RESISTANCE: THE RISE AND SPREAD OF AMR

With resistant infections on the rise, the global community faces an unprecedented challenge.

Jesse Schnall

It was September 3rd in London and the professor had just returned from a summer holiday. A physician in training but a biologist by trade, he set to work removing the left-over petri dishes in his laboratory at St. Mary’s Hospital.[1,2] Yet amidst the islands of bacteria that covered one particular dish, lay a blob of mould, clear on all sides. The fungus – later identified as Penicillium notatum – had stopped the bacterium dead in its tracks. It was 1928, and Scottish bacteriologist Sir Alexander Fleming had uncovered a breakthrough that would revolutionise medicine. The discovery was penicillin. Antibiotics were born.

Humble beginnings

It would be over 10 years before penicillin was first administered to patients, an achievement for which Fleming would jointly receive the Nobel Prize in Physiology or Medicine in 1945.[1] The following decades heralded a ‘golden age’ of drug discovery, with half of the antibiotics commonly used today being discovered between 1950-1960 alone.[3] Infections such as pneumonia, syphilis and gonorrhoea, once life-threatening, could now be cured with a jab or a pill. And yet, these medicines were no silver bullet. The first effective class of antimicrobials, the sulphonamides, were plagued by resistant bacteria since their introduction in 1937.[4] Penicillinase, an enzyme that breaks down penicillin antibiotics, was identified as early as 1940, several years before the drug was first put to market.[4]

This phenomenon of microbial self-defence, and the threat it poses to global health security, has grown over the last 80 years. Today, antimicrobial resistance (AMR) represents one of the greatest challenges facing modern medicine.

A growing problem

AMR is the ability of bacteria, viruses, parasites and fungi to grow in the presence of a drug that would normally kill them or inhibit their growth.[5] Antibiotic resistance refers to this ability in bacteria alone.

Annually, resistant infections cause an estimated 700,000 deaths – a figure projected to rise to 10 million deaths by 2050 if policy changes are not adopted.[6] There are over 2 million resistant infections reported in the US every year, at an estimated cost of 20 billion USD.[7] Uncurbed, AMR could cost the global economy up to 100 trillion USD by 2050, wiping 3.8% off the annual global gross domestic product (GDP) – more than the 2008 global financial crisis.[6,8]

Low-income countries are likely to be the most affected, with an estimated 28 million additional people thrust into poverty globally, and reductions in livestock production of up to 11%.8 Immunosuppressed patients would be vulnerable to everyday pathogens; routine surgeries could become too dangerous to perform; and previously treatable infections may once again be without cure.

The origins of resistance

Most antimicrobial drugs are naturally produced by micro-organisms, such as fungi and certain environmental bacteria, or are synthetic modifications of such compounds.[9] The emergence of antibiotic resistance – the most concerning subtype of AMR – is a natural evolutionary response of bacteria to these antimicrobials, offering protection through mechanisms such as changing drug binding sites, directly destroying drugs or active efflux from the cell.

Resistant bacteria have been identified in every environment examined so far, including soil, the sea, drinking water, food and even Antarctica.[9] Invariably, many of these resistant strains become
part of the natural microbiome – the ecosystem of commensal bacteria that begin to colonise human beings and other animals after birth.

**Selection pressures**

In the absence of external antibiotics, resistant and susceptible bacterial species tend to co-exist in a stable balance in both the environment and the human microbiome. [9] When antibiotics are administered for any reason, natural selection leads resistant strains to proliferate as susceptible bacteria are killed or inhibited. This process – known as ‘collateral selection’ – is the primary driver of resistance in many of the bacterial species posing the most significant problems today, including Escherichia coli and the ESKEP species (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter spp., Pseudomonas spp., Enterobacter spp).[10]

These resistant strains are typically transmitted through asymptomatic carriers rather than individuals with disease, and cause ‘opportunist’ infections following a change in their host, such as immunosuppression, wounds or other illness.[10,11] Resistance-conferring genes – which are often stored in mobile segments of DNA known as plasmids – can also be directly passed to neighbouring bacteria through direct connections between cell membranes, indirect transmission from gene-capturing viruses called bacteriophages or absorption of DNA fragments from the surrounding environment.[9]

Resistance can also arise in non-commensal organisms through a process called ‘targeted selection’. This occurs during an infection, in which a population of pathogens enters the body and multiplies. As these bugs replicate, some will acquire genetic mutations that make them resistance to certain antibiotics, which may then be selected for during treatment.[10,12] In contrast to the ESKEP species, this process is commonly associated with Neisseria gonorrhoea and Mycobacterium tuberculosis (TB), which are known to develop spontaneous mutations during treatment. [10] Preventing targeted selection is one of the main reasons why combination drug therapy is used in the management of TB.[13]

**The antibiotic boom**

In the context of unprecedented levels of antibiotic consumption seen in modern healthcare, veterinary medicine, agriculture and the environment, the burden of AMR has become significant.

