

# Antibiotic resistance: A challenge for the 21st century

**FACTFILE**



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## What are antibiotics?

Any substance that inhibits the growth and replication of a bacterium or kills it outright can be called an antibiotic. Antibiotics are a type of antimicrobial designed to target bacterial infections within (or on) the body. This makes antibiotics subtly different from the other main kinds of antimicrobials widely used today:

- **Antiseptics** are used to sterilise surfaces of living tissue when the risk of infection is high, such as during surgery.
- **Disinfectants** are non-selective antimicrobials, killing a wide range of micro-organisms including bacteria. They are used on non-living surfaces, for example in hospitals.

Of course, bacteria are not the only microbes that can be harmful to us. Fungi and viruses can also be a danger to humans, and they are targeted by antifungals and antivirals, respectively. Only substances that target bacteria are called antibiotics, while the name antimicrobial is an umbrella term for

anything that inhibits or kills microbial cells including antibiotics, antifungals, antivirals and chemicals such as antiseptics.

Most antibiotics used today are produced in laboratories, but they are often based on compounds scientists have found in nature (Box 1). Some microbes, for example, produce substances specifically to kill other nearby bacteria in order to gain an advantage when competing for food, water or other limited resources. However, some microbes only produce antibiotics in the laboratory.

## Antibiotic preparations

Antibiotic preparations come in many different forms, depending on where the infection they are targeting is located. Creams or ointments may be applied to infections on the outside of the body, while pills or liquids are used for most infections inside the body. Here, antibiotics are absorbed into the bloodstream or target bacteria in the digestive tract itself. Injections of antibiotics directly into the bloodstream (intravenous antibiotics) are only used for the most serious infections.

## Definitions of some key terms

Term	Definition
Antibiotic	A class of drugs used to treat bacterial infections.
Antibacterial	Used to be a synonym for antibiotics. Today, substances used to disinfect non-living surfaces are known as antibacterials.
Antifungal	A class of drugs used to treat fungal infections.
Antiviral	A class of drugs used to treat viral infections.
Antimicrobial	An umbrella term for antibiotics and antibacterial, antifungal and antiviral substances

## Box 1. Leafcutter ants



Leafcutter ants live in huge, sprawling colonies of up to 8 million individuals. To cultivate a fungus, *Leucoagaricus gongylophorus*, in 'gardens' within their colonies, the ants feed the leaves they cut to the fungus, which in turn is the colony's sole food source. Leafcutter ants thus form sophisticated farming societies in symbiosis with the fungal cultivar.

However, the ants are not the only ones who want a bite out of *L. gongylophorus*. In the warm, damp underground chambers within the ant colony, the fungus is at risk of being invaded by a range of harmful fungi. The ants have evolved defences against this constant threat – among others, they grow actinomycete bacteria on their bodies which produce antibiotics that the ants use to protect themselves and their fungus against infection.

## History of antibiotics

Antibiotics have been used for millennia to treat infections, although until the last century or so people did not know the infections were caused by bacteria. Various moulds and plant extracts were used to treat infections by some of the earliest civilisations – the ancient Egyptians, for example, applied mouldy bread<sup>1</sup> to infected wounds. Nevertheless, until the 20th century, infections that we now consider straightforward to treat – such as pneumonia and diarrhoea – that are caused by bacteria, were the number one cause of human death in the developed world<sup>2,3,4</sup>.

It wasn't until the late 19th century that scientists began to observe antibacterial chemicals in action. Paul

Ehrlich, a German physician, noted that certain chemical dyes coloured some bacterial cells but not others<sup>5</sup>. He concluded that, according to this principle, it must be possible to create substances that can kill certain bacteria selectively without harming other cells. In 1909, he discovered that a chemical called arsphenamine was an effective treatment for syphilis. This became the first modern antibiotic, although Ehrlich himself referred to his discovery as 'chemotherapy' – the use of a chemical to treat a disease<sup>6</sup>. The word 'antibiotics' was first used over 30 years later by the Ukrainian-American inventor and microbiologist Selman Waksman, who in his lifetime discovered over 20 antibiotics.

