

INSTITUTE FOR MOLECULAR BIOSCIENCE

# THE EDGE

## INFECTION

*The latest in research and discovery*



STOPPING THE  
NEXT SUPERBUG  
HOW YOU  
CAN HELP

GUT BACTERIA  
AND DIET  
WHAT TO EAT  
TO ENCOURAGE  
GOOD BACTERIA

BACTERIA VS  
VIRUSES  
WHAT'S THE  
DIFFERENCE?



THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA

CREATE CHANGE





# we dare to imagine

Institute for Molecular Bioscience

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CREATE CHANGE

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**THEEDGE**

**INFECTION**

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# Welcome

**B**acteria are amazing organisms. They came into existence billions of years ago and survive to this day. They are invisible components of many processes that we take for granted, but are crucial to life itself.

But while bacteria may help us in many aspects of life, they are most well known for causing disease. Antibiotics have helped us recover from infections for the better part of a century, but bacteria, and other microbes such as fungi, are increasingly developing resistance to these treatments.

This is a problem that affects everyone. One in two people will take an antibiotic in any one year. What if that antibiotic doesn't work? How will we treat diseases?

The simple answer is that we won't. The 2016 O'Neill Review on Antimicrobial Resistance, commissioned by the UK government in 2014, predicted up to 10 million deaths per year from drug-resistant infections by 2050 if we don't develop new antibiotics, to say nothing of the people who are dying from resistant infections right now, including here in Australia.

2050 may seem like a long time away, but it's closer in time than 1990. It's also not a problem that we can fix in an instant. It's akin to an ocean liner heading towards rocks – it takes time to turn the ship. If we wait until the last antibiotic is no good, it will be too late.

A lack of antibiotics isn't just a problem for bacterial and microbial infections. All of modern medicine is

based on having effective antibiotics to prevent infection following procedures such as surgery.

Stemming this problem needs investment, public support and advocacy. Every single person has a role they can play, actions they can take, to help turn the ship to safer waters.

At the Institute for Molecular Bioscience (IMB), we established the Centre for Superbug Solutions in 2015 to tackle the problem from different angles. We are crowdsourcing new antibiotic leads, screening compounds from laboratories around the world which were developed for different purposes, then abandoned.

We are harnessing the passion of citizen scientists to help us discover new medicines from the ground beneath our feet.

We are taking "forgotten" antibiotics and modifying them to act against today's superbugs.

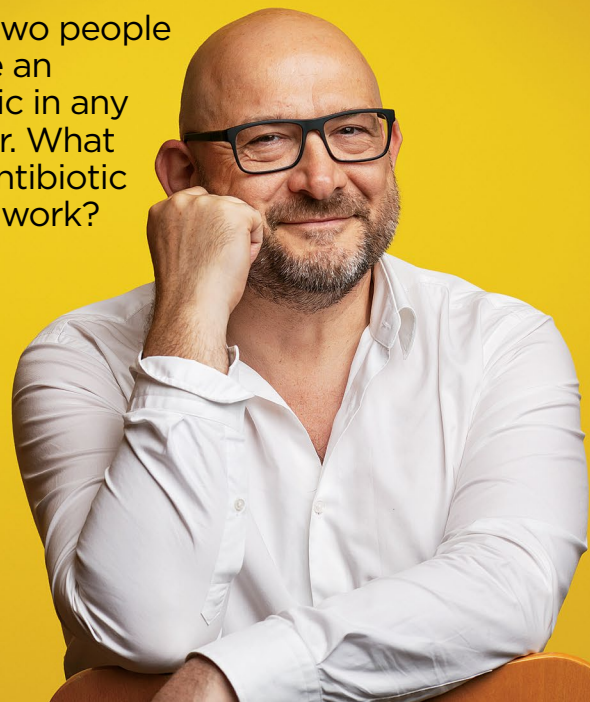
And by investigating the surface activity of superbugs at molecular level, we have discovered how these microbial marvels elude the human immune system.

This magazine is the second in our series *The Edge*, in which we explore some of the most biggest health challenges facing our local and global communities. Please read on to discover how, together, we can fight back against the threat of superbugs.

### Professor Ian Henderson

Executive Director  
Institute for Molecular Bioscience  
The University of Queensland

One in two people will take an antibiotic in any one year. What if that antibiotic doesn't work?





# Superbugs: a global issue

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## *A challenge we all face*

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**I** imagine a world in which a simple scratch could kill you. It may sound unfathomable, but this was reality before the development of antibiotics in the mid-20th century. Prior to the invention of these lifesaving drugs, over half of all deaths were due to infections, such as pneumonia and tuberculosis. A scratch or wound could ultimately lead to your death if it allowed disease-causing bacteria to enter your body. Antibiotics, which kill bacteria and other microbes, allowed us to recover from these infections and helped to increase

average life expectancy in the developed world by decades.

Developing resistance to antibiotics is a natural phenomenon found in ancient bacterial DNA from 30,000-year-old permafrosts. Bacteria are an ever-evolving foe, with the ability to build up resistance to antibiotic drugs, rendering them ineffectual.

These “wonder drugs” have been prescribed inappropriately too many times, helping bacteria develop resistance. Exacerbating the situation is the lack of development of new antibiotics – in the past

few decades most pharmaceutical companies have ended their programs.

This leaves us, less than a century since the first antibiotic came onto the market, facing a return to the pre-antibiotic era. In 2019, the most recent year for which we have comprehensive statistics, nearly 5 million deaths worldwide were associated with drug-resistant bacterial infections.

The highest burden is in Sub-Saharan Africa and South Asia, but all regions of the globe showed resistance, making it a major cause of death globally.





Deaths worldwide associated with drug-resistant bacterial infections

4.95m

If we can't find a solution to the rise of superbugs, we could revert to the life our ancestors led, where dental surgery can be fatal; you risk losing your leg because of a simple scratch while gardening; and the chance of infection during a cancer treatment or hip replacement makes them too risky to contemplate.

The number of people dying is a grim reminder of how formidable superbugs are. But our researchers are teaming with colleagues from across the world to fight back, and you can play your part too. Read on to learn more about bacteria, the changes we can each make, and how research is offering hope for the future.

**What are bacteria?**

Bacteria are prokaryotes – the smallest, simplest and most ancient cells, with free-floating genetic material. These microscopic organisms can be rod, spiral or spherical in shape. Bacteria can communicate with one another by releasing chemical signalling molecules, allowing the population to act as one multicellular organism. This is a powerful weapon against antibiotics, allowing some bacteria to become dormant when exposed to an antibiotic, then regenerate when it is gone.

**What is antibiotic resistance?**

Resistance occurs when bacteria survive and continue to cause disease even after an infected person has taken antibiotics. Antibiotic resistance is not the patient becoming resistant to antibiotics, but the bacteria becoming resistant. Bacteria reproduce quickly and can share DNA between themselves, rapidly adapting and changing over time to outwit antibiotics.

**What are superbugs?**

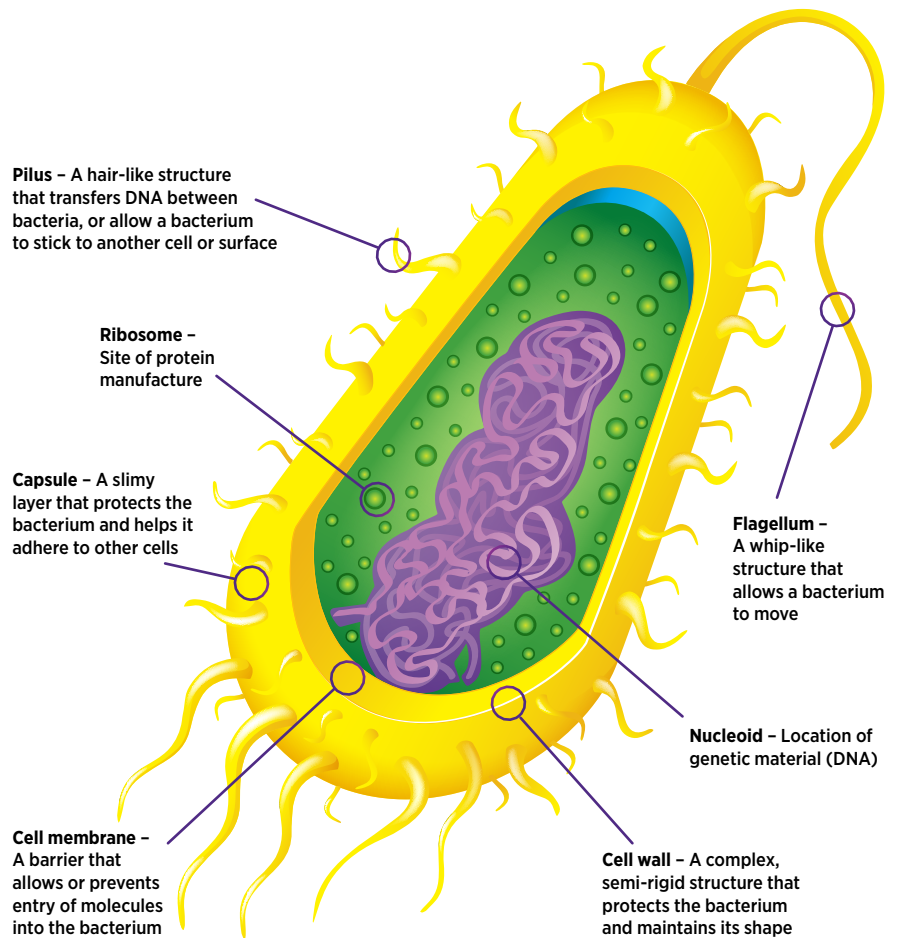
Superbugs are bacteria that are resistant to more than one antibiotic, which makes them exceptionally dangerous, especially those that are resistant to all antibiotics.

