180 YEARS

Australian Unity
Real Wellbeing

Resisting the superbugs

Australian Unity Funds Management Limited, ABN 60 071 497 115, AFS Licence No. 234454

Resisting the superbugs

Can two Aussie innovations help turn the tide?

Australian Unity was founded more than 180 years ago by Australians for Australians. We seek to provide capacity across numerous areas of health and wellbeing to meet the future needs of society. This includes investing in built-form infrastructure and cutting-edge treatment and diagnostic technology.

One of the most significant looming health challenges in Australia and the rest of the world is antimicrobial resistance – superbugs that could render minor infections dangerous and make chemotherapy and surgery that is routine today much riskier and almost impossible in the future. The World Health Organisation has defined antimicrobial resistance (AMR) as a top-10 threat to global health, and it has high relevance for both emerging markets and developed countries like Australia.

"AMR is a critical problem and a very important target for investment," says Victor Windeyer, Australian Unity's Healthcare Portfolio Manager. "In the long run there's a very tight connection between creating value for patients and creating value for investors and, with antimicrobial resistance we have an issue of enormous importance to everyone on the planet."

Read on to find out about antimicrobial resistance and two Australian-linked innovations that could help turn the tide.

Takeaway messages

Antibiotic resistance is a looming health threat on the scale of pandemics and global warming.

Antibiotics are among the most widely used medicines, but the more they are used, the less effective they become.

Minor infections, cancer treatment and routine surgery will become dangerous unless solutions are found.

Only three major pharmaceutical companies are directly involved in developing new antibiotics.

The pharmaceutical industry has pledged $US1 billion to boost the pipeline of new medicines.

Noteworthy Australian contributions include a new rapid test to reduce erroneous prescribing and a novel approach to treating serious multidrug-resistant infections.

What is antimicrobial resistance?

Think multidrug-resistant organisms or superbugs. Antimicrobial resistance (AMR) is the ability of microorganisms - bacteria, viruses, fungi and parasites - to survive in the presence of antimicrobials such as antibiotics or antifungals and to pass this ability on via their genes to other microorganisms.[1]

> "Unlike COVID-19, AMR is a predictable and preventable crisis. We must act together to rebuild the pipeline and ensure that the most promising and innovative antibiotics make it from the lab to patients."
>
> Thomas Cueni,
>
> Director General of the International Federation of Pharmaceutical Manufacturers and Associations.

1. https://www.amr.gov.au/resources/australias-national-antimicrobial-resistance-strategy-2020-and-beyond

Where it all began - Alexander Fleming prediction of 'the ignorant man'

Scottish bacteriologist Alexander Fleming, Australian pathologist Howard Florey and the German-born biochemist Ernst Chain are recognised for starting the antibiotic era. They were jointly awarded the 1945 Nobel Prize for Physiology or Medicine. But even in his acceptance speech, Fleming warned the world about the danger of antibiotic resistance.[2]

"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

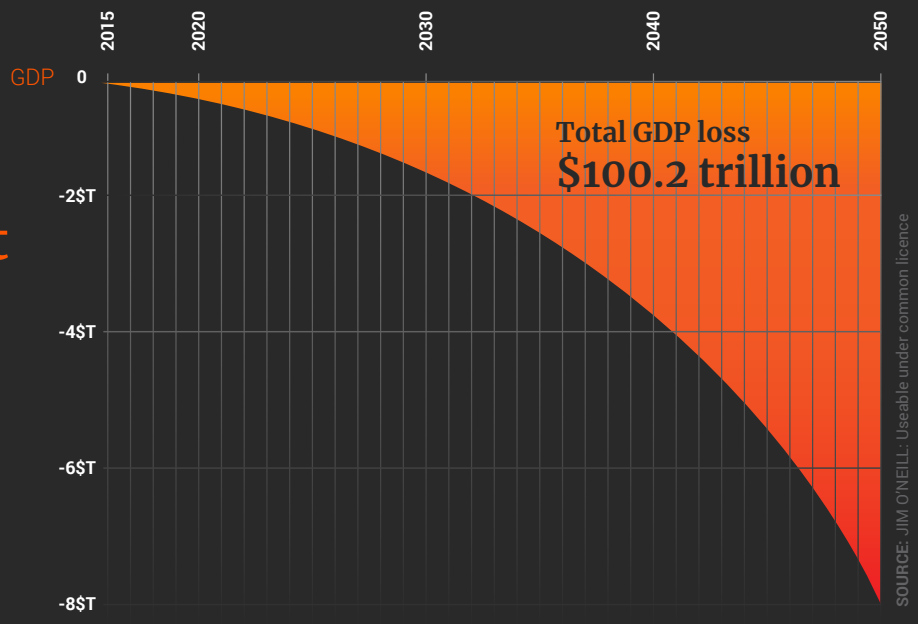
Before long, Fleming's predictions came true. The first case of antibiotic resistance was observed in 1947.