Alexander Fleming was a messy man by nature who accidentally discovered penicillin. Upon returning from a holiday in Suffolk in 1928, he noticed that a fungus, *Penicillium notatum*, had contaminated a culture plate of *Staphylococcus* bacteria he had accidentally left uncovered. The fungus had created bacteria-free zones wherever it grew on the plate. Fleming isolated and grew the mould in pure culture. He found that *P. notatum* proved extremely effective even at very low concentrations, preventing *Staphylococcus* growth even when diluted 800 times, and was less toxic than the disinfectants used at the time.

After early trials in treating human wounds, collaborations with British pharmaceutical companies ensured that the mass production of penicillin (the antibiotic chemical produced by *P. notatum*) was possible. Following a fire in Boston, MA, USA, in which nearly 500 people died, many survivors received skin grafts which are liable to infection by *Staphylococcus*<sup>7</sup>. Treatment with penicillin was hugely successful, and the US government began supporting the mass production of the drug. By D-Day in 1944, penicillin was being widely used to treat troops for infections both in the field and in hospitals throughout Europe. By the end of World War II, penicillin was nicknamed 'the wonder drug' and had saved many lives.

Scientists in Oxford were instrumental in developing the mass production process, and Howard Florey and Ernest Chain shared the 1945 Nobel Prize in Medicine with Alexander Fleming for their role in creating the first mass-produced antibiotic.



Dr Selman Waksman (left) discusses his experiments with visiting Nobel laureate Sir Alexander Fleming in 1951. Waksman was awarded the Nobel Prize in 1952 for the discovery of streptomycin, the first antibiotic effective against tuberculosis.



A Petri dish culture of the fungus *Penicillium notatum* growing on agar.



Routine surgery would be set back by decades without antibiotics.

### Why are antibiotics important?

The introduction of antibiotics into medicine revolutionised the way infectious diseases were treated. Between 1945 and 1972, average human life expectancy jumped by eight years, with antibiotics used to treat infections that were previously likely to kill patients. Today, antibiotics are one of the most common classes of drugs used in medicine and make possible many of the complex surgeries that have become routine around the world.

The public health revolution that antibiotics brought about was not without its cost. The more we use them, the more resistant bacteria become. The US Department of Health estimates that half of all antibiotics used worldwide are either unnecessary or prescribed incorrectly<sup>8</sup>.

With antibiotic resistance on the rise, increasing numbers of people die every year of infections

caused by bacteria that have become resistant to the antibiotics previously used to treat them. It is estimated that, by 2050, the global cumulative cost of antibiotic resistance will reach US\$100 trillion<sup>9</sup>.

In the 1950s and 1960s new drugs were being isolated all the time<sup>10,11</sup>. However, the rate of drug discovery has slowed markedly. This lack of effective new antibiotics means that drugs previously set aside as 'reserve' antibiotics, meant to be used only when no other treatment is available, are being used more and more regularly – and resistance is developing to them, too. Some of these reserve antibiotics are also more toxic or have more severe side effects than more standard antibiotic treatments.

If we ran out of effective antibiotics, modern medicine would be set back by decades. Relatively minor surgeries, such as appendectomies, could become life-threatening, as they were before

antibiotics became widely available. Antibiotics are sometimes used in a limited number of patients before surgery to ensure that patients do not contract any infections from bacteria entering open cuts. Without this precaution, the risk of blood poisoning would become much higher, and many of the more complex surgeries doctors now perform may not be possible.

### How do antibiotics work?

Antibiotics are used to treat bacterial infections. Some are highly specialised and are only effective against certain bacteria. Others, known as broad-spectrum antibiotics, attack a wide range of bacteria, including ones that are beneficial to us.

There are two main ways in which antibiotics target bacteria. They either prevent the reproduction of bacteria or they kill the bacteria, for example by stopping the mechanism responsible for building their cell walls.