**How do bacteria infect us – and how do we fight back?**

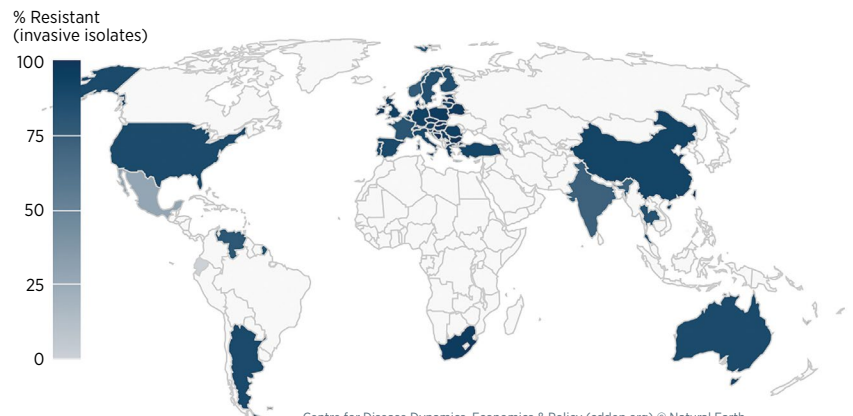
Our bodies are normally very good at keeping bacteria where they generally don't cause damage – on skin surfaces and in the digestive tract – and away from areas that should be “sterile” – such as the urinary tract or blood. Mostly this is done by using barriers that physically prevent the entry of bacteria. But every so often bacteria make it through. The body then relies on a variety of internal defences to identify, isolate and deactivate the invading bacteria. Bacterial infections occur when one of these mechanisms is breached.

Physical damage to the skin, such as cuts and scrapes, or surgery, can allow bacteria ready access to the inside of the body, potentially introducing more bacteria than the body's defence systems can handle.

Immunocompromised patients, such as those with organ transplants or undergoing cancer treatments, are more susceptible to infection because the body is less able to keep small numbers of invading bacteria or fungi at bay.



**Resistance of *Enterococcus faecium* to Aminopenicillins**



# Common bacterial diseases

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*One disease alone accounts for 20 per cent of global deaths.*

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Bacterial infections, caused by harmful bacteria growing inside the body, show up in many forms. There are skin infections, respiratory tract infections, the dreaded “gastro” or food poisoning, sexually transmitted diseases and urinary tract infections.

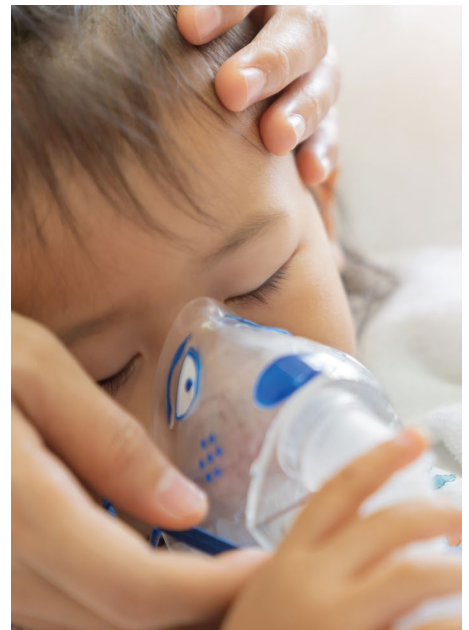
## Sepsis

One in five people worldwide die of sepsis, which occurs when bacteria enter the blood and rapidly grow, triggering an inflammatory response cascade that causes septic shock, organ failure, and, if not treated quickly enough, death. In 40 per cent of cases, the type of bacteria causing the infection isn't identified in time, making it difficult to treat and causing the cascade of bodily responses that can become fatal.



## Pneumonia

The leading cause of death in children under five worldwide, pneumonia is an infection of the lungs that can be caused by bacteria or viruses. Symptoms include difficulty breathing, cough, fever or chills and phlegm. Pneumonia caused by bacteria can be treated with antibiotics, and one of the most common types of pneumonia, caused by the bacterium *Streptococcus pneumoniae*, can be prevented by vaccination



## Urinary tract infections (UTI)

These infections occur when bacteria enter and multiply in any part of the urinary system, most commonly in the bladder and urethra. UTIs are mainly caused by the bacterium *Escherichia coli* (*E. coli*) and are the most common infection in humans worldwide. Symptoms include a burning sensation when urinating, blood in the urine, and strong-smelling urine. While UTIs can usually be easily treated with antibiotics, they can cause death if they develop into sepsis. An estimated one-third of sepsis cases begin as UTIs.





BY THE NUMBERS

Prior to the invention of antibiotics, more than half of all deaths were due to infection.

50%

**Wound infections**

A wound in your body, whether from surgery or injury, allows bacteria to enter the body and cause disease. An infected wound can swell, become red, feel warm, and ooze pus. Chronic wounds affect 40 million people worldwide, including 420,000 Australians, each year. The ageing population and increase in people with type 2 diabetes are drivers of an increase in chronic wounds. If bacteria infecting a wound spread through the body and into the blood, it can trigger sepsis.



**Meningitis**

This infection of the membranes surrounding the brain and spinal cord, the meninges, causes fever, neck stiffness and pain, and a rash of purple or red spots that remain when

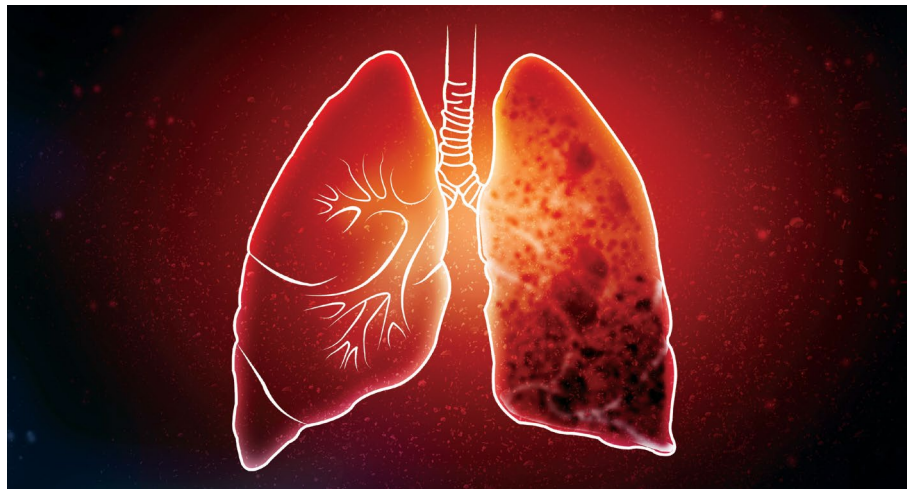
you press on them. While this disease can be caused by a virus or a fungus, bacterial meningitis is the most severe type, and can turn fatal within hours.



**Tuberculosis (TB)**

TB is a lower respiratory tract infection caused by *Mycobacterium tuberculosis*, which infects the lungs. It remains a major

killer because of a rise in drug-resistant strains. The vaccine against TB is one of the most widely used worldwide.



**Diarrhoea**

Diarrhoea is the second-leading cause of death in children under five worldwide, killing over half-a-million children of this age globally each year. Previously, most deaths from diarrhoea were caused by the accompanying dehydration, but sepsis resulting from bacterial infection represents a growing proportion. Diarrhoea is a symptom of a range of infections, including bacterial, viral and fungal. Infection with *E. coli* is one of the most common causes of diarrhoea.

# Think twice before texting at lunch

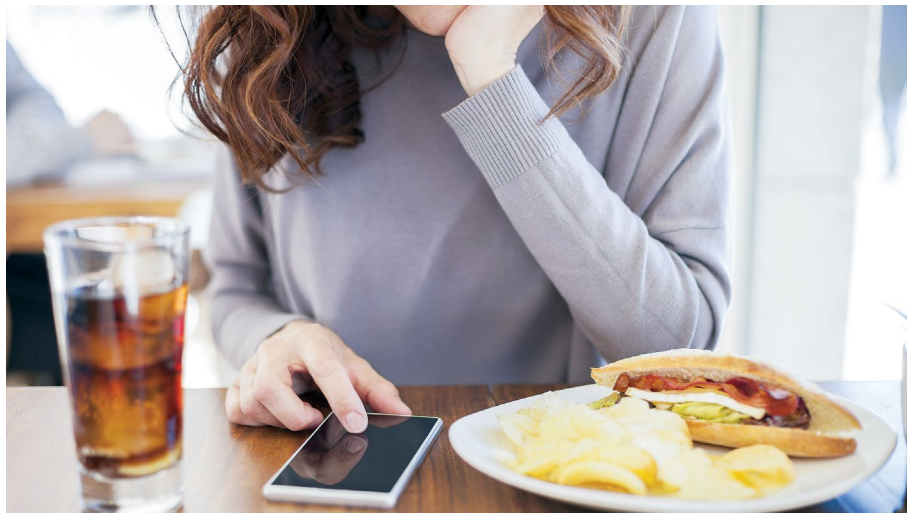
*Does a door handle or a phone have more germs?*

**W**e are all well-versed in the need to wash our hands before and after touching surfaces where germs might be lurking, to prevent the spread of disease. But while you might take care around communal surfaces like toilet door handles and lift buttons, it turns out the real culprit might be more personal. In fact, you might even be touching it right now to read this.