World Health Organization's top-10 threats to global health (January 2019)[3]

1. Air pollution and climate change
2. Noncommunicable diseases
3. Threat of a global influenza pandemic
4. Drought and conflict
5. Antimicrobial resistance
6. Ebola and high-threat pathogens (such as COVID-19)
7. Weak primary care
8. Vaccine hesitancy
9. Dengue
10. HIV

2. https://www.reactgroup.org/antibiotic-resistance/course-antibiotic-resistance-the-silent-tsunami/part-1/the-discovery-of-antibiotics/
3. https://www.jwatch.org/fw114986/2019/01/18/who-releases-list-10-threats-global-healthbal-health

AMR's impact on world GDP in trillions of USD[7]



There was little media attention on 13 March 2020 when the Council of Australian Governments (COAG) endorsed a 20-year vision to tackle one of the greatest threats to modern healthcare – antimicrobial resistance (AMR).[1] Perhaps it was the timing, coming just two days after the World Health Organization (WHO) declared the COVID-19 pandemic.

While Australians keep a daily tally of the number of COVID-19-related infections in their states, few are aware that multidrug-resistant infections have long been responsible for an average of five Australian deaths a week.[4]

Doctors fear that if left unchecked, AMR will cause a post-antibiotic era in which even minor injuries could result in life-threatening infections. Without effective antimicrobials for prevention and treatment of infections, medical procedures such as organ transplantation, chemotherapy, diabetes management, and major surgery (for example, caesarean sections or hip replacements) will become very high risk.[5]

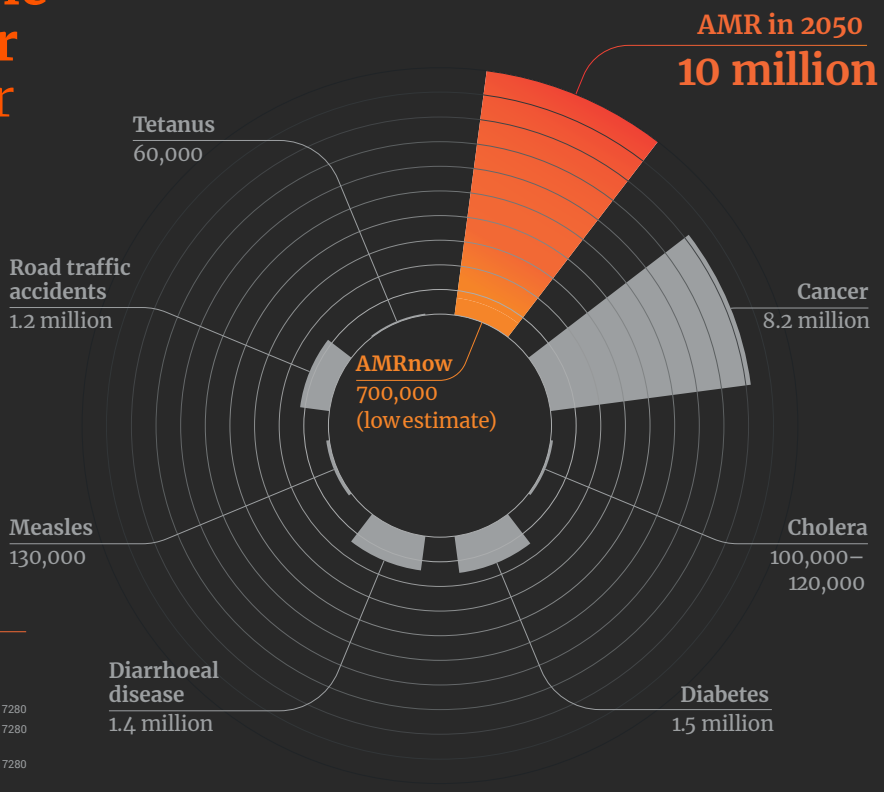
Common infections such as pneumonia, urinary tract infections, gonorrhoea, tuberculosis and gastrointestinal diseases are already becoming increasingly resistant to medicines that were previously effective.[6]

A widely cited 2014 UK Government review, chaired by economist Jim O'Neill, says doctors and anyone else who has first-hand experience of a drug-resistant infection fully understands the importance of tackling AMR. But for most people, including business leaders and policymakers around the globe, the threat of drug resistance might seem a distant and abstract risk, if it is known at all.