## How does antibiotic resistance develop?

Bacteria are quick to evolve resistance to antibiotics. This can occur through spontaneous mutations, the result of mistakes when bacteria copy their DNA as they divide. Mutations that allow bacteria to survive where others do not (Box 2) are beneficial and are passed on to successive generations; antibiotic resistance is a prime example.

Bacteria can also develop resistance by taking up genetic material containing antibiotic resistance genes from their surroundings (Box 3).

For details on how antibiotic resistance can develop and spread, see Boxes 2 and 3.

To reduce antibiotic resistance it is important that patients finish a course of antibiotics once they have started it. This is the only way to ensure that as many bacteria as possible that are causing the infection are wiped out so that none are left to start a resistant bacterial population.

## How people propagate antibiotic resistance

Resistance to antibiotics is clearly as natural as antibiotics themselves (see Box 1– Leafcutter ants) and therefore has been around for far longer than our knowledge of its existence. Recognising this, Alexander Fleming summarised the dangers of rising levels of antibiotic resistance in his Nobel Prize acceptance speech in 1945:

*“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man*

## Box 2: The science behind antibiotic resistance: types of resistance

### Examples of methods of antibiotic resistance

Method of resistance	Antibiotic
Reduced uptake into cell	Chloramphenicol
Active efflux from the cell	Tetracycline
Eliminated or reduced binding of antibiotic to cell target	$\beta$ -Lactams, erythromycin, lincomycin
Enzymic cleavage or modification to inactivate antibiotic molecule	$\beta$ -Lactams, aminoglycosides, chloramphenicol
Metabolic bypass of inhibited reaction	Sulfonamides, trimethoprim
Overproduction of antibiotic target	Sulfonamides, trimethoprim

Antibiotic resistance often arises when an antibiotic wipes out all susceptible bacteria – resistant ones survive and pass on the resistance. Spontaneous mutations in bacterial DNA are also common. Mutations can confer antibiotic resistance in several ways<sup>12</sup>.

*may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr X has a sore throat. He buys some penicillin and gives himself, not enough to kill the [bacteria] but enough to educate them to resist penicillin. He then infects his wife. Mrs X gets pneumonia and is treated with penicillin. As the [bacteria] are now resistant to penicillin the treatment fails. Mrs X dies. Who is primarily responsible for Mrs X's death?”*

Indeed, following the introduction of most antibiotics, resistant strains of bacteria tended to arise sooner rather than later. In fact, resistance

to penicillin, the very first widely used antibiotic, was reported before the drug even became available to civilians in 1945. Ever since then, there has been an ‘evolutionary arms race’ between researchers developing new drugs and bacteria becoming resistant to them.

Why is it, then, that antibiotic resistance seems to have suddenly become a pressing concern for healthcare providers and scientists around the world?

- To an extent, Alexander Fleming’s prediction of incorrect antibiotic usage has come true. In many countries, prescription and use of antibiotics is not controlled very strictly, if at all, allowing

### Box 3: The science behind antibiotic resistance: how does resistance get passed on?

Antibiotic resistance is encoded in the DNA of bacteria, on one or more genes. For example, a gene may control whether the bacterium produces a chemical that destroys antibiotic molecules. Plasmids, circular chunks of bacterial DNA that exist naturally inside many bacterial cells, may contain genes that confer antibiotic resistance. In addition to reproduction, plasmids can move between individual bacterial cells in several different ways<sup>13</sup>:

- When two bacteria are near each other, genetic material can be passed directly between cells, or via a hollow structure called a pilus, or a pore, that can form between the two cells. Plasmids can use this pilus like a bridge, sending copies of themselves from one cell to the other. DNA sequences that can move from one location on a genome to another (known as transposons) can pass through the pore from one cell to another (this process is known as conjugation).
- Transformation of genetic material occurs when a bacterium dies, at which point it breaks up and releases its DNA into its environment. Nearby bacteria can pick up bits of this free-floating DNA and integrate them into their own genomes, creating a potential pathway for antibiotic resistance dissemination.
- Transduction occurs when a virus attacks a bacterium and takes over the cell to make copies of itself. Sometimes, bits of bacterial DNA are included in the DNA of the virus particles produced. The viruses then carry these chunks of bacterial DNA to other bacteria they infect.