An experiment by IMB's Dr Alysha Elliott revealed that your mobile phone is one of the germiest surfaces in the workplace. She made the discovery after she swabbed surfaces around the office and people's hands before and after washing, then grew up the samples in petri dishes.

"We found a range of microbes on everyone's hands and on all surfaces, though some places were surprisingly cleaner than others," Dr Elliott said.

"Some of the germiest surfaces were a mobile phone screen, a computer keyboard and an office kitchen bench, while door handles, desks and chairs were much cleaner."



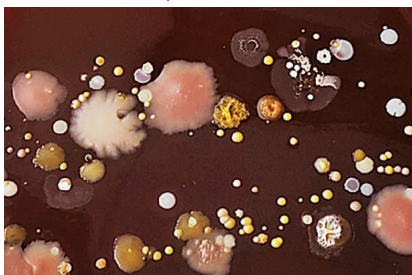
"The results are a good visual reminder of the need to wash your hands, as cleaning thoroughly with soap and water reduced the number of microbes on all hands we tested."

Dr Elliott emphasised it is important to remember that not all bacteria are harmful: "Humans carry bacterial colonies from our

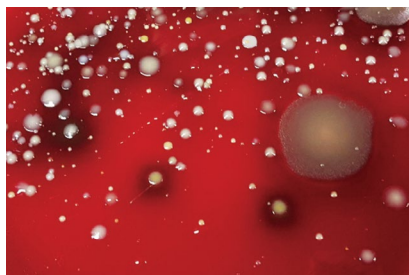
heads to our toes, and the vast majority of these are harmless or indeed beneficial to human health."

"Washing our hands is a simple, affordable and effective way to reduce the risk of picking up or passing on germs that could lead to infections such as COVID-19, pneumonia, diarrhoea and influenza."

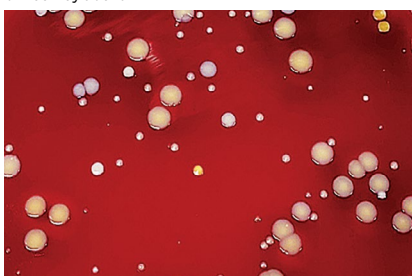
Swabs from: mobile phone



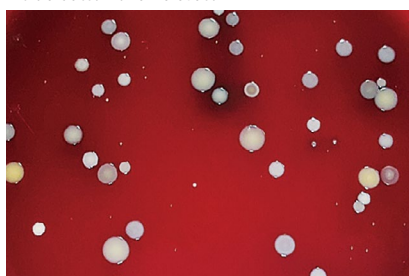
kitchen bench



office keyboard



inside button of an elevator



## BY THE NUMBERS

*Washing hands with soap and water could reduce deaths from diarrhoea globally by up to*

# 50%

## DIY ACTIVITY

Try this eye-opening experiment at home. All you need is a few slices of bread to show the importance of good hand hygiene.





# How you can prevent the next superbug

*You don't need to be a scientist in a laboratory to help prevent the next superbug.*

**I**t's becoming increasingly clear that antibiotic-resistant bacteria are a problem we are facing now, and not a threat for the future. Everyone can play their part in reducing the rise of resistance in bacteria. Researchers can develop new medicines and governments can

set policies to encourage favourable economic conditions for antibiotic development, and responsible stewardship of the antibiotics that still work. There are also steps that we can all take in our everyday lives to prevent infection, which reduces the use of antibiotics and the rise of superbugs.



## What you can do

The power to curb the spread of antibiotic resistance is in the hands of each of us. Here are some of the things you can do right now to help tackle this global problem.



**Never demand antibiotics if your health worker says you don't need them - you may have a virus which will not be affected by antibiotics.**



**Always follow your health worker's advice when using antibiotics, completing the dose as instructed.**



**Prevent infections by regularly washing hands, avoiding close contact with sick people, and practising safe sex.**



**Keep vaccinations up to date - some bacterial diseases can be prevented by vaccines.**



**Prepare food hygienically: keep hands and work surfaces clean, separate raw and cooked food, cook food thoroughly and keep at safe temperatures, and use clean water.**



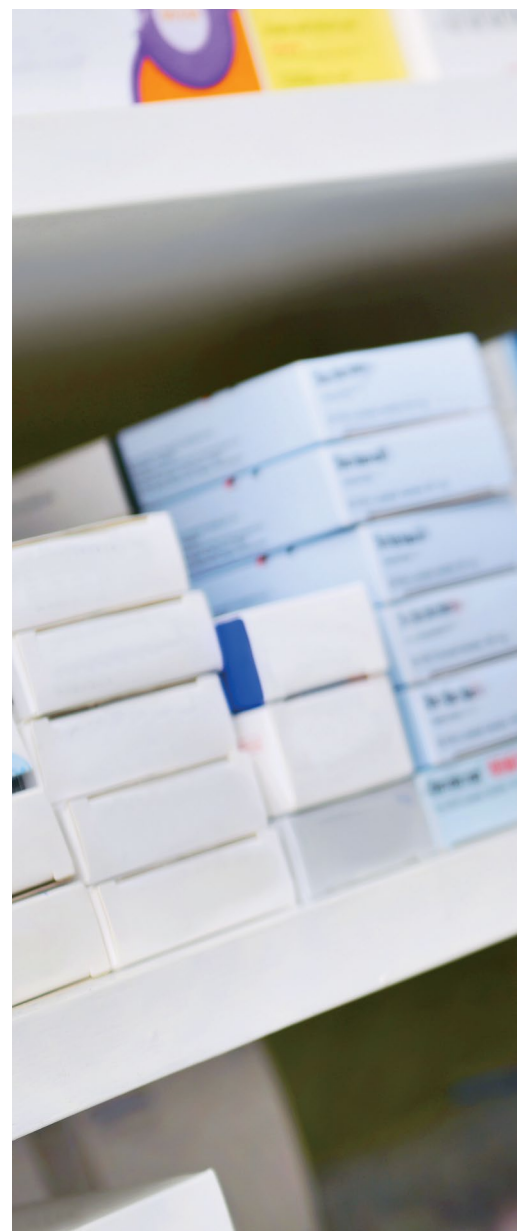
**Choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention.**

# Where are all the new antibiotics?

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*We need effective antibiotics more than ever, but a broken market has slowed down discovery.*

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**D**espite drug-resistant infections causing over a million deaths per year, the hunt for new antibiotics has not kept pace with the superbugs that have learnt to dodge their effects.

Associate Professor Mark Blaskovich, Director of IMB's Centre for Superbug Solutions, said we're no longer generating new and improved antibiotics fast enough to stay ahead of the bacteria gaining resistance.

## **So, why are there so few new antibiotics?**

A big reason is that the antibiotics market is broken, Dr Blaskovich said.

It can take anywhere between 10–15 years and over A\$1 billion to develop a new antibiotic, making it a costly and time-consuming process.

To put things in perspective, a two-week course of a new antibiotic costs around A\$15,000, while the latest CAR T-cell cancer therapy can rake in over A\$500,000 for a single treatment.

"You just don't get any economic return on all the money you're investing to develop a new antibiotic," Dr Blaskovich said.

Another problem is that bacteria quickly become resistant to new antibiotics, resulting in a short shelf life compared to other drugs.

To avoid giving bacteria a leg up, new antibiotics are only prescribed when routinely prescribed antibiotics are ineffective.

This means that they can only be

purchased in limited amounts, making it difficult for pharmaceutical companies to make a profit.

Most bacterial infections are cleared up with antibiotics that are already available, providing little incentive for companies to develop new ones that will only be used rarely.

"That's a disincentive for companies because it's counterintuitive: what they want to do is sell as much as possible," Dr Blaskovich said.

On top of this, antibiotics are typically used for a week or two at a time, while medications for chronic conditions like high cholesterol or cancer are taken over months or years.

With skyrocketing costs, meagre profits and drugs quickly becoming redundant as bacteria build resistance, most large pharmaceutical companies have pulled the pin on antibiotic development.

The bulk of the task has fallen on small biopharmaceutical companies, whose work accounts for over 95 per cent of antibiotic research and development.

While some of these companies have made progress in the hunt for new antibiotics, they don't generate enough revenue to cover the costs of bringing a new drug out of the lab and onto the market.

"This means that, fundamentally, the whole system for developing new antibiotics is not economically viable," Dr Blaskovich said.

"With skyrocketing costs, meagre profits and drugs quickly becoming redundant as bacteria build resistance, most large pharmaceutical companies have pulled the pin on antibiotic development."

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## BY THE NUMBERS

*Cost of developing a new antibiotic*

# A\$1bn





## How to fix a broken market



### Reward successful developers

A big problem with the current economic model for antibiotics is that companies need to sell large volumes to earn a profit, which is not feasible given that antibiotics are only bought in small amounts.

One possible solution proposed by UK economist Jim O'Neill is to implement a 'market entry rewards' system where successful developers are rewarded with a lump sum payment when their product reaches market.



### Create a subscription model

Instead of paying for antibiotics on a per dose basis, government organisations could pay pharmaceutical companies a set annual fee to access a variety of antibiotics, an approach that is currently being trialled in the United Kingdom and Sweden, and proposed in the USA through the PASTEUR Act. The Netflix-style model could give drug firms more incentive to develop new antibiotics, as payments are based on their overall value to public health rather than the amount of antibiotics used.