Antibiotics are a mainstay of modern medical practice, employed not only to treat active infections, but also to prevent infection in immunosuppressed patients and in the timeframe during and surrounding surgical procedures. Between 2000–2015, global antibiotic consumption increased by 65%. [14] This increase is primarily driven by low- and middle-income countries (LMICs) outside northern Europe and North America, where a significant percentage of antimicrobial use occurs without prescription. [15]

Improper prescribing is also a contributor to AMR, often due to lack of patient awareness and pressure placed on practitioner. In some developed regions, up to 50% of antimicrobials may be inappropriately prescribed, often for respiratory infections (which are typically viral).[16] While antimicrobial stewardship (AMS) practices encourage coordinated actions designed to promote and increase appropriate use of antimicrobials in the interests of conserving their effectiveness, a lack of rapid point-of-care diagnostics often means antibiotics must be given empirically to hedge against risky infections.[17]

The overuse and misuse of antibiotics in the animal sector is a major contributor to AMR. The World Health Organization estimates that in some countries, up to 80% of the total consumption of medically important antibiotics is used in food-producing animals to promote growth and prevent infection. [18,19] Resistant organisms harboured by livestock can then be spread to humans via direct contact or meat consumption.[20]

Rising antibiotic levels in the environment also lead to resistance development. Up to half of an administered dose of antibiotics – which are poorly broken down in the body – will ultimately be excreted in sewage.[21] Industrial effluent also contributes to these rising levels: an Indian wastewater treatment plant serving an estimated 90 drug manufacturers was recently found to expel an average daily ciprofloxacin load equivalent to the total average consumption of Sweden over a 5-day period.[22] Concentrations exceeded the level toxic to some bacteria by over 1000-fold.[22]

**The markets are not alright**

While resistance has always been an issue, the pace of new drug development in the 20th century allowed medications to stay a step ahead. Yet there have been no successful discoveries of novel antibiotic classes in over 30 years, resulting in what some have termed ‘the discovery void’.[23]

In an age where big pharma and modern science reign supreme, the antibiotic pipeline is paradox-
Immunosuppressed patients would be vulnerable to everyday pathogens; routine surgeries could become too dangerous to perform; and previously treatable infections may once again be without cure.

Following these developments, the UN called for the establishment of the Ad Hoc Interagency Coordination Group (IACG) to provide practical guidance on AMR.[33] Co-chaired by the UN Deputy Secretary-General and the WHO Director-General, the IACG will present its final report to the UN Secretary-General later this year.[34]

The WHO has also been making ground on the recommendations put forward in the GAP. The establishment of the Global Antimicrobial Resistance Surveillance System (GLASS) in 2015 aims to provide a central repository for AMR surveillance.[35] In 2017, a list of 10 priority pathogens was developed to guide R&D priorities for the international community.[36] The WHO’s 13th General Programme of Work for 2019-2023 also includes a platform for tackling AMR – a step in the right direction.[37,38]

Leadership has also been strong at the state level. A 2016 review commissioned by former UK Prime Minister David Cameron has elevated the public discussion around AMR, while the establishment of the Fleming Fund and Global AMR Innovation Fund (GAMRIF) by the UK Government has seen 295 million GBP poured into AMR research.[39,40] Along with funding from the Wellcome Trust and the Bill & Melinda Gates Foundation, these resources will support ambitious efforts such as the mapping of global AMR burden through the Global Research on Antimicrobial Resistance (GRAM) project, a collaboration between the University of Oxford and the Institute for Health Metrics and Evaluation (IHME) in the US.[41]
The European Union (EU) has also been active, banning growth-promoting agents in animal feed as early as 2006.[42] The recent establishment of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) will see greater efforts toward global collaboration and research, while the German government has committed up to 500 million euros towards a Global AMR R&D hub, launched early last year.[43,44]

There are glimmers of hope from the private sector, too. Despite cutbacks to AMR research, the world’s leading pharmaceutical companies have formed the AMR Industry Alliance, outlining a roadmap of principles for global action through a declaration at Davos in 2016.[45] While serious progress remains to be seen, the Antimicrobial Resistance Benchmark – a report that monitors private sector efforts towards AMR R&D – will dutifully hold big pharma to task as they attempt to turn words into action.