Artwork showing bacterial conjugation.

resistance to develop more quickly.

- Doctors may prescribe antibiotics for many reasons, for example patient pressure, even when they are not needed. Antibiotics are often prescribed to treat the common cold, a viral disease against which antibiotics are completely useless. Alternatively, poor diagnostic methods can mean that infections are not recognised correctly and broad- spectrum antibiotics are prescribed just in case<sup>14</sup>.
- Places such as care homes and hospitals, where people vulnerable to infections live together in a small area, are hotbeds for antibiotic resistance. The overuse of antibiotics in such environments, coupled with the concentration of vulnerable people, creates an ideal breeding ground for resistant bacteria<sup>15</sup>.
- Antibiotics are increasingly used<sup>16</sup> in animal husbandry. The amount of some antibiotics used in UK agriculture has increased nearly tenfold in the last 50 years<sup>17</sup>. Resistance in animals is widespread as a result<sup>18</sup>, and it is easily transmitted to humans through the meat we consume<sup>19</sup>. It also enters rivers and the sea through runoff from fields.
- The availability of international and global travel means that resistant strains of bacteria can spread globally, quickly and easily.

It's important to remember that antibiotics don't 'cause' resistance. Much rather, they create an environment which selects for resistant strains as these have a large

advantage over strains susceptible to antibiotics.

Together, the above factors paint a worrying picture – some observers have even compared the potential impact of antibiotic resistance on modern civilisation with that of global climate change<sup>20</sup>.

### Measures to slow antibiotic resistance

Antibiotic resistance develops naturally. It often evolves spontaneously and can play a role in competition between microbial species, and as a result we cannot – and do not want to – stop it completely. Much rather, the aim is to slow its advance to ensure that antibiotics remain useful and effective for as long as possible. There are several aspects to this challenge, which are summarised under the umbrella term ‘antibiotic stewardship’.

### Antibiotic stewardship

The first aspect of antibiotic stewardship is to prevent infections that require antibiotic treatment from developing in the first place, for example through good hygiene. This requires reducing the spread of bacterial infections, which means that antibiotics aren’t needed – and if we don’t expose bacteria to antibiotics, the rate that resistance evolves is much slower. This is a particularly tricky challenge in hospitals and care homes, where many vulnerable people congregate and provide an ideal environment for germs and resistance genes to spread.

The second challenge becomes relevant once an infection has occurred, or when it becomes essential to use antibiotics, such as

## Case study

### Extensively drug-resistant tuberculosis (XDR-TB)

Tuberculosis (TB) is second only to HIV in terms of the number of people that die from infections. In 2012, 8.6 million people worldwide were infected with TB and some 1.3 million people died of the disease. The bacterium *Mycobacterium tuberculosis* (which causes the infection) attacks the lungs and is spread through the air by coughing and sneezing.

XDR-TB describes TB caused by a strain of bacteria that is resistant not only to all main antibiotics used against TB, but also to half of all the alternative



drugs used if the main ones fail. This means that XDR-TB does not respond to the standard six-month treatment regimen with antibiotics that is used against normal TB. Instead, treatment can take up to two years and involve drugs that are more toxic, less effective and far more expensive. XDR-TB is present on all continents, with confirmed cases having arisen in 58 countries as of 2010 – over half of them in Europe<sup>22</sup>.

What’s more, cases of ‘totally drug-resistant TB’ (TDR-TB) have been reported from Mumbai, India<sup>23</sup>: such bacteria are resistant to all first- and second-line antibiotics currently used against tuberculosis. The report highlights the extreme difficulty of managing TDR-TB, particularly in countries with poor health infrastructure. Fifteen of the patients found to have TDR-TB had been prescribed an average of nine drugs by four different doctors over the two years preceding their diagnosis.

