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Understanding antibiotic resistance

About this free course

This free course provides a sample of level 1 study in Science

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Introduction and guidance

Introduction and guidance

This free badged course, *Understanding antibiotic resistance*, lasts 24 hours, with 8 weeks. You can work through the course at your own pace, so if you have more time one week there is no problem with pushing on to complete a further week.

The course will introduce you to the science behind the problem of antibiotic resistance. You will learn about the history of antibiotics, what they are and how they work. You will learn how antibiotic resistance develops and spreads and look at the issues surrounding antibiotic resistance. Finally, you will look at some of the cutting edge ways that scientists are trying to tackle the problem of antibiotic resistance, from promoting good hygiene to developing new antibiotics from the soil.

Although this is an introductory course to antibiotic resistance, it assumes that you have a basic understanding of DNA and proteins. If you are unfamiliar with these concepts you might want to try our free OpenLearn course *What do genes do?* or listen to our set of audios at *DNA, RNA and protein formation* before you begin this course.

There will be numerous opportunities to check your learning. This includes interactive quizzes, of which Weeks 4 and 8 will provide you with an opportunity to earn a badge to demonstrate your new skills. You can read more on how to study the course and about badges in the next sections.

After completing this course, you will be able to:

- understand what antibiotics are and how they work
- understand how bacteria become resistant to antibiotics
- appreciate the issues surrounding antibiotic resistance
- know about the challenges in developing new antibiotics
- know about alternative approaches to tackling infectious diseases.

Moving around the course

In the ‘Summary’ at the end of each week, you will find a link to the next week. If at any time you want to return to the start of the course, click on ‘Full course description’. From here you can navigate to any part of the course.

It’s also good practice, if you access a link from within a course page (including links to the quizzes), to open it in a new window or tab. That way you can easily return to where you’ve come from without having to use the back button on your browser.

What is a badged course?

While studying *Understanding antibiotic resistance* you have the option to work towards gaining a digital badge.

Badged courses are a key part of The Open University's mission *to promote the educational wellbeing of the community*. The courses also provide another way of helping you to progress from informal to formal learning.

Completing a course will require about 24 hours of study time. However, you can study the course at any time and at a pace to suit you.

Badged courses are available on The Open University's OpenLearn website and do not cost anything to study. They differ from Open University courses because you do not receive support from a tutor, but you do get useful feedback from the interactive quizzes.

What is a badge?

Digital badges are a new way of demonstrating online that you have gained a skill. Colleges and universities are working with employers and other organisations to develop open badges that help learners gain recognition for their skills, and support employers to identify the right candidate for a job.

Badges demonstrate your work and achievement on the course. You can share your achievement with friends, family and employers, and on social media. Badges are a great motivation, helping you to reach the end of the course. Gaining a badge often boosts confidence in the skills and abilities that underpin successful study. So, completing this course could encourage you to think about taking other courses.

How to get a badge

Getting a badge is straightforward! Here's what you have to do:

- read each week of the course

- score 50% or more in the two badge quizzes in Week 4 and Week 8.

For all the quizzes, you can have three attempts at most of the questions (for true or false type questions you usually only get one attempt). If you get the answer right first time you will get more marks than for a correct answer the second or third time. Therefore, please be aware that for the two badge quizzes it is possible to get all the questions right but not score 50% and be eligible for the badge on that attempt. If one of your answers is incorrect you will often receive helpful feedback and suggestions about how to work out the correct answer.

For the badge quizzes, if you're not successful in getting 50% the first time, after 24 hours you can attempt the whole quiz, and come back as many times as you like.

We hope that as many people as possible will gain an Open University badge – so you should see getting a badge as an opportunity to reflect on what you have learned rather than as a test.

If you need more guidance on getting a badge and what you can do with it, take a look at the OpenLearn FAQs. When you gain your badge you will receive an email to notify you and you will be able to view and manage all your badges in My OpenLearn within 24 hours of completing the criteria to gain a badge.

Get started with Week 1.

Week 1: A future without antibiotics?

Introduction

Welcome to Week 1 of this free course, *Understanding antibiotic resistance*.

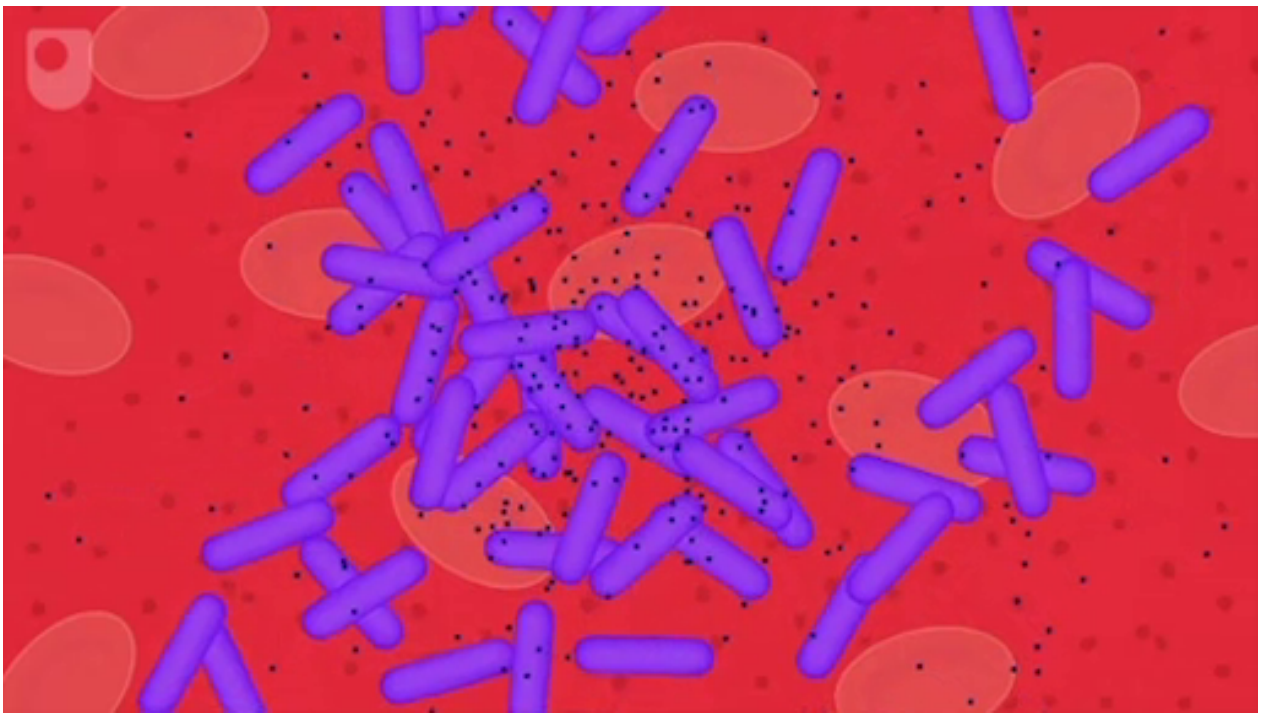
In this week you will read about common bacterial pathogens and how antibiotics can be used to treat bacterial infections. You will then step back in time, through the medium of video, to consider how and with what success infections were once treated. After a brief review of key scientific advances that heralded the discovery of antibiotics, you will consider how these life-saving drugs revolutionised medical care.

