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MEETING THE THREAT OF ANTIBIOTIC RESISTANCE:

BUILDING A NEW FRONTLINE DEFENCE

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Antibiotics have been the miracle drugs of modern medicine and the mainstay of our defence against bacterial infections. But now bacteria are fighting back and developing resistance to antibiotics at an alarming pace.

Some bacteria are now so resistant that they are virtually untreatable with any of the currently available drugs. If we do not take action to address this threat, humankind will be on the brink of a 'post-antibiotics era', where untreatable and fatal infections become increasingly common.

This paper explains what antibiotics are, how antibiotic resistance arises, and some research areas that can help build a new frontline defence against bacterial infections.

Overview

- ▶ Globally, the increase in antibiotic resistance has been driven by the unrestrained use of antibiotics in human health, agriculture and animal husbandry.
- ▶ In Australia, the increasing number of antibiotic-resistant infections appearing in the community and acquired during international travel represents a looming public health issue.
- ▶ In addition, underlying genetic causes of antibiotic resistance seen in bacteria prevalent in other countries have now been detected in bacteria already in Australia.
- ▶ Worryingly, the crisis of antibiotic resistance has coincided with a collapse in the antibiotics research and development (R&D) pipeline, resulting in an urgent need for new antibiotics.
- ▶ The pursuit of new and existing research avenues is essential to fill the current antibiotics void.

Background

Antibiotics have become the mainstay of our defence against bacterial infections. They revolutionised medical care in the 20th Century and became the miracle drug of modern medicine.

In 1928, British bacteriologist Alexander Fleming serendipitously discovered penicillin in mould that had contaminated a dish used to grow bacteria in his lab. The dish was initially discarded but then retrieved once Fleming noticed that the presence of mould had prevented bacterial growth.

However, it was not until 1940 that the Australian scientist Howard Florey and his colleague of German origin, Ernst Chain, developed the manufacturing process to produce penicillin in large enough quantities to treat infections in humans.

"Many people take for granted that antibiotics will always be available when we need them, but soon this may no longer be the case."

World Economic Forum, Global Risks 2013

Mass produced penicillin sent to the war front during World War II saved countless lives that otherwise would have been lost due to bacterial infections.

We entered the new millennium recognising that this 'golden-era of antibiotics' was coming to an end. Globally, and particularly in developing nations, there has been an alarming increase in antibiotic resistance.¹

"...untreatable infection caused by antibiotic-resistant bacteria 'poses a catastrophic threat' to humans and has urged immediate global action."

England's Chief Medical Officer,
Dame Sally Davies, 2013

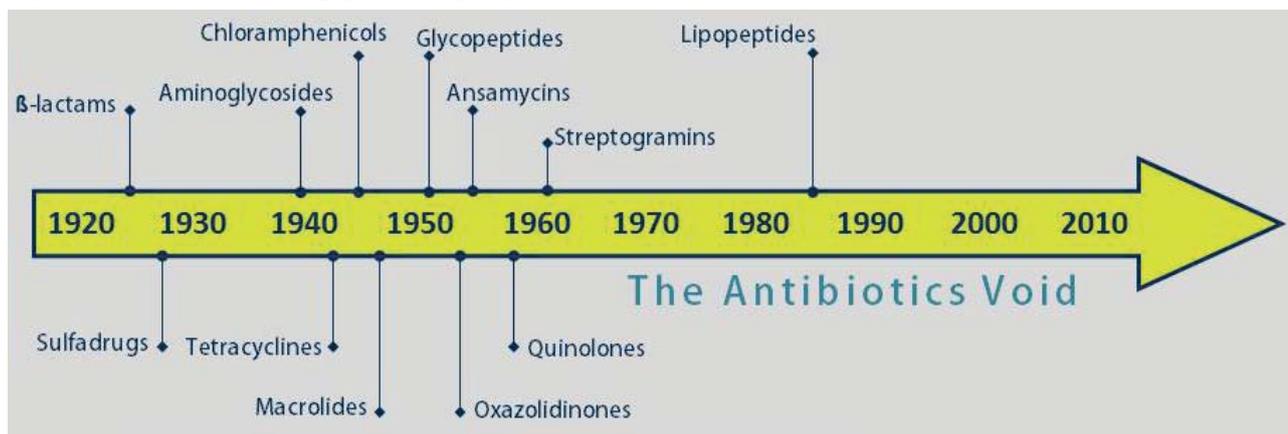
Antibiotic resistance represents a looming public health issue for Australia. Infections with antibiotic-resistant strains of bacteria typically occur within hospitals and healthcare facilities. However, in recent years an increasing number of these types of infections have appeared in the broader community.² In Australia, as with the rest of the world, it is expected that the spread of drug-resistant golden staph (*Staphylococcus aureus*) in the community will continue.³ Underlying genetic causes of antibiotic resistance observed in bacteria in other countries have now been detected in bacteria already in Australia.^{4,5} The current drug-resistant tuberculosis (TB) situation in Papua New Guinea also presents a risk to Australia's public health, particularly in Australia's Aboriginal and Torres Strait Islander population.^{6,7}

