The quest for new antibiotics is underway

BY ANDREW DANIELS
The spread of antimicrobial resistance (AMR) is well documented with reports of more resistant bacteria appearing regularly. The hunt for new antibiotic candidates is well and truly under way but the question remains will they make it to the market in time to avert catastrophic epidemics. Even if resources were allocated to developing new antibiotics today there would be a 10–15 year gap before the new antibiotics hit the dispensary.

In 2016 two reports important about AMR have been released – one in the UK and one in Australia.

Globally
The first–Tackling drug-resistant infections globally: Final report and recommendations—was prepared by economist Lord Jim O’Neill for the UK Government and was released in May.1 The second – Antimicrobial Use and Resistance in Australia (AURA) 2016: First Australian Report on antimicrobial use and resistance in human health—was prepared by the by the Australian Commission on Safety and Quality in Health Care and released in June.2 Both were blunt in their assessment about the size of the problem. The second report provides a detailed snapshot of AMR in Australia. In the forward to his report, Lord O’Neill said it was clear to him (as an economist), as it had been to scientific experts for a long time, that tackling AMR was absolutely essential.

‘It needs to be seen as the economic and security threat that it is, and be at the forefront of the minds of heads of state, finance ministers, agriculture ministers, and of course health ministers, for years to come.’1

The executive summary spells out the scope of the issue in detail and estimates that by 2050, 10 million lives a year and a cumulative 100 trillion US dollars of economic output are at risk from the rise of drug resistant infections if proactive solutions are not found now to slow down the rise of drug resistance.

‘Even today, 700,000 people die of resistant infections every year. Antibiotics are a special category of antimicrobial drugs that underpin modern medicine as we know it. If they lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as chemotherapy for cancer) could become too dangerous to perform. Most of the direct and much of the indirect impact of AMR will fall on low and middle-income countries.’1

Australia
Closer to home, the Australian Commission on Safety and Quality in Health Care concluded that antimicrobial use (AU) in the Australia was higher than in many other countries, with rates of AMR in gram-negative organisms (Escherichia coli and Klebsiella pneumoniae) lower than in other countries, but high to very high for gram-positive organisms (Staphylococcus aureus and Enterococcus faecium). (See page 29 for more) The Commission’s Senior Medical Advisor Professor John Turnidge said that AMR was one of the most significant challenges for the delivery of safe, high-quality health services, and had a direct impact on patient care and patient outcomes.

‘Antibiotic resistance has developed because of the overuse and misuse of antibiotics, and now, bacterial infections that were once easily cured with antibiotics are becoming harder to treat. In 2014, nearly half the people in Australia were prescribed antimicrobials – so the threat of antimicrobial resistance has the potential to affect every individual.’

The Australian Government Chief Medical Officer at that time, Professor Chris Baggoley, said the AURA report represented a milestone as it explored patterns in prescribing and use of antibiotics to understand where and when specific threats emerged – the kind of information needed to guide efforts to mitigate the risk of antimicrobial resistance at a local, jurisdictional and national level.

It points out that Australia’s restrictions on the use of fluoroquinolones is believed to be partly responsible for the lower rates of Gram negative (G-) resistance seen in this country.
What about solutions?

While the problems of AMR are well documented, the question now is how governments and communities worldwide tackle it?

In first part of his report, Lord O’Neill outlined steps to reduce demand for antimicrobials. These included a global public awareness campaign, improved hygiene and reducing unnecessary use of antimicrobials in agriculture.

He also recommended developing rapid diagnostic to cut unnecessary use of antibiotics. He said it was unacceptable that the technology used to inform the prescribing of medicines such as antibiotics had not ‘evolved substantially in more than 140 years.’

His recommendation was that by 2020 it should be mandatory for a rapid diagnostic test be completed to prove whether the infection is bacterial before antibiotics were prescribed.