While some of the TDR-TB patients in Mumbai are now slowly recovering following aggressive surgical and microbiological treatment, a third have since died. The silver lining, such as it is, of the discovery of such extreme drug resistance in strains of TB bacteria is that it has brought about improvements in the infrastructure for TB prevention and detection<sup>23,24</sup>.

prior to major surgery. At this point, it is crucial to use antibiotics in a targeted way and only when they are really needed. Specific antibiotics are better than broad-spectrum ones because they only affect certain species of bacteria rather than interacting with many different ones including beneficial bacteria. This

ensures that as many antibiotics as possible remain useful and effective for longer. National healthcare services are now beginning to monitor antibiotic prescription patterns and the occurrence of resistant bacterial strains and hope to better understand what makes patients more likely to acquire antibiotic-resistant infections.



Finally, developing better diagnostic methods for diseases and infections is another important way of slowing the spread of antibiotic resistance. As doctors need to wait for the analysis of samples before they even know what microbes they are dealing with, there is pressure on GPs and hospital-based doctors to prescribe broad-spectrum antibiotics. The more quickly doctors know what exactly causes the infection, the more able they are to prescribe effective, targeted treatments<sup>21</sup>.

### Why don't we develop more antibiotics?

If bacteria are developing resistance to existing antibiotics, then why do we not just discover or create new antibiotics? There are several problems with this approach. First, many bacterial species now have extensively drug-resistant (XDR) or even pan-drug-resistant (PDR) strains that are resistant to most or all known antibiotics that they were previously susceptible to. These strains are causing considerable difficulties in hospitals and the cost of treating them is far higher than for non-resistant strains.

The development of antibiotics has slowed markedly in the 21st century. From 2008 to 2012, just four new antibiotics were approved for the US market, compared with 16 during the period 1983–1987. In fact, no new antibiotics have been discovered for a class of bacteria called Gram-negative bacteria for 40 years. This is due to a mixture of scientific, economic and regulatory reasons.

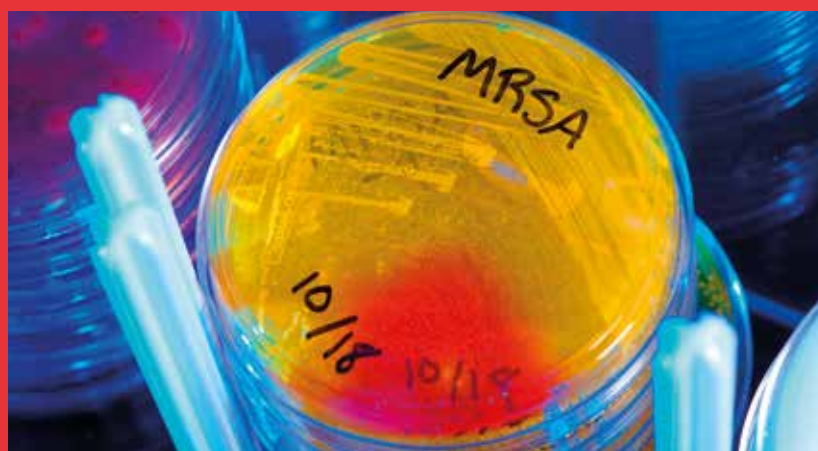
- Scientific causes: More commonly found antibiotics have mostly

## Case study

### Meticillin-resistant *Staphylococcus aureus* (MRSA)

Meticillin is an antibiotic that was widely used to treat *Staphylococcus aureus* bacterial infections after its introduction in 1959. However, just two years later the first meticillin-resistant strains were reported. Today, meticillin in its original form has been rendered all but obsolete, and MRSA has become a catch-all term for *S. aureus* resistant to all newer antibiotics that have been used to treat infections.