### Build a sustainable pipeline

The AMR Action Fund was developed by the World Health Organization, European Investment Bank and the Wellcome Trust to address the funding and technical challenges of bringing promising new antibiotics to market. The fund expects to invest more than US\$1 billion to support the clinical development of antibiotics and aims to bring up to four new antibiotics to patients by 2030.

# On the frontline in the battle against superbugs

**W**hile Australia is in a better position than many other countries when it comes to the prevalence of antibiotic-resistant bacteria, the SARS-Cov-2 pandemic could see a rise in home-grown superbugs.

One of Australia's leading infectious disease physicians, Professor David Paterson treats patients with antibiotic-resistant infections almost every day.

He fears the large number of COVID patients hospitalised with secondary infections could lead to an increase in superbugs.

Dr Paterson said it remains to be seen whether that will occur, but "that has certainly been the experience overseas when large numbers of COVID patients go into Intensive Care Units".

Dr Paterson, Director of The University of Queensland's Centre for Clinical Research (UQCCR) and an Affiliate Professorial Research Fellow with IMB, cites a case where a patient was repatriated back to Brisbane after spending time in an ICU overseas.

"They brought back with them an almost impossible-to-treat bacterium and we had to get an antibiotic from Japan (via a compassionate use program) that's not commercially available in Australia."

The treatment was a success and the patient recovered.

Dr Paterson said while COVID-19 provides a host of new problems, it has an unexpected upside: newer weapons with which to fight superbugs.

"I'm taking part in a trial on a vaccine against *E. coli* and the aim of that is to stop people getting [those] infections."

It's possible that many more infection-fighting vaccines could be developed on the back of the new vaccine technology that's been fast-tracked because of the pandemic.



Professor David Paterson

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*Doctors fear the COVID-19 pandemic could also contribute to an increase in antibiotic-resistant bacteria.*

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New contact tracing technology could also be deployed in hospital settings to work out the flow of staff members and patients who may have inadvertently spread infections.

"I think we're going to be assisted amazingly by the lessons we've learned from this fight against COVID," Dr Paterson said.

"I feel very proud, that here in Brisbane, we're at the world forefront of research into antibiotic resistance and that's going to benefit our population and save lives internationally."

Dr Paterson is collaborating with fellow UQCCR and IMB affiliate researcher Professor Jason Roberts on a clinical trial to optimise antibiotic dosing in the critically ill.

Professor Roberts is a clinical pharmacist at the Royal Brisbane and Women's Hospital and one of Australia's leading researchers on the topic.

Like Dr Paterson, he's concerned about the rise of superbugs in Australia.

Professor Roberts said it is not uncommon for Australian clinicians to be confronted by bacteria that are resistant to all antibiotics, and not able to be treated.

"It's quite a desperate and difficult situation to be confronted with, and that inspires us to



take measures that minimise the number of times that occurs," Professor Roberts said.

Whenever antibiotics are used, the potential for the emergence of resistance will occur.

Optimal antibiotic dosing regimens may differ across patient populations, and Professor Roberts said 15 years of research has been spent understanding which factors contribute to that need.

"We've now included all of those models into dosing software which provides an easy-to-access interface where we can enter information about the patient and it performs calculations to tell us the recommended dose."

The clinical trials will test whether the dosing software improves patient outcomes, as opposed to relying on a pharmaceutical company's product information.

"While we believe it will be a highly valuable intervention for patients, it may also reduce the emergence of antibiotic-resistant bacteria," Professor Roberts said.

He and his team at The University of Queensland have established a model to precisely match what is seen in patients while they're undergoing treatment.

"What we've observed is, if your dosing isn't optimal in about 36 to 48 hours, there's an emergence of resistant bacteria. By improving dosing, the model should help reduce antibiotic resistance."



Professor Jason Roberts



# A researcher's battle with sepsis

*How a sore throat turned into a fight for life.*

**I**n 2019, mother-of-two Dr Mel White was the fittest she'd ever been, thanks to a regimen of boot camp and cycling. On a holiday in the UK, before taking up a position at the Institute for Molecular Bioscience (IMB), the researcher had a sore throat, and within days was in a fight for her life.

"I developed a fever, I started vomiting and hallucinating and was screaming in agony - the pain was like nothing I'd ever experienced, and I just got sicker and sicker."

Over the next terrifying week, Dr White became critically ill. Her kidneys and liver started to fail, and an infection in her foot was spreading. Her medical team discussed amputating her leg to save her life. Her family was called in when doctors weren't sure she would survive.



"Eventually they identified a strep infection - it was in the tissue, the blood and the bones. I had been on antibiotics since I first got to the hospital but they hadn't been working. They tried different combinations of intravenous antibiotics and eventually found



four that seemed to fight the infection and they got me stabilised," Dr White said.

In Dr White's case, the bacteria were partially resistant to antibiotics. It took multiple surgeries to remove affected tissue and reconstruct her foot.

"I had to go through massive amounts of rehab and physiotherapy and I spent most of 2020 learning how to walk again," she said.

"I'm always going to limp, and I have chronic pain, but I have something that kind of looks like a foot and I still have my legs. So a much better result than we expected at the time."

Since winning her fight against sepsis, Dr White has established her laboratory at IMB and won a prestigious research fellowship. While her personal battle was with resistant bacteria, Dr White's research focuses on another devastating medical condition: defects of the neural tube.

## BY THE NUMBERS

# 20%

*of all deaths worldwide  
are due to sepsis*

"This embryonic structure forms into our brain and spinal cord," Dr White said. "The incorrect formation of the neural tube is one of the most common birth defects, affecting 300,000 babies worldwide each year."

"My research seeks to understand the underlying process of neural tube formation so we can understand the cause of these birth defects. This knowledge will form the basis of diagnostics and treatments in the future."



# Dietary diversity to promote “good bugs” in the gut

## What to eat to encourage healthy intestinal bacteria

**C**aring for our guts, or digestive system, by enhancing the growth of “good bugs” is an important focus for health. “Good bugs” are bacteria that live in our digestive systems and work with other chemical molecules to keep our entire body well. Altogether, these friendly bugs make up our gut “microbiome”.

Healthy intestinal bacteria serve many purposes, from improving digestion, reducing gut inflammation, and improving the immune system, to supporting brain health and cognition, and increasing the production of neurotransmitters – chemical messengers that allow nerves to communicate with each other and with muscles.

Being mindful of what you are feeding your gut is important and consistency is key. The good news is that healthy gut bacteria can be encouraged through making specific dietary choices. The even better news is that the gut microbiome can be changed within a week. This speedy shift can be achieved by eating more non-processed foods, for example, fruits and vegetables, legumes, nuts, seeds, whole cereals, and grains, which have been shown to keep the microbiome stable.

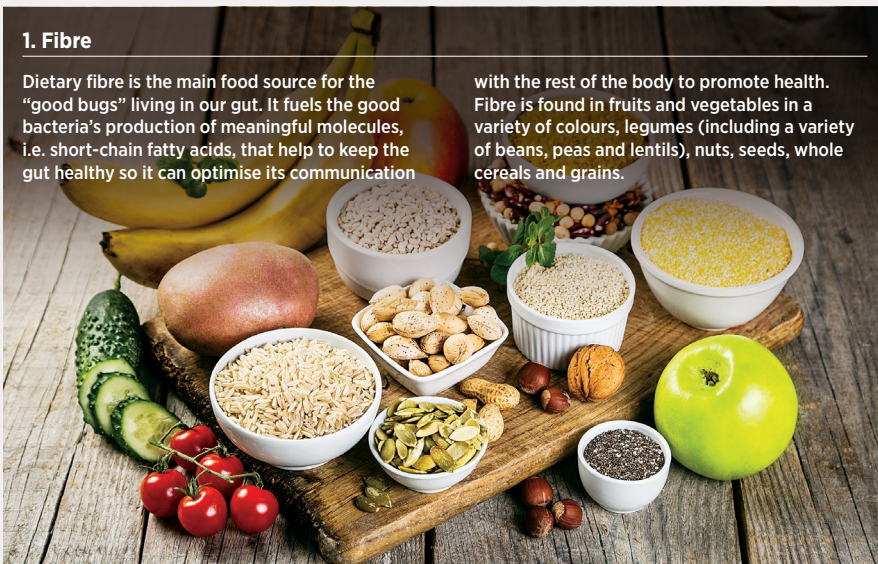


## Foods and food components that help to create and nourish good bacteria

### 1. Fibre

Dietary fibre is the main food source for the “good bugs” living in our gut. It fuels the good bacteria’s production of meaningful molecules, i.e. short-chain fatty acids, that help to keep the gut healthy so it can optimise its communication

with the rest of the body to promote health. Fibre is found in fruits and vegetables in a variety of colours, legumes (including a variety of beans, peas and lentils), nuts, seeds, whole cereals and grains.



### 2. Fermented foods



Yoghurt, kefir, fermented cottage cheese, kimchi, fermented vegetables and kombucha tea have been shown in scientific studies to increase the diversity of “good bugs” in the intestines and





## Dietary patterns that impair “good” gut bacteria

### Junk foods are not so friendly

Beware eating patterns that tip the balance towards the not-so-friendly bacteria and low bacterial diversity. These behaviours, which are so easy to adopt in a stressful, time-poor environment, give the “good bugs” the shaft. A dietary pattern rich in highly processed, energy-dense, low-fibre, nutrient-poor foods including white bread, chips, cake, high sugar foods and drinks, and “fast foods” are not the bugs’ friends. An eating pattern like this is a risk factor for chronic inflammation and chronic disease development, including type 2 diabetes and obesity. It is strongly linked with a poor gut microbiome, lacking diversity.