In a frightening irony, several medical interventions will increase our vulnerability to infection with antibiotic-resistant bacteria. Among these are: cancer chemotherapy, organ transplantation, artificial devices (e.g. catheters, heart valves) and implants (e.g. hip joints).

The rise in bacterial resistance has coincided with a collapse in the antibiotic discovery pipeline; only one antibiotic that works in a novel way (mechanism of action), has been discovered and developed for use in humans, in the last 50 years (see Figure 1).⁸

A drug taken in short courses, and to which resistance may emerge, creates disincentive for ongoing business investment. Most companies have now either abandoned the field or are in the process of reducing their commitment. Whilst some cancer medicines are sold for \$20,000 a course, we still expect to pay \$20 for a course of antibiotics.

Figure 1: Antibiotic discovery pipeline (adapted from Lewis, K., 2012)⁸



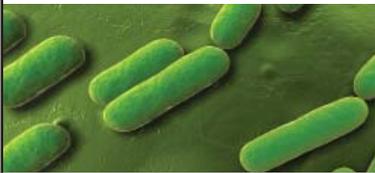
Bacteria and antibiotics

Types of bacteria

Bacteria are among the most successful life forms on the planet, and can be found in a wide range of places, from our guts to desert plains and the icy slopes of Antarctica. Not all bacteria cause disease. Many types of bacteria live on our skin surfaces and inside our bodies without causing us harm. Indeed we would not be able to digest some of our food without the bacteria in our gut.

Bacteria are broadly classified by their shape. The four main groups include bacilli, cocci, spirochaetes, and vibrio (see Figure 2).

Figure 2: Bacterial classes and examples of diseases

Class of Bacteria	Shape
Bacilli Disease example: Typhoid Fever	Rod-shaped 
Cocci Disease example: Gonorrhoea	Spherical 
Spirochaetes Disease example: Syphilis	Spiral 
Vibrio Disease example: Cholera	Comma-shaped 

Antibiotics

Most of the current antibiotics used to treat infections in humans and animals are derived from microbes (fungi, viruses and bacteria or other micro-organisms).

Microbes naturally produce defensive chemicals as a way of competing with other species for limited resources; these are known collectively as antimicrobials. Scientists have harnessed these chemicals in the fight against infections. When antimicrobials target bacteria specifically they are called antibiotics.

How an antibiotic is taken will depend on the type of infection. Topical antibiotics (e.g. creams) are often used to treat skin and external infections while oral antibiotics (e.g. tablets) can be used to treat most types of mild to moderate infections in the body. Antibiotic injections are usually reserved for more serious infections such as septicaemia, and are used mainly in hospitals.

Antibiotics can be used to treat relatively mild conditions, such as acne, as well as potentially life-threatening conditions such as pneumonia. Antibiotics used to treat human infections are broadly classified into groups based on how they attack bacteria.