O'Neill and colleagues conservatively estimated that AMR was causing 700,000 human deaths a year in 2014. But they predicted the toll would be higher than cancer and traffic accidents combined by 2050, by which time 10 million people a year could be dying from drug-resistance. The economic cost would be up to $US100 trillion.[7]

4. OECD – stemming the Superbug Tide in Australia
5. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
6. https://theconversation.com/antibiotic-resistance-cheap-diagnostic-test-could-be-a-saviour-142778
7. O'Neill J Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations; 2014

Deaths attributable to AMR every year compared to other major causes of death[7]



GRAPHIC SOURCE: JIM O'NEILL: Useable under common licence

Sources

Diabetes	www.who.int/mediacentre/factsheets/fs312/en/
Cancer	www.who.int/mediacentre/factsheets/fs297/en/
Cholera	www.who.int/mediacentre/factsheets/fs107/en/
Diarrhoeal disease	www.sciencedirect.com/science/article/pii/S0140673612617280
Measles	www.sciencedirect.com/science/article/pii/S0140673612617280
Road traffic accidents	www.who.int/mediacentre/factsheets/fs358/en/
Tetanus	www.sciencedirect.com/science/article/pii/S0140673612617280

Antibiotics are among the most widely used medicines in humans, agriculture, aquaculture and pets. They are also used in oil pipelines and industrial paints. The drawback is that the more they are used, the less effective they become, according to the 20-year vision document, titled 'Australia's National Antimicrobial Resistance Strategy, 2020 & Beyond'.[1]

Moreover, there's a limited supply of new antibiotics and those held in reserve as a last resort to treat severely ill people in whom all other antibiotics have failed.

> "Never has the threat of antimicrobial resistance been more immediate and the need for solutions more urgent."
>
> Dr Tedros Adhanom Ghebreyesus,
> Director-General of the World Health Organization.

The COVID-19 link

There has been a significant increase in antibiotic prescribing during the COVID-19 pandemic.[8]

A study published by The Lancet suggests that a significant proportion of COVID-19 hospital patients have secondary infections, including bacterial infections that are resistant to treatment with antibiotics.[9]

Another study by The Lancet uses data from the Wuhan province in China to show that half the COVID-19 patients who died had a secondary infection.[10] The research supports evidence from the 1918 Spanish flu pandemic and the 2009 flu pandemic that the death rate in viral pandemics is closely associated with secondary bacterial infections.[11]

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>
> Victor Windeyer,
> Healthcare Portfolio Manager,
> Australian Unity.

Three examples of last-resort failure

1. *Klebsiella pneumoniae* is a common intestinal bacterium that can cause life-threatening infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. All parts of the world are experiencing resistance to the last-resort antibiotics used to treat *K. pneumoniae* infections. In some countries, the last-resort treatment (carbapenem antibiotics) does not work in more than half of patients.
2. Resistance in *E. coli* to one of the most widely used medicines for the treatment of urinary tract infections (fluoroquinolone antibiotics) is widespread. There are countries where this treatment is ineffective in more than half of patients.
3. Treatment failure to the last-resort medicine for gonorrhoea (third generation cephalosporin antibiotics) has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the UK).

SOURCE: WHO factsheet July 2020

8. https://www.antibioticresearch.org.uk/about-antibiotic-resistance/antibiotic-resistant-bacteria-in-healthcare/
9. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7/fulltext
10. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext
11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5481322

Fixing a broken market

In 1980, a total of 25 large drug companies had active antibiotic discovery programs. By 2019 their numbers had dwindled to only three, Pfizer, MSD (Merck Sharp & Dohme) and GSK (GlaxoSmithKline).[12] Dozens of smaller antibiotic-focused biotechs have also exited the market or declared bankruptcy.[13]

This exit occurred because the market for new antibiotics is not viable, primarily as a result of extremely high research and development costs coupled with low demand, since new antibiotics are used sparingly to preserve effectiveness.

In January 2020, the WHO raised the alarm about declining private investment and lack of innovation in the development of new antibiotics.[14]

"Never has the threat of antimicrobial resistance been more immediate and the need for solutions more urgent," said Dr Tedros Adhanom Ghebreyesus, Director-General of WHO at the launch of two papers that illustrated a dismally inadequate pipeline of new antibiotics. "Numerous initiatives are underway to reduce resistance, but we also need countries and the pharmaceutical industry to step up and contribute with sustainable funding and innovative new medicines."