Back in the present, you will analyse data from different countries highlighting the growing problem of antibiotic resistance worldwide. You will be introduced to factors, covered in more detail later in the course, that have contributed to this problem.

Finally, you will listen to scientists discussing the potential threat to modern medicine of antibiotic resistance and will begin to form your own opinion about it.

Start by watching the video below which reveals how the natural processes of bacteria are exploited to fight infections – and how bacteria fight back!

Video content is not available in this format.
Video 1 Antibiotics.



By the end of this week, you should be able to:

- recall why pathogenic bacteria pose a threat to human health
- define the term antibiotic and give examples
- describe the importance of antibiotics in modern health care
- analyse antibiotic data and make simple deductions about antibiotic use and resistance patterns
- discuss the consequences of a future without antibiotics.

Although this is an introductory course to antibiotic resistance, it assumes that you have a basic understanding of DNA and proteins. If you are unfamiliar with these concepts, you may want to try our free OpenLearn course *What do genes do?* or listen to our set of audios on *DNA, RNA and protein formation* before you start this course.

1 Bacteria and infectious disease

Bacteria are the smallest and most numerous organisms living on Earth and are found in every conceivable habitat. The secret of their success is their relatively simple, single-cell structure which allows them to reproduce quickly and efficiently.

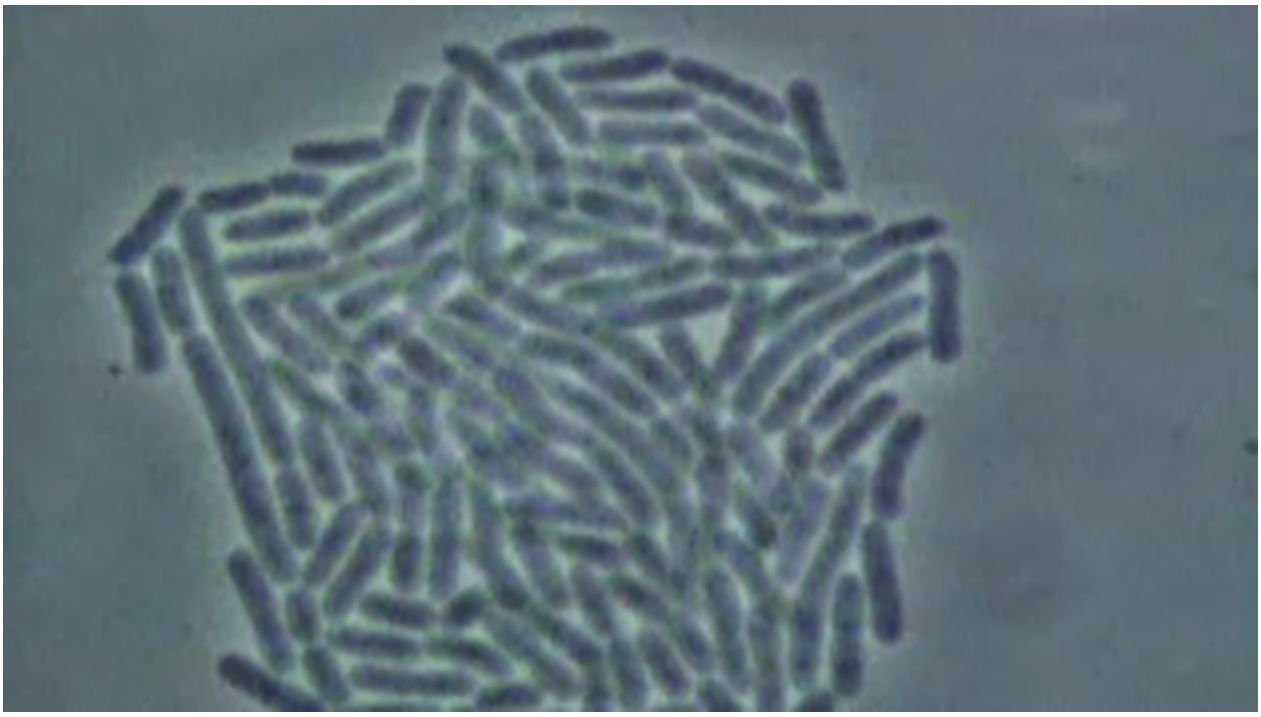
In the next section you will look at the process that allows bacteria to reproduce so quickly.

1.1 Bacterial growth

Bacteria reproduce by a straightforward process in which each cell splits into two identical, new cells. This process is called **binary fission** and you will learn more about it in Week 4.

Individual bacterial cells can divide, and the bacterial population can double, very quickly – in as little as 20 minutes in some species. Watch the following video to see a speeded-up film of binary fission.

Video content is not available in this format.
Video 2 Speeded-up film of bacterial growth.



However, bacteria do not continue growing at such a rapid rate indefinitely. This is because factors such as the availability of nutrients and rising toxin levels start to have an effect. You can explore this in the first activity. Don't worry if you don't understand all the terms, as they will be explained later.