Lord O’Neill also recommended the development and use of vaccines and alternatives to prevent infections and reduce the need for antimicrobials.

At the community level, one way is to promote better use of antimicrobials.

In Australia, NPS MedicineWise has been running campaigns with doctors and consumers for years to get the message across that antibiotics may not be the answer to the patient’s problem. In 2015 it ran consumer campaigns on bill boards promoting good hygiene and the message that colds and flu can be managed without antibiotics.

In 2015, PSA and the Royal Pharmaceutical Society (UK) sponsored a proposal which was adopted by the International Pharmaceutical Federation (FIP) to develop a briefing document on the role of pharmacists in AMR. The document would aim to prompt action on the issue of antibiotics and AMR, and serve as a foundation for future work within FIP on AMR – including a revision of the FIP statement on AMR.

AMR and responsible use of antimicrobials was also discussed at a stakeholder roundtable held before the FIP Congress in Buenos Aires last month.

Responding to the AURA Report, PSA National President Joe Demarte said pharmacists could play a fundamental role in antimicrobial stewardship in Australia and the pharmacy profession in partnership with the Federal Government, other health practitioners and consumers, should make an effective and sustained contribution to a national response to antimicrobial resistance.

He said advice about the use of antibiotics had to be given to consumers, in addition to antibiotic awareness weeks and other time-limited campaigns.

‘Pharmacists can give the proper counselling for these health problems, ensuring that patients have a good understanding of their illness and realistic expectations of its progression.

Priming the pipeline

The second part of the O’Neill report highlighted the need to increase the number of effective antimicrobial drugs to treat infections that have become resistant to existing medicines.

However, he also pointed out that there was insufficient private and public investment in research and development focused on tackling AMR. To support early-stage research, he proposed a Global Innovation Fund endowed with up to two billion US dollars over five years.

The O’Neill report recognised that progress had already happened during the lifetime of the Review, including the UK and China’s nascent Innovation Fund focused on AMR, stepped up efforts in the US via the Biomedical Advanced Research and Development Authority (BARDA), and in Europe via the Innovative Medicines Initiative (IMI) and Joint Programming Initiative for AMR (JPI-AMR) programs. Also, the US National Action Plan on Combating Antibiotic-Resistant Bacteria was launched in August.

According to the PEW Charitable Trusts there are presently 37 antibiotics at various stages of clinical development. (See: www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development)

In Australia quite a few academic groups are researching potential new antibiotics.

One such group, at the University of Queensland (UQ) Institute of Molecular Biology Community for Open Antimicrobial Drug Discovery (CO-ADD) researchers has devised a creative way to access compounds in an attempt to develop a ‘collaborative’ pipeline of new antibiotic candidates.

The group is ‘mining’ the huge number of existing compounds from around the world that have been created by researchers, made for a variety of different reasons but never tested for antimicrobial activity. With funding from the Wellcome Trust and support from UQ, Co-ADD has set out to test these forgotten compounds for potential antibiotic candidates.

CO-ADD Program Coordinator, Mark Blaskovich told Australian Pharmacist that most of the new antibiotics in the pipeline were refinements of existing antibiotics.

He said that of the approximately 40 new antibiotics in the development pipeline only 10-15 were completely novel chemical scaffolds.

Another emerging issue is that most of these new compounds are for Gram positive (G+) bacteria with few candidates for extremely drug resistant Gram negative (G-) bacteria.

Dr Blaskovich said that because of the attrition rate in clinical developments it was quite likely a significant number of those were going to fail during the clinical trial program.
The scary bit

‘The really scary thing is if you look at the normal clinical development pipeline it is shaped like a triangle. With the Phase I first stage development you have a large number and they dwindle down into Phase II as they start to get culled out at various failures for toxicity or lack of efficacy. By Phase III you’re normally at the pointy end of the pyramid where there are a smaller number of better candidates entering much larger trials,’ Dr Blaskovich said.

