EDITORIAL

Antibiotic resistance

Netflix, HAL 9000 and the $100 billion question

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With Yuval Noah Harari's 'I told you so' still ringing in our ears and the battlefield still ablaze, one cannot help but wonder what the next microorganism assault on humankind is going to involve.[1] While we are still fully engaged on our main front, another old enemy is gathering strength on our flanks. Bacterial resistance has been described as the single most important threat to public health in the 21st century.[2] The United Nations interagency group on bacterial resistance estimates that drug-resistant disease could rise from a current figure of around 700 000 deaths per annum to around 10 million a year by 2050, if we don't act.[3] The six most common bacterial pathogens in orthopaedics are currently all on the CDC (Centers for Disease Control and Prevention) 'Urgent' or 'Serious' threat list.[4] A meta-analysis estimated that 39% to 51% of surgical site infection in the USA was caused by bacteria that are resistant to the standard prophylactic antibiotics.[5] Our primary tool against resistance is antibiotic stewardship programmes. But will it solve the problem?

Traditionally, resistance was thought of as a real-world example of evolution by natural selection.[3] We now know that this type of vertical transmission of resistance genes represents only a small part of the picture. Horizontal transmission, with the sharing of genetic information among the same generation of bacteria, drives the process. And the information can also be shared with bacteria from other species. Thus, exposure to antibiotics may induce resistance in our native commensal bacteria, which can then serve as a library of resistance genes for invading pathogens.[6] With this understanding, the emphasis on antibiotic stewardship and rational prescription is certainly sensible. In particular, the use of prophylactic antibiotics has come under fire. A recent example from our field is the recommendation that Gram-negative antibiotic prophylaxis should not be used routinely in grade III open fractures.[7] The authors state that while most infections are admittedly caused by Gram-negative organisms, there is insufficient evidence to suggest that the use of aminoglycosides makes a difference. It seems that having a placebo arm in future randomised controlled trials might be prudent.

However, the problem goes beyond simply rationalising medical use of our available agents. Around 73% of all antimicrobials sold on the planet are used in agriculture and in animals raised for food.[8] The increased global demand for dietary protein has translated into a rapid growth expansion of intensive animal production, with Africa seeing a 64% growth over the past 20 years. There has been a dramatic increase in the number of resistant pathogens in animals, and evidence suggests that this trend also contributes to increased antibiotic-resistant infections in humans. In this context, antibiotic stewardship in the medical fraternity is not enough. There needs to be a global awareness of the threat, and all communities need to get involved to address the issue at the level of our entire ecosystem.[3]

The optimist might say: 'Don't worry, look what the guys in R&D did with the COVID vaccines, we will just get some new antibiotics.' Maybe not. The estimated cost of developing a new antibiotic agent was estimated around US$1.5 billion in 2017.[9] On the other hand, the estimated yearly income from an antibiotic's sale is in the region of $45 million – so, a possible return on investment in about 33 years, if resistance does not develop. And typically, the company is only given about five to ten years of exclusive rights; then the generics enter the fray. Profit depends on volume and price, but neither is controlled by the pharmaceutical company. Stringent antibiotic stewardship programmes control volume, while government establishments regulate the price based on the reasonable cost-benefit ratio principle. This is the chief reason why many large pharmaceuticals companies are abandoning the fight and looking at other more lucrative product lines. Musculoskeletal drugs are estimated to be around 11 times more profitable.[2] AstraZeneca announced that they were halting the development of new antibiotics in 2016; Novartis and Sanofi followed suit in 2018.[2] In December 2018, there were only around 11 antibiotics in development for the treatment of pathogens in the WHO critical threat list.[10] Considering that only about 3% to 5% of antibiotics in the pre-clinical phase of development make it to the marketplace, the situation certainly seems dire.

The future of our primary weapon against bacteria may now be in the hands of healthcare economists trying to convince funders and policy makers. This has yielded a few finance programmes aimed at stimulating the antibiotic development pipeline. The CARB-X programme, led by Boston University and funded by several governmental organisations in the US, UK and Germany as well as charities like the Bill and Melinda Gates Foundation, has invested $325 million in 86 innovation projects around the world. The International Federation of Pharmaceutical Manufacturers and Associations' AMR Action Fund is backed by over 20 major pharmaceutical companies. It is expected to invest US$1 billion in antibiotic development and hopes to bring two to four new antibiotics to the clinical platform by 2030. However, the fundamental factors that make antibiotic discovery such an unattractive option for investors remain unchanged. Alternative funding models are therefore being considered. The so-called 'Netflix model' involves healthcare providers, like national health departments, paying a subscription fee for the development and then use of new antibiotics. The UK is aiming to award two contracts to pharmaceutical companies using this model and the first instalments will already be paid during the expensive research and development phase.

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Another possible solution could be to reduce the cost of the research and development phase. The data scientists have now entered the race, causing a major paradigm shift by creating a new pipeline for antibiotic discovery. Traditionally, antibiotics were found testing soil samples containing bactericidal compounds produced by other microbes.[11] Stokes and colleagues recently used machine-learning algorithms in the search for novel antibiotic compounds. They trained a deep neural network capable of predicting molecules with antibacterial activity and searched chemical compound libraries comprising more than 100 million molecules. Their artificial intelligence (AI) model was able to identify eight antibacterial compounds that are structurally distant from known antibiotics.[12] They named the most promising candidate molecule Halicin, after the sentient computer 'HAL 9000' in Arthur C Clarke's *2001: A Space Odyssey*. 'In silico' (i.e., an experiment performed on a computer) drug discovery is not a new idea, but until now the predictive models were not sufficiently accurate. Previously, molecules were represented as vectors (the basic unit used for computational arithmetic in AI) reflecting only the presence or absence of certain chemical groups. However, the new neural networks can learn these representations automatically, mapping molecules into continuous vectors which are subsequently used to predict their properties.[13] In simpler terms, it could possibly be thought of as adding an n-dimensional space to the vectors representing coordinates.