Antibiotics work in one of two ways:

- ▶ They are *bactericidal*, or kill bacteria by disrupting processes essential to bacterial survival. For example, antibiotics can interfere with the formation of the bacterial cell wall or its cell contents.
- ▶ They are *bacteriostatic*, or prevent bacteria from growing. For example, antibiotics can interfere with the production of bacterial proteins or genetic material.

It is important to note that antibiotics are useless against diseases that are caused by viruses. The common cold, flu and many other infections of the upper respiratory tract, some ear and sinus infections, are not caused by bacteria, but by viruses. Using antibiotics to treat viral infections can actually do you more harm than good, as it encourages the development of resistance and can upset the natural balance of the good bacteria in your gut.

How do bacteria become resistant to antibiotics?

Antibiotic resistance is a feature of bacterial evolution. Bacteria can become resistant either by receiving genes from other species of already resistant bacteria or through spontaneous mutations or changes in their genetic code.⁹ This survival advantage is then passed on to the next generation of bacteria.

“Antibiotic resistance as a phenomenon is, in itself, not surprising. Nor is it new. It is, however, newly worrying because it is accumulating and accelerating, while the world’s tools for combating it decrease in power and number.”

Joshua Lederberg, Nobel Laureate, 1998

Genetic changes can make bacteria resist antibiotics in many ways. Bacteria can:¹⁰

- ▶ produce chemicals that destroy antibiotics;
- ▶ build machinery to pump antibiotics out of the cell;
- ▶ make the cell wall less porous to entry by antibiotics;
- ▶ modify the bacterial target of the antibiotic so that the target becomes unrecognisable; and,
- ▶ create backup or alternative pathways to those targeted by antibiotics.

The challenge we now face is that misuse (e.g. antibiotics used as growth promoters in animals), and over-use of antibiotics (e.g. prescribing antibiotics for what is probably a viral infection) have accelerated the development of antibiotic resistance. This at a time when we do not have enough new antibiotics to fight this challenge.

Next generation infection fighters

We now have a new rule of engagement in our strategy to fight bacteria. The rule is to treat infection without driving resistance. The cornerstones of our combat strategy are: use vaccines to prevent infections, discover new antibiotics to fill the antibiotics void, and develop new treatments and better tools for diagnosing infection to reduce the risk of resistance.

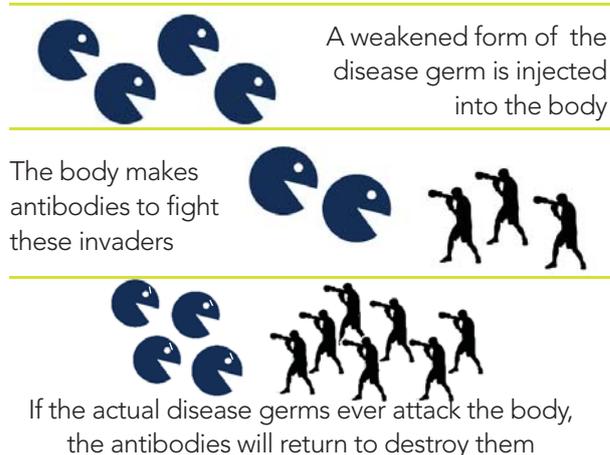
Using vaccines to prevent infections

New vaccines offer great potential to prevent infection and even eradicate diseases, both of which would eliminate the need for some antibiotics.

Vaccines deploy a person’s immune system by imitating an infection, but without actually causing disease. Exposing individuals to inactivated or compromised forms of infecting organisms causes the person’s immune system to produce infection-fighting proteins called antibodies. If the individual is then exposed to the disease-causing organism in the future, their immune system is primed to produce the correct antibodies, thereby swiftly fighting the infection (see Figure 3).

While there are significant scientific challenges, efforts to develop new vaccines can build on the success of existing vaccines, such as those against bacteria that cause meningitis.

Figure 3: How vaccines work (adapted from the CDC)¹¹



New antibiotics

Pioneering work by the American scientist, Selman Waksman, and the commercial adoption of his method for antibiotic discovery ushered in the golden era of antibiotics.

