] New treatment for drug-resistant gonorrhea to enter phase 3 development, 8th July 2017. https://www.healio.com/infectious-disease/antimicrobials/news/online/%7Bf01603b6-3d1d-4465-9d6f-1bb4f6cf36db%7D/new-treatment-for-drug-resistant-gonorrhea-to-enter-phase-3-developments

‘There’s Teixobactin which was only reported in 2015 but has generated real excitement due to both the way it was found and things it seems able to do. Lots of the drugs found in the 1950s and 1960s were natural products, as I said, and in those early days trawling through soil samples was a really productive strategy for finding organisms that made valuable drugs. But there was always a suspicion that there were plenty more goodies out there that we weren’t finding. One of the fundamental hurdles in that process was the need to grow the producing microbes in the lab. However, it turns out most soil organisms, possibly as many as 99%, simply won’t grow on agar plates[28] under standard lab conditions’[29].

‘99%, wow! I didn’t think it would be that much of a problem.’

‘Yeah, amazing, isn’t it? Now a team based out of Boston have managed to not only work out a way to grow some of those species, they’ve even managed to identify this new antibiotic Teixobactin.’

‘OK, so what was their secret?’

‘So, the key thing is obviously to keep the conditions as much like their natural habitat as possible.’

‘I could have told them that myself…’, says Peter.

‘It’s not like they weren’t trying from the beginning, but it’s easier said than done! Lots of studies have been done using new DNA sequencing methods to simultaneously check the DNA of all of the organisms that are present[30], but that just tells you there’s a lot of diverse stuff out there. To be really useful, you need to combine that with some way to actually pick out and keep the organism of interest.’

‘That sounds like a puzzle worth solving. How did they do it?’

‘They made a piece of flat plastic they called an isolation chip or iChip for short. It’s a little bit like the ones you’d use for doing a microarray[31] or next-gen sequencing

[28] Microbes are routinely grown on plates made with a jelly-like substance called agar, supplemented with whatever extra nutrients are needed

[29] Piddock (2015) Teixobactin, the first of a new class of antibiotics discovered by iChip technology? Journal of Antimicrobial Chemotherapy 70:2679-2680

[30] This approach, known as metagenomics, involves the study of DNA samples taken direct from the environment, without isolation of individual species present. When you are checking on just one gene or stretch of DNA, as is the case for 16S rRNA species identification, some people prefer the phrase metagenetics or even metabarcoding [see below].

[31] A microarray is one of the ways you can trap and study molecules like DNA and RNA as spots on a glass plate, https://en.wikipedia.org/wiki/DNA_microarray

chip[32], except this had hundreds of small holes going through it. Then they diluted a soil sample and dipped the iChip in it, so that they got roughly one bacterial cell per hole. They used a semi-permeable membrane either side of the plastic and then stuck it back into the soil for a month to allow cells to grow. Natural nutrients from the environment could diffuse into the hole, but the cells were trapped inside, so as they multiplied you started to get a colony of a single species in each well[33].'

'Very clever, but how does that tell you that they're producing a useful antibiotic?'

'Yeah, so far it doesn't, well spotted, Peter. Up to this point the method has allowed them to isolate species, but they haven't even determined what species they are, let alone if they do anything useful. So, the team sequenced the 16S ribosomal RNA genes[34] which is like a unique signature to identify which species they had. After that they grew them up in liquid cultures, rather than on agar plates. Once they'd had a few days to produce anything interesting, small amounts of the liquid were dropped onto *Staphylococcus aureus*[35] to see if any of them had killing potential[36]. If anything looked interesting then they investigated the species more thoroughly, and that's how they ended up finding this new compound. And they're really excited about what it seems to be able to do. It's too early to have any clinical data yet, but it looks in lab tests as though it's better than Vancomycin, the drug your aunt's being given, at killing Gram-positive bacteria[37].'

'That's encouraging! No benefit to Ruth, of course, but good that we're starting to find these new compounds.'

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[32] DNA sequencing was made most famous by the human genome project, but the technique that was used at that time has actually been superseded by several methods that are thousands of times more effective (faster and cheaper) these are sometimes known collectively as "next generation sequencing".

[33] This technique was first described by Nichols et al (2010) Use of iChip for high-throughput *in situ* cultivation of "uncultivable" microbial species, Applied and Environmental Microbiology76:2445-2460

[34] 16S ribosomal RNA is an essential component of the system that allows bacterial cells to read their DNA. As such it is always present, whatever the species. Very fortunately for us though, it has a section of its own gene which can vary a lot between species. This means that we can use this information to identify the specific bacterial species.

[35] *Staphylococcus aureus* is a bacterial species that can cause nasty infections.