Basic hygiene measures such as handwashing and avoiding moving patients around too often can be enough to prevent the spread of MRSA. However, if particularly vulnerable people such as patients in intensive care units are affected, more severe measures may be required. These can include bathing affected patients in antiseptic solutions every day and setting up special isolation wards to prevent MRSA from spreading further<sup>27</sup>.



Petri dish culture plates that have been inoculated with meticillin-resistant *Staphylococcus aureus* (MRSA) bacteria.

been discovered already. They tend to crop up repeatedly when researchers are screening for drugs, while new drugs are proving increasingly elusive. In addition, some potential new antibiotics cannot be used, for example due to their toxicity.

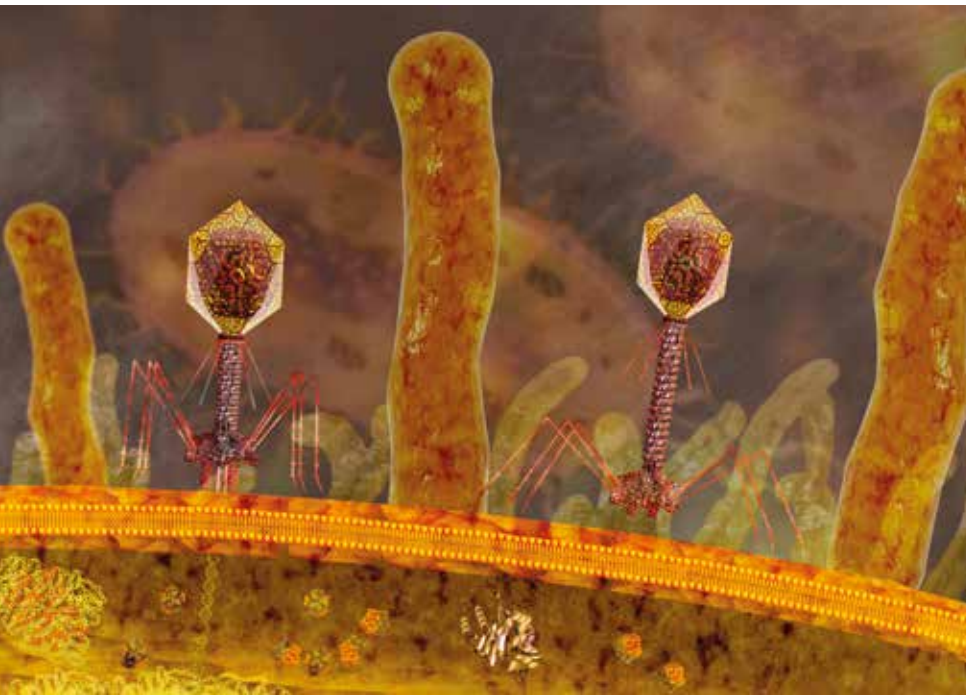
- Economic causes for producers: Antibiotics are generally prescribed for short periods of time. This makes them much less profitable than drugs that the patient has to take for the rest of their life, so pharmaceutical companies have less of an incentive to invest millions into antibiotic research<sup>25</sup>.
- Regulatory causes: The hurdles that antibiotics have to clear to

be licenced for human use have been getting higher. This means that companies have to invest more money before seeing any return at all, and the risk of the drug not being approved is higher.

Together, these factors go a long way towards explaining why antibiotic development has been stalling, and why using the ones we do have wisely is such a crucial matter<sup>26</sup>.

### Alternatives to antibiotics

Scientists have speculated what we could do if worst came to worst and we had to make do without any antibiotics. Researchers are exploring other possibilities.



Phage therapy: a bacteriophage is shown injecting its genome into the bacterium.

### Bacteriophages and phage therapy

Bacteriophages are viruses that infect bacteria – their name translates as ‘bacteria eaters’. Until recently, they received little attention from Western doctors – widely available and effective antibiotics were much easier to use. In the former Soviet Union, however, access to cutting-edge antibiotics was severely limited, and some scientists used bacteriophages to treat many infections.