## Hacks to make (some) foods more gut-friendly

There are a few tricks to make foods better for the gut after minimal processing. For example, cooling potatoes after cooking changes the fibre structure so it is more resistant to digestion. This promotes short-chain fatty acid production by the good gut bacteria because they enjoy working harder to digest the food. The same benefit can be achieved by eating bananas while they are slightly green (if you like them that way!) and by cooking pasta or rice, cooling it, then enjoying it cold.



to reduce markers of gut inflammation. Having a range of different types of “good bugs” is beneficial, as they enjoy working together to achieve optimum health effects.

### 3. Phytochemicals

The nutrients that add unique colours to fruits and vegetables are called phytochemicals and help to enhance good bug growth and function, so it is important to eat a rainbow of these healthy foods each week. For example, polyphenols

(the blue, red and purple pigments found in various fruits and vegetables) help to enhance good gut bacteria growth and function through anti-inflammatory and antioxidant actions.





# Soil: the new weapon against superbugs

*People across the nation are being asked to “dig deep” in an Australian-first project, with the next “groundbreaking” medicine potentially hiding in their backyard.*

**S**oils for Science is a citizen science project that aims to unearth new antibiotics in backyards, gardens and farms across the state, spearheaded by the Institute for Molecular Bioscience.

Soils for Science Project Manager Dr Zeinab Khalil said society urgently needs new antibiotics to treat an alarming surge in drug-resistant bacterial and fungal infections.

“Over the years, nature has given us many valuable medicines, including most of the antibiotics we use today – but with these antibiotics becoming increasingly resistant to even last-resort treatments, we urgently need new leads,” she said.

“The extraordinary diversity of our natural landscape, from tropics to deserts, encompasses an enormous untapped potential for new antibiotics and other medicines.

“The next cure could start with you.”

Dr Khalil, Professor Rob Capon and their team are mining soil samples to help scientists at IMB and other researchers across the world discover and develop new antibiotics.

Microbes from soil samples are grown on petri dishes and assessed for their potential as antibiotics. They are also cryo-preserved as a resource for future science, and



photographed so the public can see the microbes living in their backyard.

Less than a year after launching in March 2021, more than 8000 soil samples have been registered in the accompanying app, and more than 7500 samples returned to IMB.

**The long-term goal of Soils for Science is to collect 100,000 soil samples and build a vast library to sustain future research and development.**

## Help us find the next antibiotic



THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA

FOR  
**SOILS  
SCIENCE**



RESEARCHER PROFILE

## Professor Rob Capon



Meet the researcher who has spent four decades venturing to almost every continent in a quest to harness nature to develop better medicines.

A pioneer in the field of biodiscovery, Professor Capon studies the chemical and biological properties of plants, animals and microbes collected everywhere from beaches to the deep sea, and from backyard dirt to caves deep underground.

As a PhD student, he was focused on the sponges and seaweeds of Australia's southern coast but turned to microbes later in his career.

"Many organisms that don't have the ability to fight, flee or hide such as marine sponges and seaweeds, and microbes, often rely on chemical defences," Professor Capon said.

"While our chemical discoveries from sponges and seaweeds offered promise, scale-up was always a challenge. It's just not that easy to back a truck up to the ocean and fill it with one species of sponge or seaweed. Microbes on the other hand can be fermented at any scale for modest cost."

RESEARCHER PROFILE

## Dr Zeinab Khalil



It seems counterintuitive to convince a smart student with a determination to heal people not to study medicine.

Yet, Dr Zeinab Khalil credits a high school science teacher with recognising where her talents truly lay and steering her towards a career where that passion and determination could have the greatest benefit.

"I come from a family of two parents who were doctors and I always thought I'd have a career in medicine too," Dr Khalil said of her childhood in Cairo, Egypt.

"When I was around 14 years old, I had a biology teacher who really inspired me. She sparked a love of studying biology and, in particular, how the human body and immune system behaved following bacterial or fungal infection.

"She asked me why I wanted to study medicine when I could study the drugs instead.

"I knew then that pharmacy was for me – I could learn how drugs are developed, how they interact with humans and how they can impact treatment."



Request a soil kit and get digging



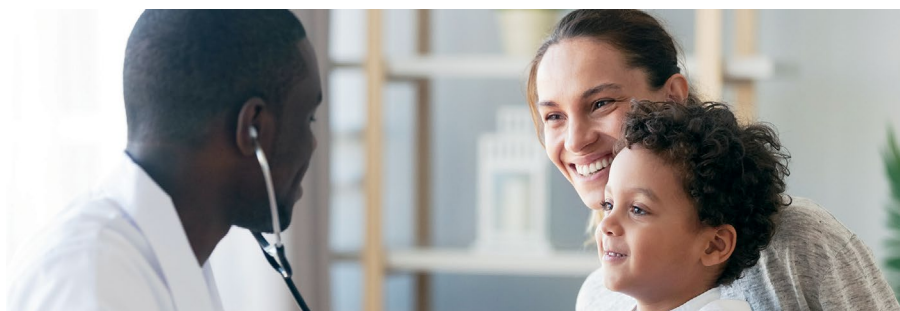
View the Soils for Science gallery

# Improving diagnostics

*One of the barriers to stemming the rise of resistance to antibiotics is their overuse, and often this is because bacterial and viral infections have very similar symptoms.*

**I**f a patient comes into a GP's office with respiratory symptoms that won't go away, it's difficult to tell if it is a viral infection or an associated bacterial infection. Without a swab that needs to be sent off to a lab for testing, GPs often don't have a definitive answer and often antibiotics are prescribed "just in case." Researchers at IMB are working on ways to be able to capture and identify bacteria from infections within hours instead of days.

These molecular tools are improving doctors' ability to identify viral or bacterial infections more quickly and efficiently – the hope is that doctors can test patients at the GP's surgery or in an emergency and find out straight away if their illness is caused by a virus or a bacterium. In this way, only patients with bacterial infections will be given antibiotics, plus an antibiotic specific to the bacteria with which they are infected.



## Overprescribing of antibiotics has sped up resistance

Antibiotics don't cure everything, only infections caused by bacteria.

"Probably two-thirds of antibiotics are inappropriately prescribed," Associate Professor Mark Blaskovich, Director of the Centre for Superbug Solutions, said.

"Colds and flu are caused by viruses, so taking antibiotics does not speed up your recovery."

Sometimes, we feel so ill that we just want a quick fix, but if you have a cold or the flu, the only treatment is painkillers to reduce your fever, rest and plenty of fluids."

## RESEARCHER PROFILE

### Associate Professor Mark Blaskovich

From a very young age, Associate Professor Mark Blaskovich knew he wanted to be an inventor.

Ironically, for the medicinal chemist who has 25 years' experience in industry and academia and is an inventor on 11 patent families, chemistry was one of his worst subjects at school. But its practical, hands-on nature appealed to the budding inventor, and he pursued it through a "co-op" undergraduate degree, where he alternated university semesters with industrial placements at companies such as Atomic Energy of Canada.

"This work at a company that made radiopharmaceuticals piqued my interest in medicinal compounds, so for my PhD I wanted to look at the potential for therapeutic

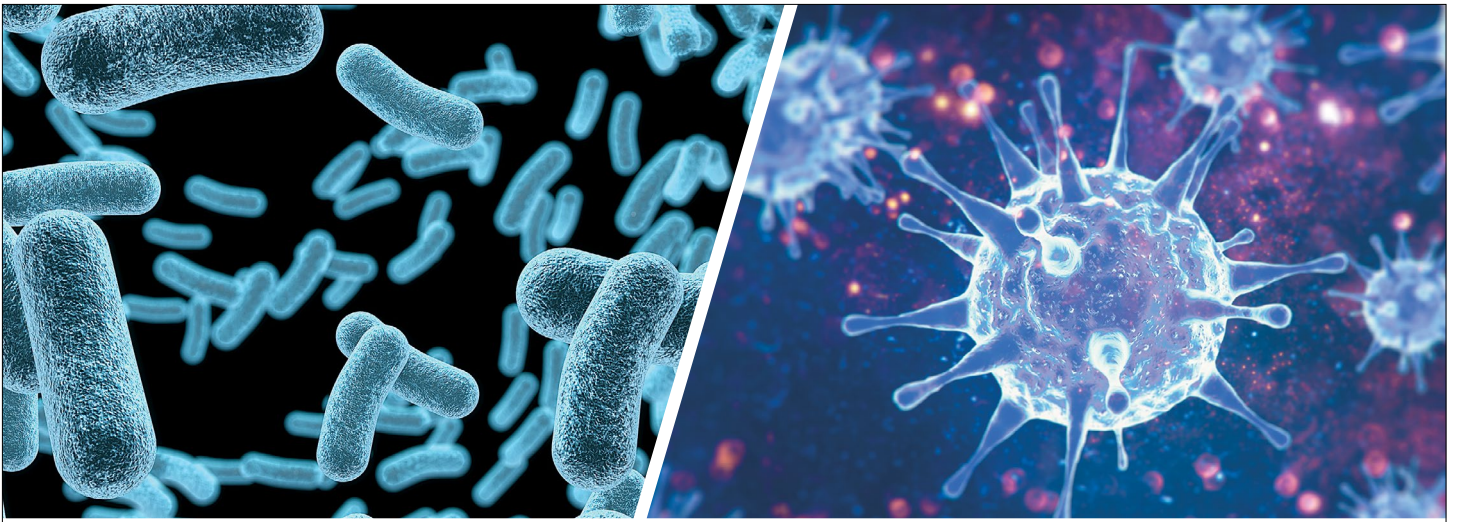
development and that triggered my interest in antimicrobial resistance.