Here at home

**When antibiotics are administered for any reason, natural selection leads resistant strains to proliferate as susceptible bacteria are killed or inhibited.**

Australia is responding proactively to the threat of AMR. The Federal Government’s first 5-year national strategy, released in 2015, has seen the establishment of a dedicated AMR website; participation in the WHO’s World Antibiotic Awareness Week (WAAW) campaign; and the development of key education and training programs for both human and animal health workers that will be key to raising awareness.[47] On the R&D front, AMR has been designated a national research priority, with over $90 million in active National Health and Medical Research Council (NHMRC) grants as of early 2017.[47]

The establishment of the Antimicrobial Use and Resistance in Australia (AURA) system and key surveillance mechanisms including the National Antimicrobial Prescribing Survey (NAPS) and National Alert System for Critical Antimicrobial Resistances (CARAlert) have been critical to monitoring of trends in resistance and antibiotic consumption. Our strong AMS and infection prevention and control (IPC) measures are vital to reducing the spread of resistant bugs, with hand hygiene rates exceeding the 80% benchmark set by the National Hand Hygiene Initiative in 2017.[47] Rates of overall and inappropriate antimicrobial use in Australian hospitals have also been on the decline.[47]

**Where to from here?**

AMR has caught our attention, yet a long road lies ahead. With the global price-tag on containing AMR pegged at between 4 and 9 billion USD per year, ongoing funding must be secured.[6,8] Coordinated, global leadership among intergovernmental organisations, state actors and non-governmental organisations will be equally critical in containing the AMR threat.

Our first step must be to gather the facts. The figures on AMR incidence remain patchy and inconsistent. The establishment of the GRAM initiative via the Global Burden of Disease (GBD) study is an important step toward a better understanding of the nature, scale and geographic diversity of this issue, and should be commended.

The WHO’s GLASS mechanism will also provide sorely needed global surveillance estimates, yet is currently hampered by limited data and country participation. While over 100 of the organisation’s 194 member states operate national surveillance systems, only 71 have enrolled in GLASS.[48,49] Ongoing global collaboration, in addition to technical and financial support for lower income nations, will be crucial to building functioning surveillance networks in all nations.[50]

Continued funding and guidance will be equally critical in ensuring the widespread adoption and implementation of national action plans for AMR. As of 2018, nearly half of all member states have no national AMR strategy in place, while those that do often struggle to convert them into action.[49]

At the same time, efforts to stimulate R&D must be intensified. The effectiveness of innovative financial incentives such as market entry rewards, extended patent licensing and the de-linkage of drug revenues from sale volumes, should be further investigated as avenues to bring the private sector back into the fold. [6] Vital international R&D mechanisms like the Global Antibiotic Research and Development Partnership (GARDP), the JPIAMR, the Coalition for Epidemic Preparedness (CEPI) and CARB-X, the latter of which has received up to $550 million USD in multilateral funding, must receive ongoing support from key donors.[50,51]

Implementation and operational research, often neglected, will be critical to optimizing antibiotic dosages and course durations, many of which are rooted in historical practices with uncertain evo-
dence.\[10\] Despite limitations in application and efficacy, antibiotic alternatives such as vaccines, bacteriophages, lysins and peptides should be further investigated for their potential roles as adjunctive therapeutics.\[52\]

As one of few high-income countries in the WHO Western Pacific Region (WPR), Australia must take an active leadership role on AMR.\[47,53\] While constrained by limited resources in the past, the Federal Government’s launch of the Indo-Pacific Centre for Health Security in 2017 will see 300 million AUD devoted to containing and avoiding nearby infectious disease threats.\[47,54\] As a member of the Global Health Security Agenda (GHSA) and a contributing country to its AMR action package, Australia is well-positioned to aid our neighbours in bolstering their health infrastructure.\[55\] This could be partly achieved through supporting ongoing implementation of the Joint External Evaluation (JEE), a voluntary assessment of country capacity to handle public health threats under the International Health Regulations of 2005. As of today, only 9 WPR member states (including Australia) have participated in the JEE.\[56\]

Members of healthcare professions have a key role to play. Educating ourselves and others on the causes and scale of AMR; promoting WAAW and the need for proper antimicrobial prescribing; and remaining vigilant around hand hygiene and other IPC measures are but a few actions we can take to shift the dynamic around this issue. While progress has been made, more than 60% of Australians with presumptively viral respiratory tract infections are still prescribed antibiotics.\[47\] We have a long way to go.

Nearly a century has passed since Fleming and his petri dish, and the protection this discovery afforded us against illness and disease. Yet we now encounter the possibility of returning to the proverbial dark ages of medicine. In the face of this threat, a global commitment to curbing drug resistance would be a wise investment in our collective future. While the challenge is great, the cost of inaction will be far more severe.

\[Jesse Schnall is a final year medical student at Monash University with an interest in communicable diseases and antimicrobial resistance.\]

\[Conflicts of interest\]
Jesse Schnall is employed by the University of Oxford Big Data Institute as a casual data analyst for the Global Research on Antimicrobial Resistance (GRAM) project.

\[Ethics\]
No formal ethics review process was undertaken for this article.

\[Correspondence\]
jasch13@student.monash.edu

\[References\]
25. DI Masi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J...