Activity 1 Bacterial growth phases

Allow about 10 minutes

In nature, bacterial growth follows a typical pattern shown in Figure 1. The growth curve is comprised of four phases.

- Lag phase: during the lag phase, the bacteria are adapting to their environment; nutrients are plentiful and the cells grow in size without dividing. Cell number remains constant.
- Exponential phase: the exponential phase marks a big increase in cell number. Maximum growth rate is achieved with a constant doubling of the bacterial population. Growth then slows as nutrients become depleted and bacterial waste products build up to toxic levels.
- Stationary phase: the bacteria enter the stationary phase when the number of new cells equals the number of cells dying. The total number of cells in the population remains constant.

- Death phase: unless nutrients are replenished and waste products removed, the bacteria progress to the death phase. More cells die than are produced and the number of cells in the population declines.

(a) Using drag-and-drop, match the descriptions above to the correct phase of the growth curve. Don't worry if you are not sure of the correct answer at this stage. You can check your answers by clicking on the buttons below Figure 1.

Interactive content is not available in this format.

Figure 1 Graph of bacterial growth showing how the number of cells changes with time in a culture in which the bacteria are reproducing by binary fission.

Answer

- During the lag phase, the bacteria are adapting to their environment; nutrients are plentiful and the cells grow in size.
- The exponential phase marks a big increase in cell number. Maximum growth rate is achieved with a constant doubling of the bacterial population. Growth then slows as nutrients become depleted and bacterial waste products build up to toxic levels.
- The bacteria enter the stationary phase when the number of new cells equals the number of cells dying.
- Unless nutrients are replenished and waste products removed, the bacteria progress to the death phase. More cells die than are produced and the population declines.

Because they can divide so rapidly, bacteria adapt quickly to changes in their surroundings. Advantageous characteristics which allow the bacteria to flourish in the new conditions are passed on to successive generations and the species evolves rapidly. In Week 4 you will learn about the genetic mechanisms underlying this process.

1.2 Common bacterial pathogens of humans

Most bacteria found in or on the human body are harmless **commensals** living on the body without having any detrimental effect. However, a tiny proportion – about 500 species – are **pathogenic**, that is they are capable of causing disease. These bacteria may evade the body's normal defences to colonise or invade body cells and tissues, or they may produce harmful toxins. Many bacteria are **opportunistic pathogens**. These take advantage of an unusually vulnerable host and adapt quickly to the changed conditions.

Activity 2 Common bacterial pathogens and infectious diseases

Allow about 10 minutes

You might recognise the names of some important pathogenic bacteria shown in Figure 2. Note how different species of bacteria have characteristic shapes: for example, the spherical (coccus)-shaped *Streptococci* and the rod-shaped *Klebsiella*.

Can you name the infectious diseases that they cause? Click on reveal to see the answer.

Interactive content is not available in this format.

Figure 2 High magnification images of common bacterial pathogens in humans taken using a scanning electron microscope.

Answer

(a) *S. pneumoniae* is a common cause of pneumonia and ear infections.

(b) Pathogenic strains of *E. coli* are a common cause of diarrhoeal disease, for example as a result of food poisoning, and of urinary infections.

(c) MRSA is a particular threat in healthcare settings where it can cause sepsis and death if not treated quickly.

(d) *M. tuberculosis* causes tuberculosis (TB).

(e) *K. pneumoniae* is a common cause of many healthcare-associated infections including pneumonia, and bloodstream and wound infections.

(f) *N. gonorrhoeae* causes the sexually transmitted infection gonorrhoea.

Until the mid-twentieth century, bacterial infections were notoriously difficult to treat and were a leading cause of human **morbidity** and **mortality** worldwide. Then, in the 1930s, antibiotics were introduced and the outcomes for bacterial infection improved dramatically.

The next section introduces these new wonder drugs of the twentieth century – antibiotics.

2 Antibiotics

Antibiotics are chemicals which kill bacteria, that is they are **bactericidal**, or inhibit bacterial growth, that is they are **bacteriostatic**. They are produced naturally by soil-living bacteria and fungi in order to stop rival bacteria competing for nutrients and other resources. Antibiotics specifically target bacteria – a characteristic that humans have exploited for their own advantage to manage infectious diseases.

Narrow spectrum antibiotics affect only a few bacterial types. Broad spectrum antibiotics affect a wider range of bacteria.

- In Section 1 you learned about the different phases of bacterial growth. Most antibiotics target the exponential phase of growth. Can you suggest a reason for this?
- The exponential phase is when bacterial cells are at their most active, continually growing, dividing and forming new cells. The various metabolic processes which underpin this period of growth – such as the synthesis of DNA/RNA, proteins and the cell wall – are good opportunities for antibiotics to disrupt and/or kill cells.

You will learn how antibiotics work in Week 2.

2.1 Classification

There are numerous different antibiotics, some of which are naturally occurring while others are semi- or fully synthetic. Don't worry if you don't understand these terms, as they will be explained later. One of the most useful ways of classifying antibiotics is by chemical structure because structurally similar antibiotics tend to have similar antibacterial activity.

Examples of common antibiotic classes are shown in Table 1.

Table 1 Common classes of antibiotic

Antibiotic class	Example	Cellular process targeted*	Effect on bacteria**
ß-Lactams (penicillins)	ampicillin	bacterial cell wall synthesis	bactericidal
ß-Lactams (cephalosporins)	cephazolin	bacterial cell wall synthesis	bactericidal
ß-Lactams (carbapenems)	imipenem	bacterial cell wall synthesis	bactericidal
Glycopeptides	vancomycin	bacterial cell wall synthesis	bactericidal
Aminoglycosides	streptomycin	protein synthesis	bactericidal
Macrolides	azithromycin	protein synthesis	bacteriostatic
Tetracyclines	tetracycline	protein synthesis	bacteriostatic
Oxazolidinones	linezolid	protein synthesis	bacteriostatic
Fluoroquinolones	ciprofloxacin	DNA synthesis	bactericidal
Rifamycins	rifampicin	RNA synthesis	bactericidal
Not applicable	trimethoprim	metabolic reactions	bactericidal

* You will learn more about these cellular processes in Week 2.