"Antibiotics have probably saved more lives than any other medicine, and we are facing the potential of returning to a pre-antibiotic era," he said.

Now as the Director of the Centre for Superbug Solutions, he is harnessing the expertise of IMB's multidisciplinary researchers to develop solutions for the global problem of antimicrobial resistance.







# Bacteria vs viruses: what's the difference?

*Both bacteria and viruses are invisible to the naked eye and cause your sniff, fever or cough, so how can we tell the difference?*

**W**ith bacteria rapidly developing resistance to antibiotics, it is increasingly important that we know the distinction between bacteria and viruses, because viruses can't be treated with antibiotics, nor bacteria with antivirals.

Rapid and effective testing is imperative, so we can successfully treat the offending microorganism.

COVID-19 taught us the hard way – we had no treatment for a new virus until we had vaccines specifically targeted against it, and specific anti-viral drugs.

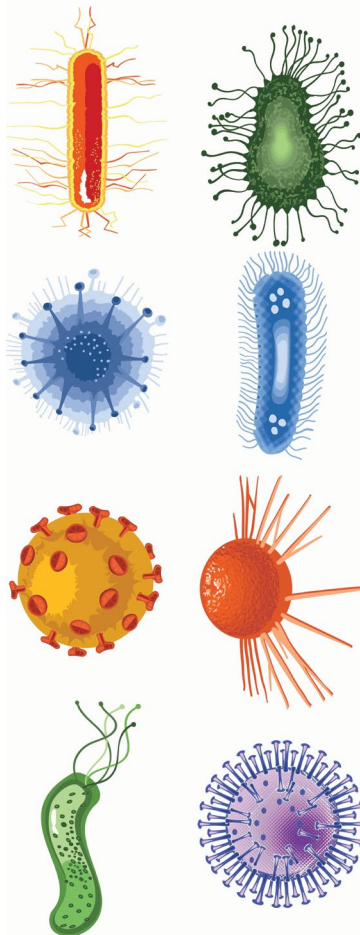
Therapies developed against an existing virus often do not work, or work poorly, against a new virus. For new emergents, our best weapons are handwashing and physical distancing.

On a biological level, the main difference is that bacteria are free-living cells that can live inside or outside a body, while viruses are a non-living collection of molecules that need a host to replicate.

Many bacteria help us: living in our gut digesting and helping absorption of our food, fixing nitrogen and decomposing organic materials in soil. Similarly, not all viruses are bad – we now know there are also beneficial viruses present in our gut, skin and blood that can kill undesirable bacteria and more dangerous viruses.

## Why is it so important to tell the difference?

It is important to know the difference between a viral and a bacterial infection so doctors can



treat the right illness, and antibiotics aren't used unnecessarily, contributing to the rise of antibiotic-resistant bacteria.

It is also why you shouldn't expect your doctor to prescribe antibiotics if you're suffering from a viral infection such as a cold.

## Bacterial and viral infections are often related

While bacterial and viral infections are different, they are often related.

Severe cases of viral pneumonia often end up with an associated bacterial infection. This is particularly true with COVID-19, where up to 50% of the severely ill hospitalised patients have also developed a bacterial infection. So, despite COVID-19 being caused by a virus, antibiotics are really important to treat the associated bacterial infections.

As antibiotic-resistant bacteria are an increasing global problem, researchers at IMB are investigating the surface activity of bacteria at the molecular level and have discovered how they elude the human immune system. They are also looking at developing new therapies to treat resistant bacteria, and working to help researchers around the world discover new antibiotics.

We're now well on the way to developing preventative therapies, biomarkers and vaccines to foil these elusive microbial assassins from plaguing our world.

# Crowdsourcing superbug solutions

*A global shout-out has uncovered hundreds of thousands of antibiotic leads.*

**S**cientists from IMB have turned to crowdsourcing to help solve the superbug challenge, tapping into researchers the world over to discover the next generation of antibiotics through CO-ADD, the Community for Open Antimicrobial Drug Discovery.

This not-for-profit initiative, founded by Professor Matt Cooper and Associate Professor Mark Blaskovich in 2015 in partnership with the Wellcome Trust and other groups, screens compounds for antimicrobial activity, free of charge to academic researchers globally.

There are currently 57 million compounds registered in the Chemical Abstracts Service (CAS) registry whose chemical properties remain unknown, leaving a plethora of potential antibiotics to be discovered.

"It is still not clear how to design a better

antibiotic, and understanding the desirable chemical properties would help," Dr Blaskovich said.

"We are now applying artificial intelligence methods to study a unique dataset of compounds crowdsourced from academic groups from all around the world to develop predictive models for antibacterial activity and membrane penetration.

"We will then apply these models to design new antibiotics, which will be synthesised and tested for antimicrobial activity."

After a global shout-out, CO-ADD has screened over 300,000 unique compounds sent in from researchers in 45 countries – a fantastic opportunity to investigate what this mysterious reservoir of chemical compounds can offer in the world's race to defeat superbugs.

## BY THE NUMBERS

*Number of unique compounds received by CO-ADD for screening for antimicrobial activity*

# 300k+



## Finding the right dose

One size doesn't fit all when it comes to medication doses, but patients are often prescribed the same dose as one another despite differences in how people process medicine.



Dr Robert McLeay was inspired to solve this problem by developing a tool that allows doctors to personalise doses for an individual patient.

Dr McLeay drew on his skills in bioinformatics – developing software to understand biological data – previously cemented with a PhD at IMB, to found the company DoseMe in 2014. Its software, DoseMeRx, builds a virtual model of a patient and allows a doctor to calculate the most effective dose for that patient. Doctors can also simulate different dosing regimens ahead of prescribing medication.

The software is available across a range of medications, including antibiotics. DoseMeRx has enabled hospitals to reduce the incidence of antibiotic-associated acute kidney injury by 83 per cent – a win for patients, doctors and hospitals alike.

After fewer than five years of operation, DoseMe was acquired by US-based Tabula Rasa Healthcare. It is now used by hundreds of hospitals in 10 countries, while Dr McLeay continues his journey of helping patients at an individual level by completing studies to become a medical doctor.



# Supercharging old antibiotics: the potential of potentiators

Dr Alysha Elliott is forging a new weapon in the fight against superbugs – and it's not antibiotics.

Instead, she is tapping into potentiators, non-antibiotic drugs that increase the potency of existing antibiotics to which bacteria have become resistant.

Dr Elliott said potentiators have been shown to help some antibiotics regain their activity against bacteria that have developed high levels of drug resistance, and reduce the amount of antibiotic required to effectively kill bacteria by up to 100-fold.

"The benefit is that we can potentially restore the use of cheap generic antibiotics that are widely used in low and middle income countries, where there are high levels of drug-resistant bacteria," Dr Elliott said.

"We are also sharing our expertise and technologies with researchers in countries such as Pakistan, Nepal, Egypt, Nigeria, Brazil, Thailand and Indonesia so they can genetically sequence resistant bacteria strains in real-time as they emerge."

## RESEARCHER PROFILE

# Dr Alysha Elliott

The passing of a close relative and working with a great team have fuelled Dr Elliott's passion to tackle anti-microbial resistance.

She has won funding to take her work to less-developed countries – an ambition she is juggling with raising two young sons.

"There has been a lot of media coverage about superbugs, but on an individual level, the message often doesn't get through until it happens to someone you care about," Dr Elliott said.

"Then you realise, for some infections, there really aren't any treatments left."

Dr Elliott had that "close to home" moment when her grandfather passed away from kidney failure.

"It really hit me then, when he got an infection and the antibiotics



couldn't save him – this happens every day in hospitals, but this time it happened to someone I love."

"More people die every day of infection than some other diseases, but it's just not known or talked about as it is usually the kidney failure, heart surgery or cancer which is written up as the cause of death."

# Fluorescent probes: a glowing hope

Shining a light on how an individual bacterium develops resistance

Associate Professor Mark Blaskovich's team is using tiny fluorescent probes derived from antibiotics to investigate how and why bacteria are becoming resistant to antibiotics.

"Using these probes we can measure and monitor the interactions of antibiotics with hundreds to thousands of individual bacteria, something you don't normally see when studying bacterial populations as a whole," Dr Blaskovich said.

"It can help to uncover different ways in which bacteria are developing resistance to antibiotics and understand how we can develop better ways to kill bacteria more effectively, especially those that are becoming resistant."

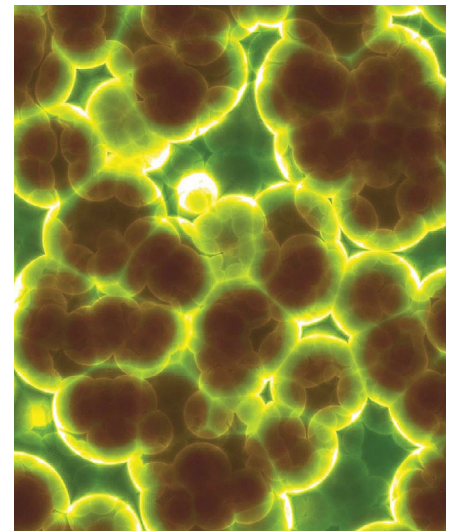
By using an antibiotic tagged with a fluorescent probe, the researchers can see the rate at which the antibiotic is being taken up by the bacteria.