However, there is still a large failure rate getting from Phase III to an approved drug. The problem with the antibiotic pipeline is that pyramid is essentially reversed.

‘You’ve got few early stage Phase I candidates that are currently known to be in testing. The larger bulk of them are in Phase II and Phase III testing. That’s because of the large lag time it takes to get the drug to market. Those compounds were discovered 15 years ago and have progressed their way through the pipeline and made their way to the Phase II and III trials, he said.

The problem, according to Dr Blaskovich, is with the higher resistant strains that have appeared more recently. Research started now to develop antibiotics effective against them – the basic research – will take a minimum of five years before there is anything close to being ready to enter clinical trials. Progression into the development pipeline takes another 5–10 years.

‘So starting right now you are looking at 10 years minimum and more likely 15 years before something you start researching now would actually be a drug on the market. In that period of time the potential for resistance to spread and become an epidemic, that’s the scary part of the resistance story.

‘It may not happen but there’s a good chance that it could,’ Dr Blaskovich said.

AURA highlights AMR in Australia

The Australian Commission on Safety and Quality in Health Care (the Commission) report Antimicrobial Use and Resistance in Australia (AURA) 2016: First Australian report on antimicrobial use and resistance in human health highlights antimicrobial use and resistance as a critical and immediate challenge to health systems in Australia and around the world. It provides a comprehensive picture of antimicrobial resistance, antimicrobial use and appropriateness of prescribing in Australia.

Commission Senior Medical Advisor Professor John Turnidge said that AURA 2016 set a baseline that would allow trends to be monitored over time and highlighted areas where future work would inform action to prevent the spread of antimicrobial resistance.

Key findings

• In 2014 10.7 million Australians were prescribed antimicrobials – 46% of the population.
• In 2014, Australia had one of the highest rates of vancomycin resistance in Enterococcus faecium in the world. Resistance to ampicillin was even higher in this species.
• Antimicrobial resistances are having a major impact on seriously ill patients in hospitals and require major efforts in hospitals to control their spread.
• On any given day in an Australian hospital in 2014, 38.4% of patients were being administered an antimicrobial. Of these, 24.3% were noncompliant with guidelines, and 23% were considered inappropriate.
• Antibiotics used in surgery are often not required and are given for too long. In 2014, 40.2% of surgical prophylaxis was inappropriate, mainly because of incorrect duration (39.7%); incorrect dose or frequency (15.7%); or lack of documenting the reason (22.9%).
• Data on antimicrobial prescriptions show strong seasonal variance, with some antimicrobials being prescribed more in winter. Colds and flu are viral infections, and antibiotics do not help treat viruses.
Viral or bacterial test developed

Researchers from The University of Queensland (UQ) and Imperial College London have developed a method to distinguish viral and bacterial infections in children, which will save lives and reduce antibiotic use.

Dr Coin, said previous studies had suggested that specific infections could be identified by the pattern of genes activated by the fever.

‘We analysed the gene patterns in the blood of children presenting with a fever at some hospitals in the United Kingdom, Spain, the Netherlands and the United States between 2009 and 2013, and discovered two genes that can distinguish bacterial infection from other causes of fever,’ he said.

Dr Coin said multidrug-resistant bacteria, or superbugs, were serious cause for concern.

‘Unless we tackle this problem, by 2050 superbugs could be claiming the lives of 10 million people each year,’ he said.

Our idea was that chemists all around the world have been synthesising unusual compounds for many, many years and a lot of those compounds had never been synthesised for antimicrobial activity.

CO-ADD offers free testing to see if compounds can kill any one of five key pathogenic bacteria or two fungi.

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Searching for candidates

Dr Blaskovich said one of the hypotheses the group had about why new antibiotics were not being discovered was that pharmaceutical companies were not looking the right kind of chemical space. Over the past 30 years they had shifted their collection of corporate compounds to focus on compounds with properties that made them more drug like, but for other indications. However, antibiotics tend to have different physicochemical properties from most other drugs.