** Common effect but partly depends on the concentration at which the antibiotic is used.

(Source: OpenStax College Microbiology, n.d.)

2.2 How much do you know about antibiotics?

Try this short quiz to find out how much you know about antibiotics. Don't worry if you don't know the answers to all the questions. By the end of this course you should be able to answer them all.

Activity 3 The antibiotics quiz

Allow about 5 minutes

1 Antibiotics can be used to treat infections caused by:

- bacteria and viruses
- bacteria
- viruses
- all microorganisms

Feedback

Antibiotics specifically target bacteria. They are not effective against infections such as the common cold and flu which are caused by viruses.

2 Antibiotics:

- have non-therapeutic uses
- are only active against pathogens
- do not cause side effects
- stimulate the body's immune system

Feedback

Antibiotics are used for many non-therapeutic purposes, for example as growth promoters in farm animals.

Antibiotics are not selective and will inhibit or kill 'good' bacteria along with 'bad' bacteria in the gut. This can lead to common side effects such as upset stomach and loose stools. Antibiotics neither enhance nor inhibit the body's immune response.

3 What should you do with left-over antibiotics that have been prescribed by your doctor?

- Return them to your doctor to dispose of
- Throw them away
- Nothing – you should always complete the course
- Save them for when you get another infection

Feedback

It is important to take antibiotics at the dose prescribed and to complete the full course. Otherwise, the effectiveness of the drug may be reduced which could lead to antibiotic resistance.

4 Antibiotic resistance occurs when:

- bacteria are no longer susceptible to the antibiotic
- a person develops an allergic reaction to a prescribed antibiotic
- the drug stops working in the individual
- the antibiotic changes in some way

Feedback

It is the bacterial pathogen that develops antibiotic resistance and is no longer susceptible to its effects.

5 Antibiotic-resistant infections:

- may require treatment with more expensive and more powerful drugs
- may require hospital treatment
- may take longer to cure
- all of these

Feedback

Antibiotic-resistant infections may not respond to common antibiotics and/or may require treatment with combinations of drugs. Some antibiotic-resistant infections may be fatal.

In the next section you will learn how the medical profession managed before antibiotics were available.

3 Pre-antibiotic era

Before antibiotics were discovered, the treatment options for bacterial infections were limited, as you will see next.

Activity 4 Life without antibiotics

Allow about 15 minutes

Watch the following video about infection in the pre-antibiotic era. As you watch, consider:

(a) which bacterial infections were common and what the usual outcome was

(b) how bacterial infections were treated.

Video content is not available in this format.
Video 3 Living in the eighteenth century.

Discussion

(a) It is striking that common infections such as sore throats, which are considered 'non-serious' today, were often killers in the pre-antibiotic age. Routine procedures such as childbirth were also dangerous. People were not only vulnerable to potentially deadly infections like TB (tuberculosis) and meningitis, but also the infection of simple cuts or more serious wounds by opportunistic pathogens could lead to sepsis and death.

(b) In the absence of powerful, antibacterial drugs, treatment was largely ineffectual. Examples referred to in the video are 'bloodletting', which was an established treatment until the 1940s, and the draining of pus from wounds and sores. Other treatments from this period, but not mentioned in the video, include herbal remedies, noxious chemicals such as mercury – used as a treatment for syphilis – and fresh air for TB. While these approaches could have helped relieve a patient's symptoms, they did little to treat the underlying cause of the infection and outcomes were generally poor.

Unlike George Washington's physicians, we now know that infectious diseases are caused by **microorganisms**. This discovery, known as **germ theory**, was a pivotal moment in medicine.

Activity 5 Proving germ theory

Allow about 10 minutes

Read the short article below about the work of Louis Pasteur and Robert Koch who provided the scientific proof of germ theory. Why was their work so important to understanding how infectious diseases could be successfully managed?

Article 1 The history of germ theory.

Discussion

Pasteur discovered the link between microorganisms and disease, while Koch established that a particular type of bacteria was responsible for a specific disease. Being able to identify the pathogen responsible prompted research into potential tailor-made treatments for specific infections.

By the early twentieth century, efforts to tackle infectious diseases were focused on finding drugs that killed the bacterial pathogen without harming the patient – so-called 'magic bullets'. Alexander Fleming's chance discovery in 1928 of the first antibiotic – penicillin – paved the way for research into other 'magic bullets' to cure bacterial infections. This was the start of the antibiotic era, which you will look at in Section 4.

4 Modern times

Since their introduction in the 1930s, antibiotics have saved millions of lives (Figure 3). Once-deadly diseases such as pneumonia and TB are now treatable and everyday infections and minor injuries are no longer potentially life-threatening.

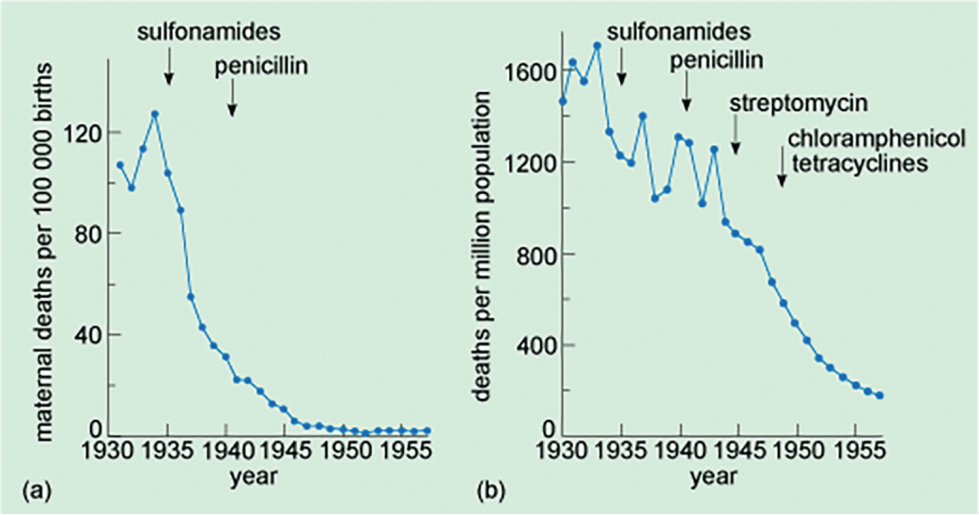


Figure 3 Effect of antibiotics on death rates in England and Wales between 1931 and 1957 from (a) childbirth-related infection (puerperal fever) and (b) all infectious diseases. Data from Barber (1960). (The arrows indicate when specific antibiotics were introduced.)