In July 2020, big pharma answered the call and launched the $US1 billion AMR Action Fund to save the collapsing antibiotic pipeline.[15]

Harnessing the spirit of collaboration that has been a feature of the search for a COVID-19 vaccine, 24 companies and foundations have banded together to bring two to four new antibiotics to market within 10 years.

"Unlike COVID-19, AMR is a predictable and preventable crisis. We must act together to rebuild the pipeline and ensure that the most promising and innovative antibiotics make it from the lab to patients," said Thomas Cueni, Director General of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), one of the organisers of the new fund. "The AMR Action Fund is one of the largest and most ambitious collaborative initiatives ever undertaken by the pharmaceutical industry to respond to a global public health threat."

12. https://www.theguardian.com/business/2019/mar/27/nationalised-drug-companies-may-be-needed-to-fix-antibiotics-market
13. https://www.businesswire.com/news/home/20200709005154/en/%C2%A0New-AMR-Action-Fund-steps-save-collapsing
14. https://www.who.int/news-room/detail/17-01-2020-17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections
15. https://www.businesswire.com/news/home/20200709005154/en/%C2%A0New-AMR-Action-Fund-steps-save-collapsing

Antibiotic Stewardship - Lowering the inappropriate use of antibiotics

We know that antibiotic resistance is a looming health threat on the scale of pandemics, and that antibiotics are among the most widely used medicines, but the more they are used, the less effective they become.

Australia is taking a pioneering role in the fight aimed at reducing multidrug-resistance through infection control and appropriate prescribing of antibiotics. Much of the focus is on hospitals, but GPs write most antibiotic prescriptions and the Royal Australian College of General Practitioners acknowledges there is a significant amount of over-use and inappropriate prescribing.[16]

A report by the Center for Infectious Disease Research and Policy at the University of Minnesota states that most inappropriate use of antibiotics among GPs occurs when antibiotics are prescribed for viral respiratory infections, ear infections, and sinusitis. Another issue is that GPs sometimes use broad-spectrum antibiotics when a narrow spectrum medicine would be preferred.[17]

The report says that prescribing antibiotics before test results confirm a bacterial infection is a significant cause of misuse. Another reason is patient pressure to receive an antibiotic prescription even though the GP knows it is not appropriate.

The report recommends point-of-care diagnostics to establish whether an illness is viral or bacterial as an intervention to prevent antibiotic overprescribing by GPs. Other interventions may include patient education, including that antibiotics are ineffective against the common cold and other viruses and that they should not usually be taken as a preventative measure, for example, when travelling overseas.

Significantly, a 2020 CSIRO study shows that 92% of Australians don't know the difference between a viral and bacterial infection.[18]

Four aims of the AMR Action Fund:

1. Invest in smaller biotech companies focused on developing innovative antibacterial treatments.
2. Provide technical support to portfolio companies and provide access to the deep expertise and resources of large biopharmaceutical companies.
3. Bring together a broad alliance of industry and non-industry stakeholders, including philanthropists, development banks and multinational organisations.
4. Encourage governments to create market conditions that enable sustainable investment in the antibiotic pipeline.

SUPPORTERS OF THE FUND:

Almirall, Amgen, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eisai, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, LEO Pharma, Lundbeck, Menarini, Merck, MSD, Novartis, Novo Nordisk, Novo Nordisk Foundation, Pfizer, Roche, Shionogi, Takeda, Teva, UCB.

16. https://www1.racgp.org.au/newsgp/clinical/antibiotic-prescribing-down-but-%E2%80%98superbug%E2%80%99-threat
17. https://www.cidrap.umn.edu/asp/overuse-overprescribing-of-antibiotics
18. https://outbreakproject.com.au/2020/05/14/public-information-key-to-combatting-rising-superbug-threat/

Vaccines

Australia's COAG's 20-year strategy document states that without effective infection prevention and control in human health, and biosecurity measures in animal health and food production, antimicrobial resistance will continue to rise.[1]

Vaccines are a pillar of hope, according to a 2019 review published in the International Journal of Infectious Diseases. The authors write that vaccines have a significantly more promising development pipeline than antibiotics. They argue that vaccines can be used in the fight against AMR, both directly, by reducing the incidence of bacterial infections such as pneumococcal pneumonia, and indirectly, by the multiple ways in which they can reduce the use of antibiotics.

The authors list six benefits of vaccines:

1. They prevent disease and the proliferation of bacteria.
2. They are not prone to inducing resistance.
3. They reduce antibiotic use because of fewer infections.
4. They prevent resistant strains from occurring and spreading.
5. They reduce antibiotic misuse.
6. They prevent viral diseases prone to bacterial co-infections or superinfections requiring antibiotics.