[36] George's description here actually misses out a couple of steps, but it's close enough for our purposes.

[37] Bacteria are generally split into two large groupings terms Gram-negative and Gram-positive based on a staining test developed by a Danish scientist called Hand Christian Gram. The different response to the stain reflects fundamental differences in the cell wall of the bacteria. This is of relevance to our discussion here because some antibiotics are effective against Gram-positive cells but not against Gram-negative, whilst the reverse is true for other drugs.

‘So, that’s another interesting thing – sorry, you can see you’ve got me onto one of my favourite topics. A lot of the current impetus is not on *new* drugs, as such, it’s about going back to look at *old* drugs. There’s real interest in resurrecting drugs that were previously abandoned by the companies that were developing them.’

‘You mean the ones left high and dry when the likes of SmartaPharma closed down their research units?’

‘Yes, in part, but it’s more fundamental and more exciting than that, or more desperate, depending on your viewpoint. Drugs have been abandoned at different stages of production for all sorts of reasons. Sometimes, as you suggest, it was because, the emphasis of the company’s research changed or maybe they were bought out by a bigger player who wasn’t interested in pursuing this compound. There were all sorts of reasons. But at other times is was because the drug had side-effects for the patient, or maybe it wasn’t as good at challenging infections as a drug we already had.’

‘I see where this is going’, Peter says. ‘Those decisions were made back in the halcyon days when we appeared to be on top of infection control and felt able to pick and choose. But those days are gone.’

‘Exactly. Beggars can’t be choosers! Now we might have to say “ok, this new drug X isn’t as effective as antibiotic Y was under perfect conditions. But these are not perfect conditions; the species we need to treat has become resistant to Y and so we need to invest effort into developing drug X after all”. Or maybe we’ll have to do a new costs/benefits analysis and say “yes, there are unpleasant side-effects with drug Z, but without it the patient is going to die, so let’s give it a go”.’

‘Right. It’s like classic chemotherapy drugs. They have very nasty side effects, but the alternative may be letting the patient die, so it’s still worth using them. It’s all a balance: if the need is higher, you can tolerate higher unwanted consequences. So, what happened, then? Did they already find a good antibiotic going over the discarded ones?’

‘There’s been a famous example of one company successfully picking up somebody else’s cast-offs, yes. Have you heard of Daptomycin?’

Peter shakes his head, ‘Can’t say I have, no.’

‘OK, well Daptomycin is another of these compounds that started life as a natural product from a soil microbe. It was being developed by the American pharmaceutical giant Eli Lilly in the late 1980s and early 1990s. Lab tests were promising, they took it into clinical trials, but they hit a brick wall in Phase 2 due to muscle toxicity. At about that time the company were thinking of moving away from random screening of natural products to a more genomics-based approach[38], and to cut a long story short, Eli Lilly decided to stop work on Daptomycin.’

‘I can see why they dropped it.’

‘Yes, it made sense at the time, I agree. And that might have been the end of it, but one of the scientists who’d been working on the project included discussion of the drug in a presentation he gave as part of the interview process with a different firm, called Cubist. The latter liked both the scientist and the product and eventually wrestled both away from Lilly. They tweaked the way it was delivered to patients, principally reducing the administration from twice-a-day to once-a-day, and those changes were enough to sort out the muscle problems.[39]’

‘As simple as that?’, Peter asks.

‘Incredible, isn’t it?’

‘Sometimes it just takes a bit more tinkering.’

‘But it’s difficult to predict when this ‘tinkering’ is going to be short and cheap, with a happy ending, or a long and winding process that’s going to take you nowhere. You really can’t blame companies for making these strategic decisions.’

‘I guess.’

‘Well, as a result of this extra work, and a bit of luck, Daptomycin was approved for use against certain infections. It’s that kind of success story that people want to replicate now. I read recently that a crowd-funded project has allowed scientists to set up an open-access database that’s got details of all the potential antibacterials going

[38] When you are trying to develop a new drug you need to go fishing for “lead compound”. A lot of this process involved quite random screening. The rise of DNA sequencing was supposed to throw up a more logical, information-driven approach. However, so far, this has not been as successful as was hoped.

[39] Eisenstein et al. (2010), Daptomycin: From the Mountain to the Clinic, with Essential Help from Francis Tally, MD, Clinical Infectious Diseases 50:S10–5

through clinical trials at the moment, plus information about over 800 compounds that were discontinued[40].'

'That all sounds much more collaborative and open than drug companies used to be. Quite refreshing to see them changing their ways!'

'I agree it is, Peter, and maybe that's an acknowledgement of the seriousness of the problem.'