Antibiotics are used extensively in medicine, for example to improve the survival rates of transplant and cancer patients, or for **antibiotic prophylaxis**, that is they are taken before routine surgical procedures to prevent infection. They are also used in dentistry and

veterinary medicine, for agriculture and for many other non-therapeutic purposes. You will learn more about how antibiotics are used in Week 5.

Unfortunately, antibiotics are no longer the 'magic bullets' they once were. Our over-reliance on these drugs to prevent and/or treat a range of infections in both humans and animals, and for multiple other purposes, has left many antibiotics powerless as bacteria become resistant to them.

Antibiotic resistance can develop naturally in bacteria. However, the widespread use of antibiotics increases the selective pressure on bacteria to adapt and survive – that is, to develop resistance. You will learn more about this Weeks 4 and 5.

It is no coincidence that as antibiotic use has risen, so too has antibiotic resistance. For example, between 2000 and 2010, total global antibiotic consumption increased by over 30%, although there were country and regional variations (CDDEP, 2015).

4.1 The rise of antibiotic resistance

By analysing country-specific data, we can build up a picture of antibiotic use and resistance worldwide.

Activity 6 Antibiotic consumption

Allow about 10 minutes

Review Figure 4 which shows country-specific antibiotic consumption data for the period 2000 to 2010.

What trend(s) can you identify?

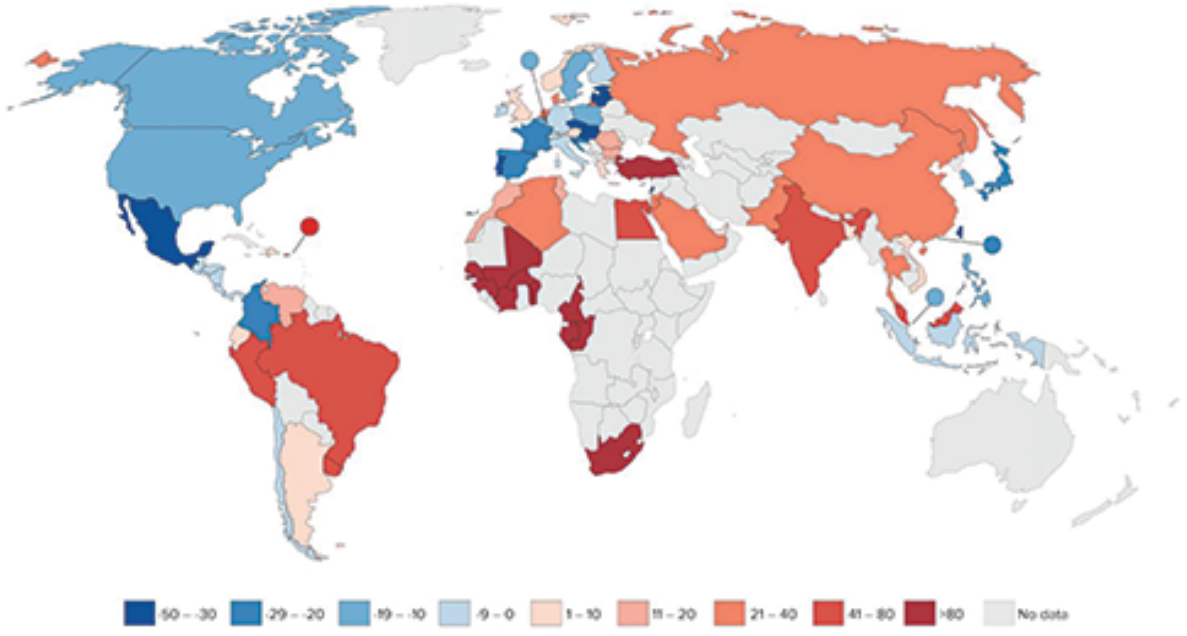


Figure 4 Percentage change in antibiotic consumption per capita 2000–2010. Percentage decrease is indicated in blue while percentage increase is indicated in red. Lower percentage changes are indicated by lighter colours.

Discussion

High-income countries, for example in Western Europe and the USA, maintained or even reduced antibiotic consumption between 2000 and 2010. In contrast, antibiotic consumption increased in low and middle income countries (LMICs) such as South Africa and India.

You will explore some of the reasons for the changing patterns of antibiotic use later in the course.

Global levels of antibiotic resistance have similarly increased this century. However, the resistance shown by individual bacterial species to a particular antibiotic can vary considerably between, and even within, countries (Figure 5).