‘We thought we’d try finding a different source of chemical diversity. Antibiotics have traditionally come from natural products in the environment. That was the way most of them were discovered in the 1940s, 50s and 60s.’

Dr Mark Blaskovich, CO-ADD Program Coordinator

The research team will seek to translate the discovery into clinical tests suitable for use in hospitals.

‘We need to conduct more research, but we are quite confident we will be able to harness existing DNA sequencing technology to develop a revolutionary low-cost and rapid way to analyse and diagnose infections in children,’ Dr Coin said.

The study was, published in the Journal of the American Medical Association, was led by Professor Michael Levin of Imperial College London.

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we’ll screen it against five different types of bacteria – one G+ (MRSA), four of the most serious G- bacteria – and two fungi because there is a lack of drugs that are active against fungi. (Cryptococcus and Candida)

CO-ADD screens the compound and if it is active they complete follow up assays to determine a concentration profile to see how effective the compounds are and whether they are cytotoxic against mammalian cells. If they kill human cells as easily as they kill bacteria cells without any selectivity they are too toxic. All that data is sent back to the person who sent the compound. They retain all the rights to it.

‘The researcher gets all the rights and the information back and they can do whatever they want with it. They can publish a paper. If the results are really good they can try taking the compound forward for development as an antibiotic. We are able to provide guidance to them as to what things they should be trying or who they could go to next for funding,’ Dr Blaskovich said.

CO-ADD tries to encourage people who would never have considered antimicrobial research to get interested, particularly if they get active compounds.

‘Most academic people are keen to follow up on something of interest. If they’ve had a compound sitting around that hasn’t been of any use to them but suddenly find it is potentially an antibiotic then they are going to start researching it further.

CO-ADD has attracted huge interest. In the first 18 months more than 120,000 compounds were submitted from over 150 groups worldwide. To date 50,000 have been screened and more than 500 have been identified as having promising activity.

Dr Blaskovich said CO-ADD was at the stage of validating those hits.

‘There is a number of interesting compounds in there but it is still early days.’

To promote collaboration CO-ADD has developed contacts with other organisations including Compounds Australia, IMI ENABLE (the European Union Innovative Medicines Initiative – European Gram-negative Antibacterial Engine), ChEMBL, ANTRUK (Antibiotic Resistance UK), NPS MedicineWise, the RACI, Royal Society for Chemistry and American Chemical Society.

Importantly, the output of CO-ADD (validated antimicrobial activity under standardised conditions, coupled with additional characterisation) is the data package that IMI-ENABLE is asking for in submissions for hit-to-IND (investigational new drug) development, and is potentially sufficient to attract funding from the new CARB-X initiative.

A unique resource

All of the CO-ADD screening data will be collated into a publicly accessible database and made available to scientists to see what types of compounds have antimicrobial activity, and importantly, what types do not.

One of the requirements for people submitting compounds is that they have to let CO-ADD know what the structure is within two years after they have the data back.

‘The idea for that is so we can have this publicly accessible database where we have all the data on compounds’ structures and whether they are active or not active.

‘It will be a unique resource which will be incredibly helpful for future researchers trying to develop new antibiotics, getting a better idea of what type of structures have potential as antibiotics.

The problem now, when trawling through the literature is that when people are testing for antimicrobial activity there are all sorts of different conditions; different bacteria, different concentrations, different testing methodologies. So it is difficult to compare one set of data with another.

CO-ADD however, is going to have hundreds of thousands of compounds compared under standardised conditions against a relatively large set of different types of bacteria.

‘It potentially could be a game changer for researchers in the future. Particularly as computational chemistry methods become more advanced it could be very useful for trying to pick up structure activity relationship for things that are either G+ or G- or picking up what things make it selective for bacteria versus mammalian cells,’ Dr Blaskovich said.

References