'But I think that's not going to be enough. Alongside all that cool drug development, there has to be a push for improving diagnosis, so that you know exactly what organism is the cause of an infection and whether it is already resistant to any of the front-line antibiotics.'

'Yes, that's essential', George agrees. 'Compared with some other medicines, antibiotic prescriptions themselves have historically been quite cheap, whereas the diagnosis process has been more expensive and time consuming. Hence the tendency for doctors to make a best-guess of appropriate medicine or give you a "broad spectrum" antibiotic that will work against a range of possible suspects, rather than one tailored specifically to the actual culprit.'

'Yes, we have to stop that. And you can be sure that I've already been doing that for years.'

George smiles at how Peter reacted.

'I never doubted it, Peter!'

'I understand that we need to cut down unnecessary opportunities for bacterial to become exposed to powerful antibiotics. And I'm not the only medic that sees that. There's plenty now that understand the issue.'

'Of course. I'm convinced that the tide is turning. But, again, this is only one of the issues. We need to attack from all fronts. That's why there are also concerns to cut down the release of antibiotics into the environment. A recent study found significant levels of antibiotics, including some big-hitting drugs present in over 70 major rivers around the world[41].'

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[40] The AntibioticDB.com database was funded by Antibiotic Action (see Farrell et al (2018), Revitalizing the drug pipeline: AntibioticDB, an open access database to aid antibacterial research and development. Journal of Antimicrobial Chemotherapy 73:2284-2297).

[41] World's rivers 'awash with dangerous levels of antibiotics' https://www.theguardian.com/society/2019/may/27/worlds-rivers-awash-with-dangerous-levels-of-antibiotics

‘But some of that release is inevitable, George. Whenever someone is taking a course of antibiotics, some of the drug is going to pass through them unused into the sewage system.’

‘Naturally, that part is not going to change, although giving shorter courses of antibiotics will clearly cut that a bit. Did you know, by the way, when scientists were first trialling penicillin for human use back in the 1940s, it was in such short supply they actually collected it from the urine of the first patients so they could reuse it for someone else?’

‘Yeah, I heard that story before. Gross.’

‘…But effective. There’s quite a bit of unused drug that gets washed away with urine. So, some antibiotic is going to get into the water that way. Unsurprisingly, I guess it’s medicines for treating urinary tract infections that are most commonly associated with domestic sewage. But there also needs to be better education and monitoring to make sure both hospitals and the companies that manufacture antibiotics take more care to avoid much the release of these compounds into the environment. Sadly, India is in the spotlight there again, but for all the wrong reasons; there are a lot of factories making generic copies of drugs and studies of neighbouring lakes have demonstrated shocking levels of antibiotic-resistant bacteria[42].’

‘Yes, that needs to be carefully controlled, of course. And what do you know about phage therapy? I heard something about it being a promising alternative to the classic antibiotics. Do you know how it works?’

‘A bit’, George admits. ‘It’s not quite the same as the stuff I used to work on, but I’ve read some of the literature on it.’

‘What I saw was a news report, something about a girl that got treated successfully with a virus found on rotting eggplant, I think. Was that it?’

‘Yes, that aspect of the story really seemed to catch the imagination of most of the journalists that covered it’, says George nodding his head dismissively. ‘I think the more formal version is that there was teenage girl with cystic fibrosis was dying of a bacterial infection, despite having a double lung transplant. As a last-gasp attempt to

[42] How antibiotic resistance in driven by pharmaceutical pollution. New Scientist (22nd May 2019). https://www.newscientist.com/article/mg24232310-900-how-antibiotic-resistance-is-driven-by-pharmaceutical-pollution/

save her life they gave her an experimental treatment with a cocktail of three bacteriophages[43]. One of the phages was the one they'd found on the mouldy eggplant and nicknamed Muddy. The other two had been tweaked to switch them from a dormant "temperate" version into the lytic version that cause bacteria to burst open and die. The treatment was a long shot, which is why the doctors were as surprised as everyone else when the approach was a success and she's survived[44].'

'But the phage therapy didn't cure her cystic fibrosis, of course.'

'No, she's still got the underlying condition, but the treatment with phages has brought under control the bacterial infection which she'd had for years and was the reason she needed the transplant in the first place.'

'That's a really clever idea – using a virus that only attacks bacteria to treat an infection without harming the patients. It's amazing that no-one thought of it sooner.'

'Well that's one of the fascinating things about this story, Peter. There was quite a lot of interest in this strategy back in the early years of the 20th Century, but that declined once antibiotics became available. Well, more specifically, it declined in the West; doctors in Eastern Europe and the former Soviet Union carried on developing phage therapies, but their work has largely been ignored by Western medicine.'