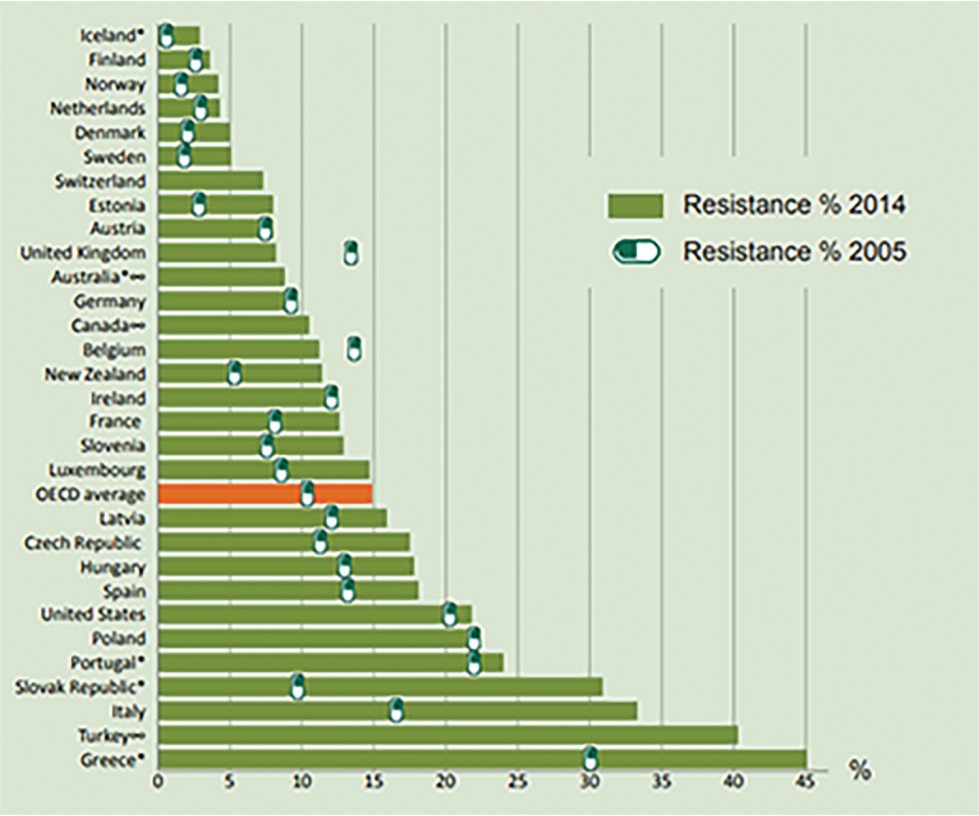


Figure 5 Antibiotic resistance in Organisation for Economic Cooperation and Development (OECD) countries in 2005 and 2014.

4.2 Superbugs

An increasing and serious concern is that the more antibiotics are used, the greater the likelihood that bacteria develop resistance to multiple antibiotics and so become even more difficult to treat.

Watch this short BBC video about the rise of superbugs and then read an excerpt from the accompanying BBC article.

Video content is not available in this format.

Video 4 What is a superbug?

Accompanying article: Article 2 Bacteria that resist 'last antibiotic' found in UK.

In 2017, the World Health Organization (WHO) published a list of antibiotic-resistant bacterial pathogens for which alternative treatments are urgently required. Five of the bacteria featured in Activity 2 are on the list (see Table 2). The sixth – *M. tuberculosis* – continues to be a serious health threat but was not included on the WHO list for operational reasons.

Table 2 WHO 'priority pathogens' in 2017

Bacterium	Antibiotic resistance	Priority rating
K. pneumoniae	multi-drug	critical
E. coli	multi-drug	critical
S. aureus	methicillin, vancomycin	high
N. gonorrhoeae	cephalosporins, fluoroquinolones	high
S. pneumoniae	penicillin	medium

In the next section you will find out about a particular class of antibiotics.

5 Case study: the link between antibiotic use and antibiotic resistance

In this case study you will further explore the link between antibiotic use and antibiotic resistance, by looking at a specific class of antibiotics, the cephalosporins.

Cephalosporins are a group of ß-lactam antibiotics which target cell wall synthesis. Discovered in the late 1940s, cephalosporins have a wide range of activity, have few side effects, and are one of the most commonly used antibiotics in the world.

Activity 7 Finding out about cephalosporins

Allow about 25 minutes

The images provided for this case study are taken from Resistance Map, a web-based programme that allows antibiotic use and antibiotic resistance data from different countries to be compared.

Study Figures 6a and 6b which compare cephalosporin use from 2000 to 2015 in the UK and South Africa. Then answer the following questions.

(a) How did cephalosporin use change over time in each country?

(b) Which country had the lowest consumption of cephalosporins in 2015?

(c) What factor is most likely to have accounted for the change in cephalosporin consumption in the UK since 2007?

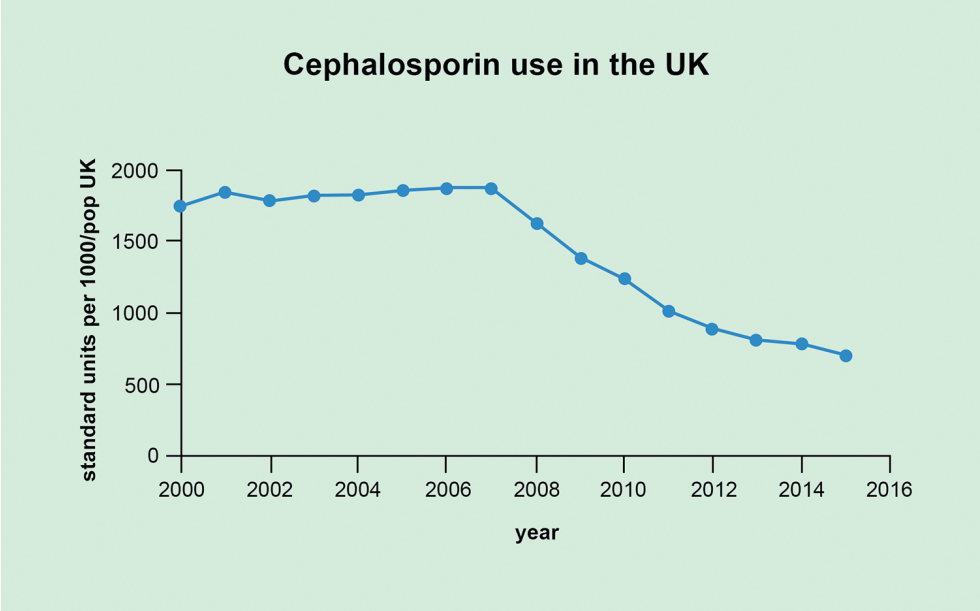


Figure 6a Cephalosporin use in the UK. (Data source: CDDEP, 2017)

