Antimicrobial resistance and the race to find new antibiotics

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The race is on for researchers to develop new classes of antibiotic to tackle the global crisis of increasing antimicrobial resistance (AMR). But with few new antibiotics against Gram-positive bacteria becoming available in recent years, and no new class of antibiotic for Gram-negative infections for more than 40 years, what hope is there on the horizon?

Never has a race against time been framed with such dire warnings of the consequences of failure. But the quest to discover new antibiotics or, at least, find a way of holding back antimicrobial resistance (AMR) is a stark matter of life or death. Ten million deaths a year by 2050, according to the latest accounting.¹

Superbugs overpowering medication is a dilemma snaking through the corridors of political power and racing through hospitals and GP surgeries in the UK. Common infections such as pneumonia will kill again, warns Dr Margaret Chan, director general of WHO, adding: “On current trends, a common disease like gonorrhoea may become untreatable. Doctors facing patients will have to say: ‘I’m sorry – there’s nothing I can do for you’.”

The United Nations elevated AMR to crisis level at a meeting at its New York headquarters, on 21 September 2016, signalling unprecedented co-operation from heads of state, who signed up to tackle the root causes of AMR.²

The global fault-lines of antimicrobial resistance – unregulated use, prescription profligacy and food-chain contamination among others – have led to a procession of doom-laden predictions with AMR even being ranked alongside terrorism as a threat to mankind. But, despite the bleak outpourings, there is cautious hope for the next generation of antibiotics.

Laboratories are humming late into the night exploring new discoveries, ingenious modes of action and the repurposing of existing drugs to roll back the antimicrobial resistance frontier. The novel use of some existing drugs, including those available over-the-counter, to energise antibiotics is showing promise with a topical nail fungal cream, a diarrhoea treatment and the active ingredient of the spice turmeric all contenders for a new class of antimicrobial resistance breakers designed to prolong current antibiotic use while new therapies are being pursued.

Governments are also discussing how to recalibrate reimbursement systems to encourage more industry research and development and global awareness campaigns have been launched, such as WHO World Antibiotic Awareness week, to shake all sections of society from inertia.
New antibiotic candidates that offer potential

The scientific wires are crackling with hope that the long antibiotic barren spell is about to end. A team from Northeastern University’s Antimicrobial Discovery Centre, in Boston, USA, believes its small-molecule antibiotic, teixobactin, can thwart common bacterial infections such as those caused by Clostridium difficile, Mycobacterium tuberculosis and Staphylococcus aureus. It is derived from microbes found in soil, long-term targets for potential antibiotics that have previously failed to grow in laboratory conditions. The Northeastern programme developed an electronic device – an assembly of plastic plates called the iChip (isolation chip) – which cultures micro-organisms in their natural habitat and isolates their antibiotic chemical compounds. Teixobactin could be in clinical trials next year and the iChip technique is being hailed a game-changer as it will allow scientists to explore the array of micro-organisms teeming in the soil for new prospects.

Teixobactin kills Gram-positive bacteria but is not active against gram-negative bacteria, such as Escherichia coli, which are particularly complex foes. But PhD student Shu Lam has discovered a novel way of targeting Gram-negative bacteria using star-shaped polymers, officially titled structurally nanoengineered antimicrobial peptide polymers (SNAPPs). Applying the engineered peptide polymers to the bacterium causes its protective cell wall to destabilise and puts stress on the inner cell, which has, until now, been hard to reach for existing drugs. The extra good news is that these polymers are easy to produce in large numbers.

Shu, a 25-year-old member of a research team based at the University of Melbourne’s polymer science unit, says: “We came upon these peptide molecules that are produced by our bodies as part of the natural immune system to defend against bacterial infections and we thought we could possibly mimic this system by making peptides in a polymer form easily in the lab. We looked at how these peptides target bacteria and found that we could optimise from there.”

The benefit of the polymers, adds Shu, is that they attack and kill bacteria with a variety of methods, making it much harder for resistance to develop. “They kill in multiple ways, the most prominent being that they bind to the cell wall and break it apart, and this is even before they enter the cells,” she explains. “They don’t need to enter to have a killing activity and that makes it very difficult for the bacteria to resist.

“My polymer disrupts and breaks the outer membrane and can have a harmful effect on the bacteria without even getting into the inner layer, which is different to any antimicrobials being developed.”

The testing and refining work is expected to continue for next five years before clinical trials start.
Another promising lead has recently been discovered within the human nose. Scientists at the University of Tübingen, Germany found that the bacterium *Staphylococcus lugdunensis* was effective at preventing *Staph. aureus* from growing. They discovered that the bacterium produced an antibiotic compound, which they named lugdunin, which is even effective against antibiotic-resistant strains of *Staph. aureus* such as MRSA.

The researchers believe that the human microbiome may be the source of many more similar antibiotics.

**What are pharmaceutical companies doing?**

A full stream of research funding is crucial to the fight but the Association of the British Pharmaceutical Industry (ABPI) is keen to highlight that 34 antibiotics and infection-preventing vaccines are in the pipeline. Although many companies have departed from the field, others remain committed, with GSK a founding partner of the Innovative Medicines Initiative “New Drugs for Bad Bugs” programme, which now has a €700 million war chest and has grown to a community of 11 pharmaceutical companies and more than 100 academic and public groups sharing information and boosting research.