'How come?'

'The Soviet government was always quite secretive about the work, so before the fall of the Iron Curtain no-one was really sure what was happening. Then, when studies were published they were often in Russian and easily overlooked because, as you know, English is the standard language for most scientific journals. And then, even after the end of communism, the research was treated with caution because it hadn't been conducted according to the standards expected of clinical trials in the West.'

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[43] Bacteriophages (phages for short) are viruses that attack bacteria. There is some controversy in the scientific community should be bacteriophage or bacteriophages (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109450). Here we have used bacteriophages and phages as the plural form, not least to make it clearer to the reader whether we mean one or many!

[44] In 2018, fifteen year old Isabelle Holdaway was treated with a cocktail of phages from a library of the viruses being accumulated by a scientist at the University of Pittsburgh. The study was written up in the journal Nature Medicine (https://www.nature.com/articles/s41591-019-0437-z) but it was picked up widely by the newspapers (e.g. https://www.theguardian.com/science/2019/may/08/teenager-recovers-from-near-death-in-world-first-gm-virus-treatment)

‘Isn’t that’s kind of ironic though, because that girl who got treated using Muddy and his friends[45] wasn’t part of a clinical trial.’

‘I know, right. That was a last roll of the dice scenario and it happened to work. But it’s not exactly unusual. We’ve seen it other times. Either way, it does demonstrate that phage-based treatments have got genuine potential and it will definitely boost enthusiasm for more thorough clinical trials. The eggplant case does also highlight one of the things that has held back the phage therapy approach.’

‘What’s that?’

‘It’s the fact that phages generally have a narrow host range; they only affect one or two specific bacterial species. Now, that’s a bit of a double-edged sword. It’s a good thing because it reduces the likelihood of other organisms such as our “good” gut bacteria being affected, causing diarrhoea which a patient often gets when they’re taking antibiotics. But the downside is the process of picking exactly the right phages to target your infective agent takes time. Sadly the researchers in this case didn’t manage to track down the right phages in time to save a second potential patient and that person died.’

‘And presumably the reason for giving a cocktail of phages is to reduce the likelihood of resistance developing?’

‘Correct, Peter – it’s the same rationale as any combination therapy. The bacterium being targeted is unlikely to develop resistance to several phages simultaneously. Plus, if the phages used do have a slightly different host range then there’s a higher probability that at least one of the others is going to be right to challenge the infection. And there’s also another thing in favour of using phages as a means of treating infections: they kind of control their own dosage.’

‘How do you mean?’

‘Phages kill the target bacteria by basically turning them into factories for making more phages and causing them to burst open when it’s time to release the baby phage.’

‘Like most viruses always do.’

‘Yes, precisely. They can increase their own concentration by replicating in a way that an antibiotic drug doesn’t. However, the more host bacteria get killed, the

[45] The other phages in the cocktail had also been given exotic names, they were ZoeJ and BPs

less phage-factories there are available, and so the number of phages will also go down. That's bad news if you're a phage species set on world domination, but it's great news from an infection control point of view – once you've cleared the bacteria that was causing the problem, the phage population dwindles away too.'

'Neat. That's much better than antibiotics! Sounds like going back to the old ways may actually be the answer…'

'An answer, certainly. Improving hygiene, reducing infection, reducing inappropriate use of antibiotics in both humans and animals… All of these are parts of the solution. Education of the public, and of doctors, is crucial. But most of it's not exactly rocket science! There are some creative things to do in terms of incentives to promote investment in new drug development and in better diagnosis but there's no time for fannying around.'

Peter nods, then pulls his phone out from his pocket and looks at the screen.

'I'd better go, there's still a couple of urgent things I need to do this afternoon'.

George also looks at time.

'My goodness! I didn't think it was so late! See what happens when you get me talking?'

'I didn't do anything!', Peter says raising his hands. 'You wind up yourself without help, when a topic interests you.'

'Guilty as charged!', George admits.

'So much so that you forgot to eat…'

They look at George's plate, still with most of his food intact.

'No problem', says George waving his hand. 'I'll take it with me and I'll finish it while I type the paper I'm working on. Send my best wishes to your aunt. I hope she makes a speedy recovery!'

'OK, cheers. I'll let you know how she's getting on.'

From: Peter Williams <Peter.Williams9Z9@gmail.com>

Sent: 30 October 2019 20:13

To: GP0987@hotmail.com – Dr George Preston

Subject: She's home

Aunt R made it home OK. Got rid of the nasty bug. It's not the end of the world: the antibiotics still work! :) Call you sometime next week for lunch?

Cheers,

P