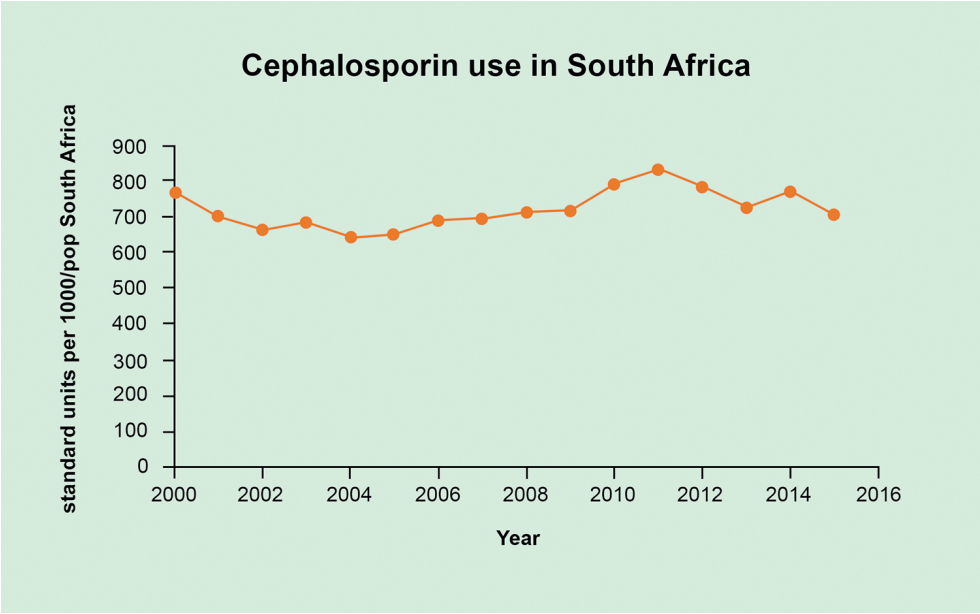


Figure 6b Cephalosporin use in South Africa. (Data source: CDDEP, 2017)

Discussion

(a) Over the period 2000 to 2015, antibiotic consumption decreased in the UK and remained relatively stable in South Africa.

(b) In 2015, the UK and South Africa had similar levels of cephalosporin consumption – about 700 standard units per 1000 population.

(c) The fall in cephalosporin consumption use in the UK since 2007 was probably due to a switch in prescribing away from cephalosporins towards other antibiotic alternatives.

Now study Figures 7a and 7b which compare cephalosporin resistance among *K. pneumoniae* and *E. coli* clinical isolates in the UK and South Africa. Then answer the following questions.

(a) What was the resistance pattern for each organism in each country?

(b) Which country had the highest levels of cephalosporin resistance for these bacterial species in 2015?

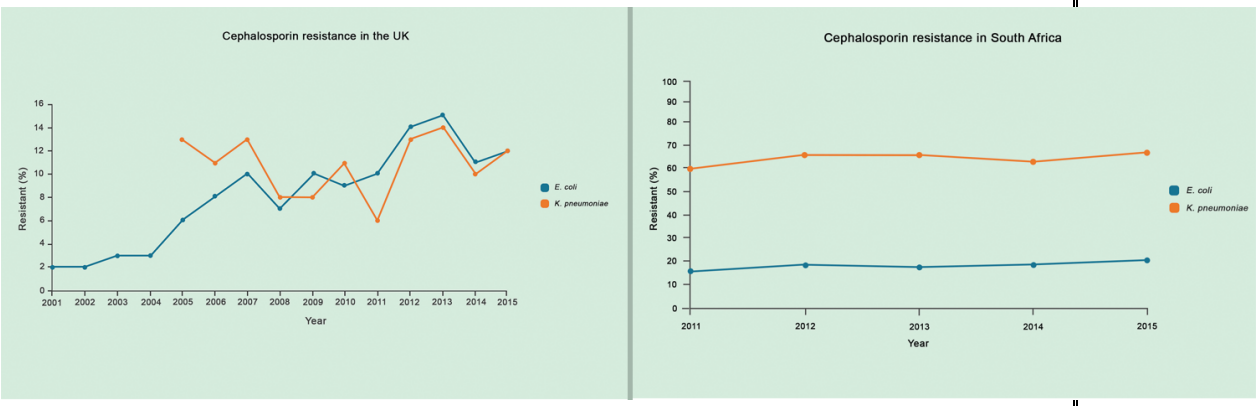


Figure 7a Cephalosporin resistance among *K. pneumoniae* and *E. coli* clinical isolates in the UK. (Data source: CDDEP, 2017.)

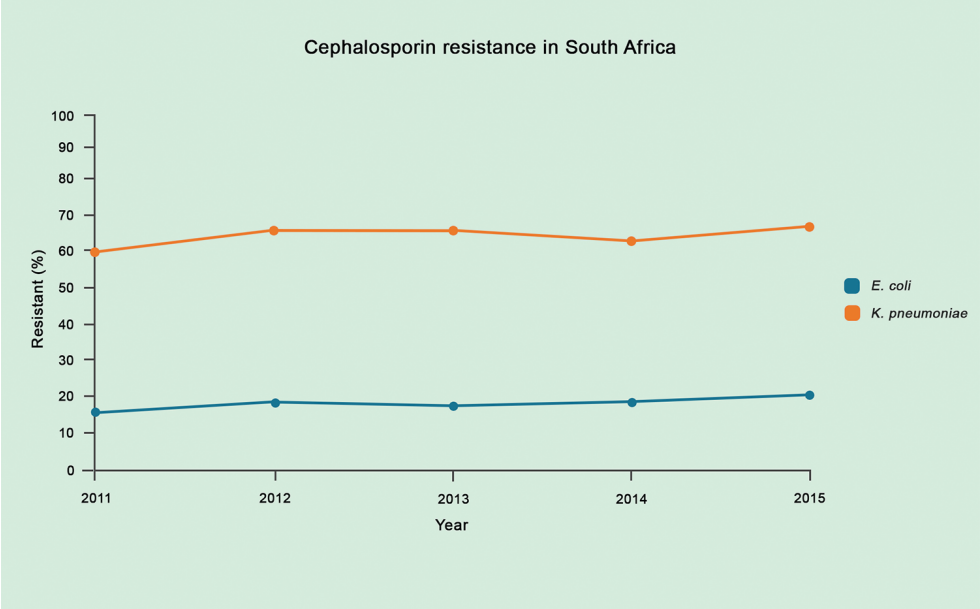


Figure 7b Cephalosporin resistance among *K. pneumoniae* and *E. coli* clinical isolates in South Africa. (Data source: CDDEP, 2017.)

Discussion

(a) In the UK, cephalosporin resistance remained relatively stable in *K. pneumoniae* over the period 2000–2015, but increased from about 2% to 12% in *E. coli*.In South Africa, there was a slight increase in cephalosporin resistance in both *K. pneumoniae* and *E. coli* from 2011 to 2015.