Other scientists are exploring alternatives to antibiotics that target either the bacteria themselves or the processes they use to attack their host. The Wellcome Trust recently commissioned a portfolio review of antibiotic alternatives. They identified 19 possible approaches for systemic use that justify further investigation.[14] Tier 1 approaches were defined as options in the clinical phase of development. Antibodies, targeting either the pathogen or their toxins, have considerable basic science backing and were the top contender for making a clinical impact. The development of prophylactic vaccines is also relatively far advanced (phase 2 and 3 trials ongoing) but have not yielded the much-expected benefits. Vaccination against *Staphylococcus aureus* infections, for example, have mostly failed in human trials.[15] Probiotics might provide some protection against antibiotic-associated diarrhoea, but might also be useful as an adjunct to other therapies (like phages).

Bacteriophages (phages, either wild-type or engineered) are the natural enemy of bacteria and have the potential to make a high impact as an antibiotic alternative. Their versatility of application and antibiofilm activity make them an attractive option and their use has already found some traction in Orthopaedics. Onsea and colleagues have described their protocol and experience with bacteriophage treatment in four cases with severe difficult-to-treat musculoskeletal infections.[16] The procedure is quite complex and involves intraoperative and postoperative administration through an irrigation system (reminiscent of the Lautenbach method) three times a day for seven to ten days. As bacteriophages are host-specific, a cocktail of several different phages was used. After a single course of phage therapy with concomitant antibiotics, there was no recurrence because of the original causative strains. Several therapeutic and preventative strategies are also being investigated in periprosthetic joint infection.[17] Phage lysins are the enzymes produced by bacteriophages to break down the target bacterial cell wall. They are currently considered to have the greatest potential of all the antibiotic alternatives due to their anticipated clinical impact and feasibility as a therapeutic approach. A phase 3 trial of a lysin acting on *S. aureus* (aptly entitled DISRUPT) is currently underway and could be eligible for registration by 2022.[18] Phage lysins also have great potential as adjunctive agents due to their potent biofilm eradication ability, synergistic effect with antibiotics, and low propensity for the development of resistance. Antibiotics depend on an appropriate host-immune response for success. Immune stimulation has been proposed as an adjunct to shift the balance in favour of the antibiotics. Currently, the focus is on repurposed drugs and bacterial extracts to induce the expression of innate antibacterial peptides. With a high potential for side-effects and response varying among different individuals, this development pathway will probably be more complicated.

Tier 2 antibiotic alternatives were defined by the expert group as approaches in the pre-clinical phases of development.[14] Here, antimicrobial peptides, host defence peptides and antibiofilm peptides are leading the chase. Antimicrobial peptides (AMPs) are found in most organisms, including fungi, plants and animals, and form an indispensable component of our own immune response.[19] They depend on the fundamental differences between prokaryotic and eukaryotic cells, and the typical mechanism of action is thought to involve integration of the peptide into the bacterial cell membrane thereby disrupting it, causing cell lysis.[20] AMPs have been investigated in clinical trials, with disappointing results, and many projects have been abandoned. Originally thought to exhibit broad-spectrum activity against Gram-positive and -negative bacteria, new evidence seems to suggest a somewhat more intricate model. AMPs are now known to exhibit high levels of specificity, genetic variability and functional diversity. This complexity results in an estimated price tag of approximately £600 million to get one successful product to clinical practice.[14]

Then there are some outside contenders.[14] Much of the morbidity resulting from bacterial infections is a result of the host's inflammatory response, and selective immune suppression might curtail that. Gene therapy is theoretically an option. Anti-resistance or anti-bacterial nucleic acids could possibly be delivered by transmissible genetically modified vectors inducing altered gene expression in the bacterial targets. Other novel approaches include custom-made RNA-guided nucleases (RGNs) targeting specific DNA sequences delivered by bacteriophage or plasmids and liposome decoys for bacterial toxins. However, these approaches are still viewed as somewhat speculative in nature.

During the Second World War, penicillin was introduced to treat infections, both in the field and in hospitals across Europe. Its widespread success earned it the title of 'the wonder drug' and Alexander Fleming a share of the Nobel Prize for Medicine in 1945.[21] Aside from the antibiofilm peptides which were discovered in 2013, the rest of the top 10 current antibiotic alternatives candidates have all been around for more than 15 years.[14] Funding, again, seems to be the major stumbling block. The Wellcome Trust review panel fittingly captured the level of commitment needed in their closing remarks by recommending an investment somewhere between that of the Large Hadron Collider (£6 billion) and the International Space Station (£96 billion) in antimicrobial therapy. Let's say roughly $100 billion...

Where is the money going to come from? If we move towards the 'Netflix model', it may put pressure to invest on other countries who will not want to get left behind. But where would this leave us in middle- and lower-income countries? It is essentially the same problem we are currently facing with the COVID vaccines. On the positive side, this global challenge is spurring on innovation and creative thinking. And it appears that science will be responsible for the solution. However, this time, it seems highly unlikely that we are going to find it on someone's messy desk.

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