Waksman's great leap forward was to systematically test for the presence of natural antibiotics in soil bacteria.⁸ This led to the discovery of the first effective antibiotic, streptomycin, which was used to treat TB. Waksman was awarded the Nobel Prize in Physiology or Medicine in 1952 in recognition of this work. Despite extensive 'mining' of a small proportion of soil bacteria, the following decades resulted in fewer and fewer antibiotics being discovered.

Recent advances in growing soil bacteria in the lab mean that Waksman's approach can now be used to sample a greater proportion of soil bacteria.⁸ The potential of discovering new antibiotics is increased by combining Waksman's method with genetic studies. In addition, the search for new antibiotics has been extended to bacteria occupying different, often extreme environments, including volcanic vents and sub-glacial lakes.

Research and development in synthetic antibiotics will complement work to discover antibiotics from natural sources.¹² Synthetic antibiotics face the daunting challenge of breaching the defences mounted by the cell wall of bacteria.

As a result of the problems associated with antibiotics and the development of resistance, researchers are also looking towards long-term infection fighting solutions.

Reducing the risk of resistance

1) Targeting bacteria in novel ways

There are treatments in early stages of development, which target bacteria directly but do not drive resistance. Such treatments include immune-based therapies directed against bacteria. Immune-based therapies involve injecting components of the immune system (such as commercially-made antibodies) into an infected person to kill bacteria — a modern advance on the century-old serum therapy used to treat diphtheria.

Researchers are also evaluating viruses (or their components) that are able to kill bacteria without harming the infected person. The advantage of using viruses that kill bacteria — known as bacteriophages — is that although the target bacteria can still evolve and become resistant to the virus, viruses are in turn also capable of rapidly evolving to maintain their advantage over bacteria. However, these bacteria-killing viruses are only suitable for treating a very limited range of infections to the skin or exterior of the body.

2) Targeting the patient's response to infection

The symptoms of diseases are triggered as much by a patient's immune response to infection, as from the bacteria themselves.

An option is to target the patient's response to an infection using treatments that dampen their inflammatory response. Steroids and non-steroidal drugs can be used for this

purpose; however, this will not always clear the infection. Alternatively, treatments can block harmful bacteria accessing resources from the patient. An example of such an approach is the potential use of probiotics to compete for nutrients against harmful bacteria that cause gut infections.

3) Tools for diagnosis

Novel diagnostic tools to identify, confirm and monitor the status of bacterial infections will also be among the new generation of infection fighters. Rapid and accurate diagnostic tests will restrict antibiotic use in patients with confirmed infections only. Further, these tests will assist in shortening the duration of antibiotic courses by monitoring the progress of an infection up to the point when treatment is no longer necessary.

Conclusion

The discovery of antibiotics led to a major improvement in human health in the early 20th Century. The rapidly rising threat of antibiotic resistance has the potential to cause just as dramatic a change. However, rather than advancing human health, it will herald 'an end to modern medicine as we know it.' There is now a genuine threat of humanity returning to an era where mortality due to common infections is rife.

"A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."

Director General of the World Health Organisation,
Dr Margaret Chan, 2012

The convergence of antibiotic resistance and the collapse in the antibiotics R&D pipeline calls for urgent action. Nothing short of a global revival in antibiotics R&D is required. Although some research is already underway, we need to ensure that we can address emerging medical and societal needs. It is also critically important that we build up a new arsenal of effective treatments and diagnostic tools to combat resistance in the longer term.

This will go hand-in-hand with the prudent use of all currently available antibiotics; and global infection control through better sanitation, hygiene practices and surveillance of infections.

About this series

These occasional papers from the Office of the Chief Scientist aim to bring to the public's attention scientific issues of importance to Australian society. Each issue has been prepared by a multi-disciplinary team and has been through an external review process. We would like to thank the Chief Medical Officer, Professor Chris Baggeley, and Professor Matthew Cooper for reviewing this paper.

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