"While one group of bacteria started glowing at the same time, indicating they were taking up the antibiotic simultaneously, another group was very variable as to when or if they picked up any of the probes," Dr Blaskovich said.

"This variability might explain why these bacteria are able to survive – they aren't picking up any of the antibiotics at all."

While the researchers don't yet know why these bacteria aren't being affected by antibiotics, it gives them an idea as to avenues to explore to figure out the mechanisms bacteria are using.

Dr Blaskovich hopes the findings will inspire further studies to understand why some bacteria are able to resist antibiotics, and lead to better antibiotics that can kill bacteria more effectively.



# No antibiotics required

*The “garbage trucks” of the body might help us fight infection.*

Training our immune system to better defend against infection could provide another avenue to treating bacterial diseases.

**P**rofessor Matt Sweet, from IMB's Centre for Inflammation and Disease Research, is trying to understand how our immune system detects and responds to infections.

“Although new antibiotics are being developed, bacteria can rapidly evolve to defend against them,” Dr Sweet said. “Of course, such approaches to combat bacterial infections are still incredibly important, because if there's no antibiotic that can be used, you're in serious trouble. But we're trying another approach – to manipulate or 'train' the immune system to better defend against infection.”

Dr Sweet's research focuses on characterising genes and pathways in immune cells called macrophages, which both drive inflammation and are involved in the clearance of bacterial pathogens.

“Macrophages are cells that are present in every tissue in our body. They detect danger – if we cut ourselves or have an infection, for example,” Professor Sweet said. “These cells are often long-lived, and they use a number of different strategies to defend against pathogens.”

Professor Sweet describes macrophages as the “garbage trucks of the body”, gobbling up and destroying pathogens and unwanted debris: “Once they take up the pathogen, they engage a range of different pathways to try to kill the ingested microorganism.”

But this is not always effective. Pathogens actively evade the immune system – and many actually do so by hiding out inside the macrophages – a cunning strategy employed by a number of different viruses, bacteria, parasites and fungi.

“Over the past decade, scientists have discovered several antimicrobial strategies that are used by macrophages to successfully overcome infections. We found that macrophages use toxic concentrations of metal ions to kill intracellular bacteria.”

Metals such as zinc and iron are essential for survival. Many of the enzymes in both

our own cells and in bacteria need zinc and iron to function. One of the responses of the immune system involves starving bacteria of these metals. But another strategy relies on the delivery of toxic concentrations of zinc and copper to kill the bacteria in macrophages.

“We have previously found, in collaboration with other researchers at The University of Queensland, that macrophages take up copper and zinc from outside the cell to clear bacterial pathogens within these cells,” Professor Sweet said.

If Professor Sweet and his lab can understand how macrophages defend against bacteria, they might be able to reprogram these cells to be better equipped to fight superbugs.

In recent times, there's been a lot of interest in this approach, which Professor Sweet says reflects the concern about the rapid increase in multidrug-resistant bacteria. And that's pushed the field into thinking about different ways of tackling bacterial resistance – no antibiotics required.

“We do have some exciting new data in development,” he said. “These findings suggest that we can indeed manipulate macrophages to more effectively clear intracellular bacterial infections.”

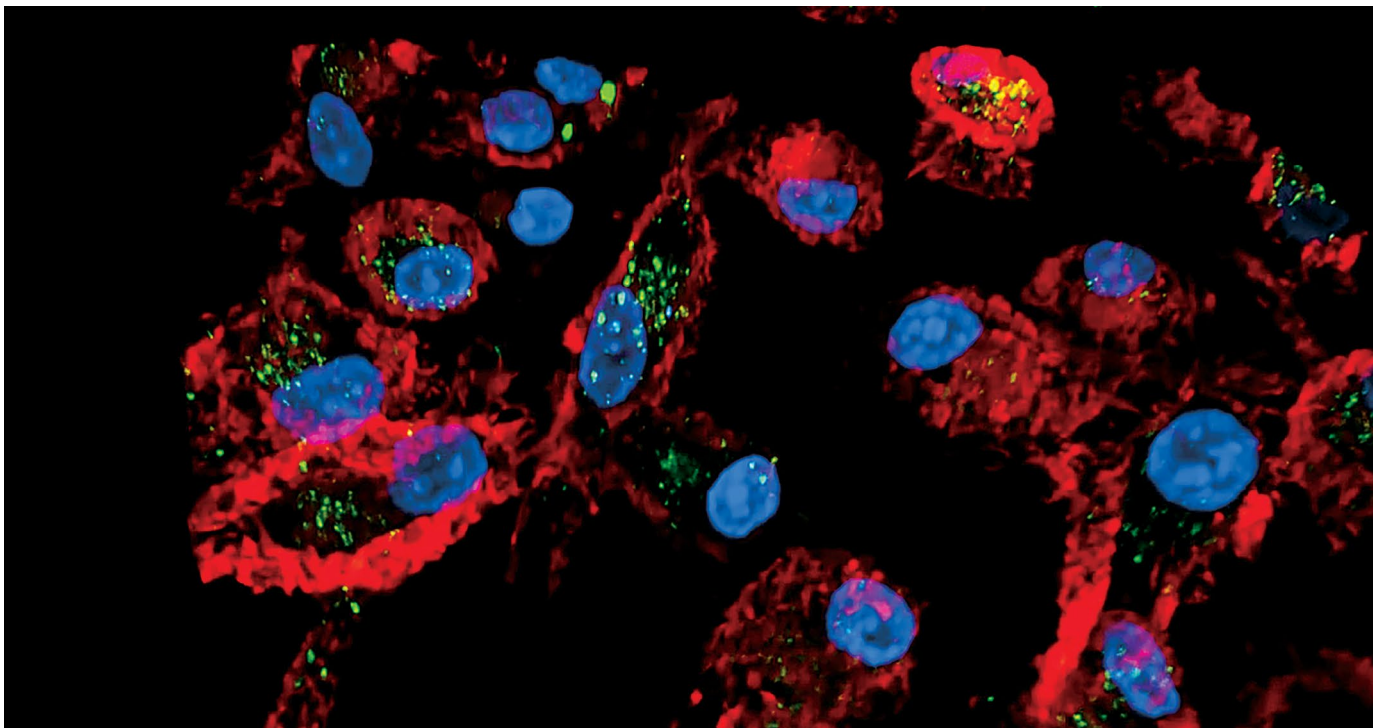


Image: Macrophages (blue nucleus and red membranes) harnessing zinc (green) to fight off infection.



RESEARCHER PROFILE

# Professor Ian Henderson

It was a knowledge of history that inspired this researcher to study some of the world's smallest living organisms.

Professor Henderson, who is Irish born and bred, says he has always been fascinated by how decisions in history shape the world in which we live today.

"Growing up in Ireland, the microbe that stands out most in the school curriculum is the one that caused potato blight, which directly led to the Irish famine.

This event had a massive impact on Irish society, causing mass deaths and emigration, depleting three-quarters of the population, and it was all caused by a tiny organism – this really drove my interest in microbes.

"But microbes aren't a historical footnote. I think people forget, or don't know, the impact that microbes continue to have in all sorts of diseases: communicable, the infections that we normally associate with microbes, but also non-communicable disease. Microbes play a role in diabetes, cancer, causing stroke and heart attacks – this is not really recognised by the public or even by some of our peers," Professor Henderson said.



His research is focused on solving the problem of infection.

"All cells, including bacteria, have a surface, and the structure of this surface is crucial to how they interact with their environment.

"If we can understand the relationship between the surface of a bacterial cell and its environment, then we can disrupt those interactions and stop infection, and the negative consequences of coming into contact with some microorganisms."

His research has already led to an effective new treatment, nicknamed "vampire" therapy. Dr Henderson found that some patients overproduce antibodies. These

proteins are designed to kill bacteria, but in these patients, the antibodies actually protect the bacterial cell from death, leading to severe infection.

Dr Henderson and his team found that some patients could be treated by draining a non-lethal amount of their blood – hence the nickname "vampire" therapy – filtering it to remove the antibodies, and returning it to the patient before applying the drug therapy.

It's not a course of action for every patient or every infection, and right now it's not available to enough clinicians for them to discover if their patients would benefit, but it is another tool in treating severe infections when all other treatments have failed.

## The Edge: Conversations



Listen to the personal and inspiring stories of people with infection, pain and other chronic illnesses, and the researchers seeking a cure.



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CONVERSATIONS



# Antibiotics from nature

*Outer space has long been a source of fascination and exploration but if you're serious about discovering new life forms, swap telescopes for microscopes and shift your gaze downwards instead.*

The natural world remains a remarkable resource for science and discovery, informing our understanding of the world in which we live, and inspiring breakthroughs in medicine and agriculture.

**M**ore than half of the world's currently prescribed antibiotics come from natural sources as do more than 60 per cent of anticancer drugs.