The research, development, and licensure of novel vaccines to prevent human and animal diseases, as well as drugs against resistant infections, must remain a focus of industry and governments to ensure success against the increasing AMR problem worldwide, write the authors.

Innovation Case Study 1: Point of care diagnostics

As stated above, inappropriate antibiotic prescribing for viral infections is a major concern in GP settings, and Australia's 20-year AMR strategy document calls for research into rapid diagnostic technologies to support effective stewardship.

Australian Unity has agreed to invest in medtech company Lumos Diagnostics. The Future of Healthcare Fund participated in a pre-IPO Convertible Note offering an attractive risk-adjusted return for the Fund. This provides a clear path to return upside while mitigating some of the downside risks.

For Lumos Diagnostics, the Convertible Note provides flexibility and capital to pave the way for an IPO within the next 24 months.

One of Lumos' most exciting products is a ground-breaking rapid testing device called FebriDx which tells doctors if their patient has a viral or bacterial infection.

The FebriDx test combines two clinical biomarkers to provide a differentiated diagnosis. This patented test has all the essential ingredients for real world application in the point of care market. It is:

- Cost effective: costing circa US$20 as advised by Lumos;
- Accurate: a high negative predictive value;
- Timely: takes under 10 minutes; and
- Easy to use: portable and no specialist equipment or readers required

The point of care test is approved in Europe and by the TGA in Australia.

Lumos describes FebriDx as the first and only rapid, all-in-one point-of-care test that can differentiate viral from bacterial infections.

A patient can be tested on arrival at the GP's practice, with the results ready in time to allow the doctor to make an informed decision about whether an antibiotic is needed. In the current COVID-19 pandemic environment the test has utility in triage and separation of potential COVID-19 positive patients whilst they wait for confirmatory test results.

Windeyer knows the Lumos leadership team well and has worked with them in the past.

"We worked together on taking a novel tissue processor that I invented to market, and it's still sold around the world today. Now they've created another new great engine for innovation.

"One of the things we look for when we're investing is a management team who have the capability and track record in developing real products for the market, and actually getting them there," Windeyer says. "Not only do they have that track record, but we've got personal experience of that." This gives us confidence in their ability to do it again and to create real value that's enduring and long term.

"Australia has a very good reputation for core science. It is better translation of that solid research capability into products and clinical practice that solves global-scale problems where transformational businesses can be built. Lumos is an example of a company that could do well, not only for Fund investors but also for society," says Windeyer.

"There are also a number of promising therapies being developed in Australia, for instance another interesting but more nascent technology targeting AMR being advanced in Australia is Phage Therapy which really developed in Eastern Europe before WWI and during the Cold War years."

Innovation Case Study 2: Phage therapy

Almost a decade before the discovery of penicillin, scientists were experimenting with bacteriophages (phages) as a treatment for bacterial infections.[19]

A phage is a virus that can infect and kill bacteria. But the therapy fell by the wayside after the mass production of penicillin in the 1940s.

Now, because of AMR, phage therapy is widely being reconsidered and researched as an alternative to antibiotics, or where antibiotics are ineffective.

One of the teams at the forefront of this research is based at the Westmead Institute for Medical Research (WIMR) in NSW, which is collaborating with the Westmead Hospital (Western Sydney Local Health District) and the University of Sydney in the use of phages to treat patients with multidrug-resistant infections.

The researchers led by Professor Jon Iredell are investigating the safety and efficacy of AB-SA01, a form of phage therapy, in patients with life-threatening Staphylococcus aureus bacteraemia, which occurs when bacteria enter the bloodstream.

In a study published in the journal 'Nature Microbiology' in February 2020, they treated 13 critically ill patients with phage therapy in addition to their prescribed antibiotics. They found the approach was well-tolerated and potentially effective.

"We found that our patients had no adverse reactions to the phage therapy," Professor Iredell said in an article published on the WIMR website.

"Importantly, we also identified a decrease in Staphylococcal DNA load, which tells us that the combination of antibiotics and phage therapy was effective in targeting the bacteria."

Professor Iredell said more evidence in support of phage was needed before it could be used on a larger scale. "However, our study makes it clear that it could potentially offer a safe treatment for serious infections, and help reduce the impact of antibiotic resistance," said Professor Iredell.

Windeyer noted: "In the future there may be global banks of phages that can be used in cases of multidrug resistant infections where for instance otherwise untreatable septicaemia might ultimately lead to untimely and early death, or severe and long-term morbidity."

19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5547374/
20. https://www.nature.com/articles/s41564-019-0634-z
21. https://www.westmeadinstitute.org.au/news-and-events/2020/new-research-demonstrates-safety-of-phage-therapy

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