“The spread of resistance to antibiotics is one of the biggest threats to public health our world is facing, reducing the options available for doctors to manage life-threatening bacterial infections,” says Dr Stephen McDonough, vice president medical director UK for GSK, which has spent more than $1 billion on antibiotic research and development over the last 10 to 12 years.

“Discovering new antibiotics is extremely difficult science, and running antibiotic clinical trials in hospitals is challenging. Another hurdle is making this research economically attractive to companies. Researching new antibiotics can be very expensive and we know their use will need to be limited and very targeted to avoid increasing resistance.

“We also need to incentivise appropriate use of antibiotics. I know awareness of the situation has improved since I was a GP around 15 years ago but there’s more we can do. GSK is providing scientific advice and funding aimed at encouraging the development of fast, accurate and cost-effective diagnostics that will direct the use of our antibiotics only in patients that need them.”

**A multifaceted problem**

This is no easy battle and Dr David Brown, chair of the charity Antibiotic Research UK’s scientific and technical advisory committee, warns that the pipeline is slightly flattering in that the majority of candidates are derivatives of old drugs that may only extend an antibiotic’s efficacy by a few years. “Of those 34 [in the pipeline], we may only get two to four that are effective but even if they make it, resistance will still rise by the same rate as the last 10 years, so the best we can do is stand still,” he warns.

Antibiotic Research UK (ANTRUK) figures show that sepsis causes 44,000 deaths in the UK every year, compared...
with 35,000 from lung cancer and 16,000 from bowel cancer. Antibiotic Research UK states: “The failure to develop new antibiotics is of great concern. Antibiotic resistance is life threatening, with the young and old being most at risk of resistant infections. This is because these two groups have lower immunity, making them more susceptible to infection.”

Dr Brown adds: “Doctors and pharmacists have a serious problem as the whole antibiotic and bacterial infection area is incredibly complicated. The first thing they have to do is get educated – that is not a criticism of them, it is just that things are changing. In the past, they had the luxury of a large choice of antibiotics and low infection rates but that has been reversed with high resistance and more serious infections.”

He worked on the Bill Gates project to reduce the horrendous child death toll from diarrhoeal disease, which peaked at two million a year, and the multifaceted problem of tackling different viruses and bacteria has brought home the immense challenge facing the world. Doctors have to deal with dozens of bacteria with varying symptomatology and multiple possible antibiotic treatment plans, he explains, adding: “It needs an enormous amount of expertise and it is really impossible for GPs to have that expertise, no matter how educated they are.”

A new role for old drugs?

Dr Brown believes that a new commercial model is imperative to encourage research and development, and a rapid diagnostic test that could be employed at GP surgeries needs to be developed so doctors can determine if a patient has a viral or bacterial infection to help prescription levels. But his Perspectives paper in Nature Reviews Drug Discovery shows that a range of drugs can synergise with existing antibiotics and make them more effective against multidrug-resistant bacteria.

It is termed a ‘salvage’ operation; injecting added efficacy into an existing class while new discoveries, which "could take decades", are developed. The paper states: “As an interim solution, antibiotic resistance could be ‘broken’ by co-administering appropriate nonantibiotic drugs with failing antibiotics. Several marketed drugs that do not currently have antibacterial indications can either directly kill bacteria, reduce the antibiotic minimum inhibitory concentration when used in combination with existing antibiotics and/or modulate host defence through effects on host innate immunity, in particular by altering inflammation and autophagy.”

These drugs include ciprofloxin, a topical treatment for fungal nail infections, which has antibacterial qualities against both Gram-positive and Gram-negative bacteria, and loperamide, an opioid-receptor agonist normally used to treat diarrhoea, which synergises with several classes of antibiotics and increases the efficacy of eight tetracycline antibiotics. Berberine, an alkaloid compound found in several plants, has proved effective against multidrug-resistant bacteria such as *E. coli* and curcumin, found in the common cooking spice turmeric, has been tested for its ability to tackle *C. difficile* colitis.

New classes of antibiotic are crucial

Dr Brown’s report highlights that: “A few new antibiotics against Gram-positive bacteria have become available in recent years [see Figure 1] but no totally new class of antibiotic has been introduced for the treatment of Gram-negative infections for more than 40 years.”

Dr Brown adds: “We have failed for 40 years to come up with any new chemical templates, which is why we have to focus on saving our current antibiotics while we work on new treatments over the next 10 to 15 years. In the meantime, we have to salvage existing treatments with antibiotic resistance breakers.”

A five-year £14 million project to develop a rapid test for clinicians to quickly tell if a patient has a viral or bacterial infection will provide another potent weapon in the AMR arsenal. “Lack of an accurate, reliable and rapid test to distinguish bacterial infections from the vastly more common viral infections is a major factor leading to widespread prescription of antibiotics in both hospitals and in the community,” says Mike Levin, professor of international child health at Imperial College London, who leads the EU-funded project involving groups in Liverpool, Newcastle and Oxford.

It is clear that outstripping AMR will require unheralded levels of political co-operation, scientific ingenuity, novel thinking and practical application across the clinical spectrum.

References


Declaration of interests

See http://www.mjaук.org/author/bucklandd/

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