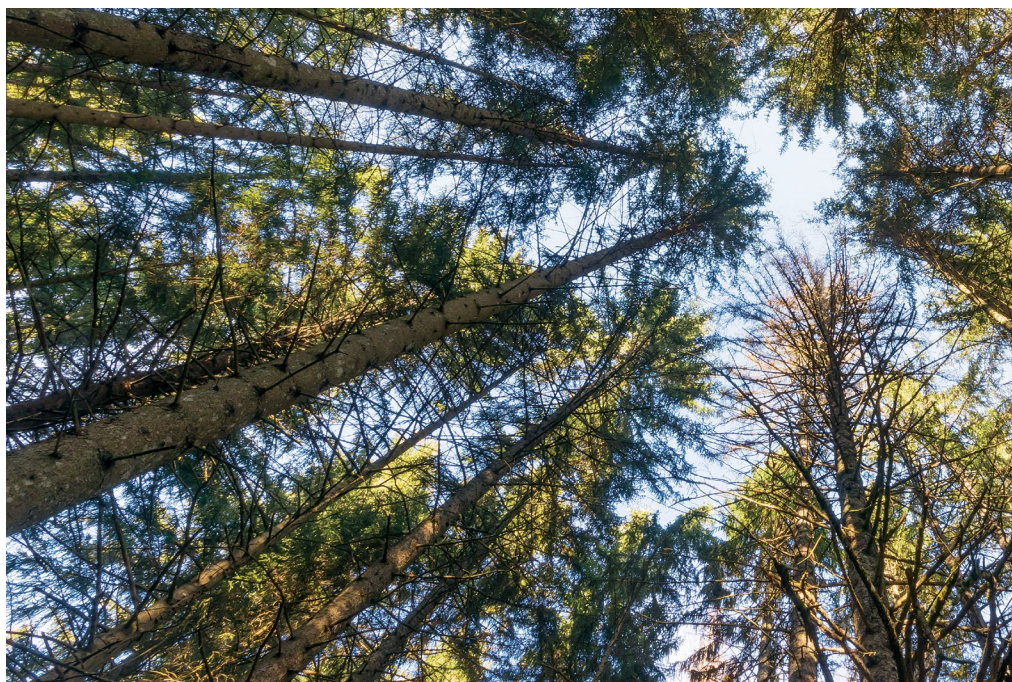
Here are five common antibiotics derived from nature:

## Capreomycin

An anti-inflammatory antibiotic, Capreomycin was discovered in the United States in 1960 and developed from the soil bacterium, *Streptomyces capreolus*. It is used in combination with other antibiotics to treat tuberculosis.

## Penicillin

British microbiologist Alexander Fleming discovered penicillin, from the *Penicillium notatum* mould, in 1928. Howard Florey and Ernst Chain turned penicillin into the world's first antibiotic during subsequent years of research. This groundbreaking drug is still used to treat bacterial infections caused by strains of staphylococci and streptococci such as pneumonia, meningitis and septicaemia. It can also be used to treat anthrax, botulism and tetanus.



## Rifampicin

Rifampicin is an antibiotic, developed in 1965 from the soil bacterium *Amycolatopsis rifamycinica*, which was discovered in a soil sample taken from a pine forest on the French Riviera. It is used to treat several types of bacterial infection including tuberculosis, *Mycobacterium avium* complex, leprosy and Legionnaires' disease.



## Vancomycin

A soil sample collected from the interior jungles of Borneo by missionary Rev. William M. Bouw yielded the *Amycolatopsis orientalis* organism, which led to the development of vancomycin in 1953. This antibiotic is used to treat bacterial skin and bloodstream infections, endocarditis, bone and joint infections and meningitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

BY THE NUMBERS

Number of bacterial species present in a gram of soil

1000



BY THE NUMBERS

Deaths worldwide each year directly caused by antimicrobial resistance

1.27m



### Aureomycin

Aureomycin, also known as chlortetracycline, was the first tetracycline antibiotic identified. It was discovered by plant physiologist Benjamin Minge Duggar in 1945 as the product of *Streptomyces aureofaciens*, a bacteria he cultured from a soil sample collected from the University of Missouri's Sanborn Field. It is used to treat allergic dermatitis in humans as well as conjunctivitis, infected wounds and respiratory tract infections in animals.

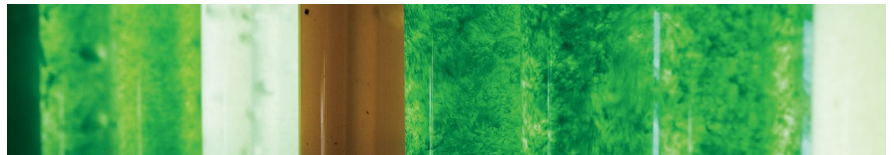


# Future sources of antibiotics

*Nature still has secrets to share.*

### Algae

Microalgae – single-celled algae – could be the light-driven “factories” of future medicines to fight bacterial infections. IMB researchers are investigating the use of photobioreactors filled with microalgae to produce lysins, a type of enzyme that targets the bacterial cell wall. Lysins are highly specific and able to target disease-causing bacteria, while causing no harm to the body's natural healthy bacteria. Very low resistance from bacteria has been observed so far. Production of lysins in microalgae is fast and cost-effective, making it a promising way to fight bacteria.



### Metals

Compounds containing metals such as silver, manganese, zinc, ruthenium and iridium have a much greater chance of killing bacteria or fungi than more traditional compounds without a metal component, IMB researchers have found. Importantly, many of these metal compounds are selective at killing microorganisms, but not human cells. This potential for metal complexes as a new class of antibiotics was discovered through more than five years of research by CO-ADD, an international initiative to uncover untested chemical diversity (see pg 18).

CO-ADD has screened hundreds of thousands of compounds that would not otherwise have been tested as potential antibiotics against seven disease-causing bacteria and fungi. Together with the Shared Platform for Antibiotic Research (SPARK), a public database enabling scientists to share data and insights from past research and generate new knowledge on killing bacteria, it is a powerful global resource that provides researchers the world over with the tools to fight back against superbugs.



### Cannabis

Synthetic cannabidiol, better known as CBD – the main nonpsychoactive component of cannabis – can penetrate and kill a wide range of bacteria. IMB researchers have shown that CBD can even kill some types of Gram-negative bacteria such as *Neisseria gonorrhoeae*, which causes gonorrhoea. Gram-negative bacteria have an extra outer membrane, an additional line of defence that makes it harder for antibiotics to penetrate. The same study showed that CBD was also effective against Gram-positive bacteria, including MRSA, also known as golden staph.

Researchers showed that CBD is particularly good at breaking down biofilms – the slimy build-up of bacteria, such as dental plaque on the surface of teeth – which help bacteria such as MRSA survive antibiotic treatments.

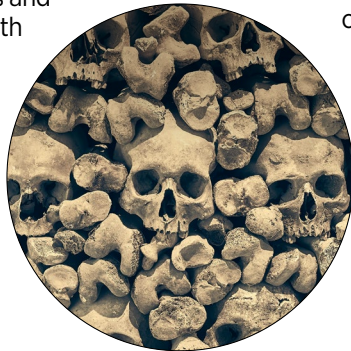


# The bacterial timeline

Researchers around the world continue to develop new ways of combating bacterial infection.

## ~ 30,000 YEARS AGO

– Earliest evidence of humans using bacteria (roots and tubers fermented with microorganisms), in the Solomon Islands



## 1861

Louis Pasteur presents his “germ theory” that microorganisms can cause disease



## 1950s

Half of all antibiotics in use today are discovered



## 1346

Outbreak of bubonic plague, caused by the bacterium *Yersinia pestis*, which killed an estimated 50 million people (50-60 per cent of population of Europe at the time)

## 1928

Alexander Fleming discovers penicillin

## 1947

The first instances of bacterial resistance against penicillin arise or are documented?

## ~ 2500 YEARS AGO

Ancient antibiotics: fungus that grows on soybean curd is used to cure boils



## 1940

Howard Florey and Ernst Chain discover penicillin can treat bacterial infections in humans

## 1942

Penicillin is mass produced for the first time



## 1673

Antoine van Leeuwenhoek invents the microscope and describes microbes for the first time

## 1881

Robert Koch is the first to grow bacteria in the lab, allowing him to identify the organisms responsible for tuberculosis, septicaemia, cholera and anthrax, and paving the way for future research into bacterial disease



We've been harnessing the helpful properties of bacteria for tens of thousands of years, but have also been prey to the diseases they cause. As we fought back with antibiotics, so did bacteria, by developing resistance. Researchers around the world continue to develop new ways of combatting bacterial infection.

### 2013

The UK Chief Medical Officer and the Director of the US Centers for Disease Control and Prevention separately warn of the "catastrophic threat" of antibiotic resistance



### 2017

*Klebsiella pneumoniae* resistant to all antibiotics is described



### 1980s

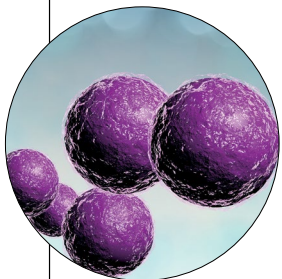
The last new class of antibiotics that are currently used is discovered. Most pharmaceutical companies exit antibiotic discovery

### 2015

Widespread resistance to colistin is described. This was widely considered to be the antibiotic of last resort

### 2021

Launch of Soils for Science (see pg 14) to discover new antibiotics from soil samples sent in by the public



### 1995

Sequencing of the first bacterial genome, *Haemophilus influenzae*

### 2016

'Vampire' therapy shown to be an effective treatment for resistant infections (see pg 21)



### 1959

The first bacteria resistant to multiple drugs (multi-resistant *S. aureus*) occurs

### 2015

The Community for Open Antimicrobial Drug Discovery and the Centre for Superbug Solutions are launched with a mission to develop new antibiotics, improve diagnosis and educate the community

### 2019

The World Health Organization declares antimicrobial resistance one of the top 10 global public health threats facing humanity

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