Voluntarily letting bacterial viruses into our body is an unpleasant idea for many of us, even if they kill pathogenic bacteria – this in part is why phage therapy has been slow to take off in Western countries. With antibiotic resistance becoming an ever more real issue, though, the US National Institute of Allergy and Infectious Diseases is planning large-scale clinical trials of phage-based therapies<sup>28</sup>.

One advantage of bacteriophages over antibiotics is their availability: thought to be the most abundant organisms on Earth, they are so diverse that no two identical phages

have ever been found. This means that the bacterial hosts and phage co-evolve so when bacteria become resistant to a phage the phage will often evolve to re-infect it. Because of this, phage are described as ‘bacteria specific’.

Of course, there are difficulties that need to be addressed before bacteriophages can progress beyond the trial phase. For example, regulating such a rapidly evolving drug will be a formidable challenge. And because the methods are not novel, pharmaceutical companies are unlikely to be able to register patents, cutting into their profits.

While phage therapy is unlikely to completely replace antibiotics, scientists can imagine it being used on topical infections as an alternative therapy in cases where antibiotics have proved ineffective<sup>29</sup>.

### Antivirulence drugs

Traditional antibiotics inhibit the growth of bacteria or kill them outright. A novel class of drugs called antivirulence drugs instead

## Case study

### *Acinetobacter baumannii*

Troops in Iraq and Afghanistan faced an unexpected but powerful enemy – not on the battlefield but on the sickbed. While soldiers now have a very good chance of surviving even severe battle injuries, their wounds and amputations make them prime targets for infectious diseases – particularly a bacterium called *Acinetobacter baumannii*. *A. baumannii* has been nicknamed ‘Iraqibacter’ for its common occurrence in military medical facilities in war zones – and it has since spread back to the USA and Europe.

*A. baumannii* can kill patients in a variety of ways including high fevers, pneumonia, meningitis, spinal infections and blood poisoning. Infections were initially easily treatable with basic antibiotics, but *Acinetobacter* species seem particularly good at acquiring genetic material from other organisms and developing antibiotic resistance.

The US military is understandably keen to fund research into new drugs that can cure *A. baumannii* infections and important headways have been made, but the disease is still very much at large. *A. baumannii* continues to spread around the world, however, infecting increasing numbers of civilians in countries such as Colombia<sup>30</sup> and Pakistan<sup>31</sup>. More and more strains with varying levels of drug resistance are being isolated, necessitating large-scale national surveillance networks to keep the bacterium in check<sup>32</sup>.

disables the specific proteins the bacterium uses to attach to our cells, preventing it from establishing an infection.

Because antivirulence drugs 'disarm' rather than kill bacteria, they may not drive development of antibiotic resistance because susceptible organisms can still pass on their genetic material: resistance is not selected for. A study of antivirulence drugs has shown that drug-resistant bacterial strains will not come to dominate susceptible ones; this means that the drug can remain effective<sup>33</sup>.

An antivirulence drug has recently been found to be effective against MRSA infections in mice<sup>34</sup>. MRSA is a dangerous strain that causes infections in hospitals, care homes and even in gym locker rooms, so to find a drug that is effective against this bacterium is a positive step forward.

## Bacteriocins

Bacteriocins are proteins produced by bacteria that are toxic to similar or closely related bacteria. Essentially, they are narrow-spectrum antibiotics that bacteria produce to eliminate competitors. Bacteriocins that attack pathogens and are produced by bacteria that are harmless to us would make ideal antibiotics.

A number of bacteriocins are now being studied for potential use as antibacterial medication. They are also increasingly used to prevent the growth of dangerous bacteria in food, extending shelf life and delaying food spoilage<sup>35</sup>. One example is nisin, which is approved and used in food production and is known as E2<sup>34</sup>.

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## Factfile: Antibiotic resistance: A challenge for the 21st century

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**Front cover and right** Coloured scanning electron micrograph of *Enterococcus faecium* on the surface of the small intestine villi. *E. faecium* is a bacterium, commonly found in the gut of humans, which may be vancomycin-resistant.