(b) Levels of cephalosporin resistance were higher in South Africa than in the UK – considerably so for *K. pneumoniae*.

What conclusions, if any, can you draw from the data in Figures 6 and 7?

Discussion

The link between antibiotic use and antibiotic resistance is complex and factors other than the amount of antibiotics used can affect the levels of resistance found. For example, the underlying mechanism by which the bacterial population becomes resistant to the antibiotic and the frequency at which resistance spreads is also important. You will learn more about this in Weeks 3 and 4.

Note also that the resistance data in Figures 6 and 7 are for clinical isolates from healthcare settings, whereas antibiotics are increasingly used for non-therapeutic purposes such as agriculture.

In the next section you will explore what the rising global levels of antibiotic resistance mean for us now and in the future.

6 What does the future hold?

How serious a threat to public health is antibiotic resistance? In this final section, some scientists give their views.

Activity 8 The view of the UK's Chief Medical Officer

Allow about 10 minutes

First, watch the short video of Professor Sally Davis, the UK's Chief Medical Officer, talking in 2013 about antibiotic resistance. Then read the more recent interview with Professor Davis published in 2017.

Finally, answer the following questions.

(a) What does Professor Davis warn against?

(b) What explanation does Professor Davis give for public complacency about the perceived threat(s) of antibiotic resistance?

Video content is not available in this format.
Video 5 'A very serious issue': Sally Davis talking in 2013.

Article 3 Sally Davis' 2017 interview in The Guardian.

Discussion

(a) Professor Davis warns of a post-antibiotic apocalypse if antibiotic resistance is not tackled on a global scale. Medical interventions we currently take for granted could become a thing of the past and simple infections could once again become killers.

(b) Antibiotic resistance is a 'hidden' problem. People are not aware that deaths from infectious diseases are the result of treatment failure.

What does all of this mean for you?

Activity 9 Personal reflections

Allow about 10 minutes

First, listen to the following short audio clip of four scientists' opinions about what the future holds for the treatment of bacterial infections.

Audio content is not available in this format.
Audio 1 Scientists' perspective on the antibiotic resistance threat.

Second, use the following questions to help form your own opinion.

(a) On a scale of 1 (low) to 10 (high), how serious a problem is antibiotic resistance?

(b) What, if anything, can be done about antibiotic resistance?

(c) Whose responsibility is it to address this problem? You might like to think about:

- whether individuals should take some responsibility or whether it is up to the medical profession, governments, etc.
- the extent to which different countries and regions should work together to address this problem.

(d) How urgent a problem is it? How soon should action(s) be taken?

At the end of the course you will be asked these questions again to see if what you have learned throughout the course has changed your opinion.

7 This week's quiz

Well done – you have reached the end of Week 1 and can now do the weekly quiz to test your learning.

Week 1 practice quiz

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link. Return here when you have finished.

8 Summary

This week introduced the key themes discussed in this course. You now know what antibiotics are and which pathogens they are active against. You have learned that our over-reliance on antibiotics has encouraged the development of resistance and led to many drugs becoming powerless against common bacterial infections. You have also heard from eminent scientists that antibiotic resistance poses one of the biggest threats to public health today.

Having had a glimpse of how limited medical options were in the pre-antibiotic age, you can now begin to speculate on what the future might be like without these 'wonder' drugs.

You should now be able to:

- recall why pathogenic bacteria pose a threat to human health
- define the term antibiotic and give examples
- describe the importance of antibiotics in modern health care
- analyse antibiotic data and make simple deductions about antibiotic use and resistance patterns
- discuss the consequences of a future without antibiotics.

Next week you will find out how different types of antibiotic work and how they can target bacteria in the body yet leave body cells unharmed. You will also explore why some antibiotics are active against a wide range of bacteria but others are not.

You can now go to Week 2.

Week 2: How do antibiotics work?

Introduction

In Week 1 you learned that antibiotics are used to treat bacterial infections. They either kill the bacteria outright or prevent them from growing and replicating. You were also introduced to the concept of 'magic bullets' – drugs such as antibiotics that are highly effective at treating infections without unduly harming the patient.

This second week of the course looks in more detail at how antibiotics work.

You will start by exploring how antibiotics can exert powerful antibacterial effects and yet be generally well tolerated by people and animals. You will then study the different modes of antibiotic action, looking in more detail in this week's case study at the precise mechanism used by ß-lactam antibiotics. Finally, you will consider factors that determine antibiotic type, such as spectrum of activity and bactericidal or bactericidal nature.

Begin this week by watching the video below about the pioneering work of Paul Ehrlich (1854–1915). He discovered the first 'magic bullet' in 1909 – Salvarsan, a derivative of arsenic – which could cure syphilis. Ehrlich hoped that other 'magic bullets' which could be safely used to treat bacterial infections would swiftly follow. However, the world had to wait another ten years for penicillin to be accidentally discovered!

Video content is not available in this format.
Video 1 In pursuit of 'magic bullets': the seminal work of Paul Ehrlich.

By the end of this week, you should be able to:

- recognise different types of commonly used antibiotics
- recall the characteristic features of bacterial and human or animal cells
- explain why antibiotics have selective toxicity
- demonstrate how commonly used antibiotics affect bacterial growth
- summarise the main mechanisms by which antibiotics stop infections from spreading and kill bacteria.

1 Selective toxicity

As you saw in Video 1, Ehrlich's seminal work on syphilis proved that 'magic bullets' existed. It also led to wide acceptance of the principle that drugs should demonstrate 'selective toxicity'. That is, they target the disease-causing organism while causing no or minimal harm to the patient. This principle is still firmly entrenched in medical research and practice today (Valent et al., 2016).

Underpinning **selective toxicity** are the differences between pathogens and human or animal cells. It is these differences that antibiotics (and other drugs) exploit to exert their specific effects.

1.1 Cell structure

There are two distinct types of cell. Bacteria are **prokaryotes** while human and animal cells are **eukaryotes**.

Activity 1 Exploring cell basics

Allow about 15 minutes

(a) Study the general organisation of prokaryotic and eukaryotic cells in Figure 1. Then read more about each component below.

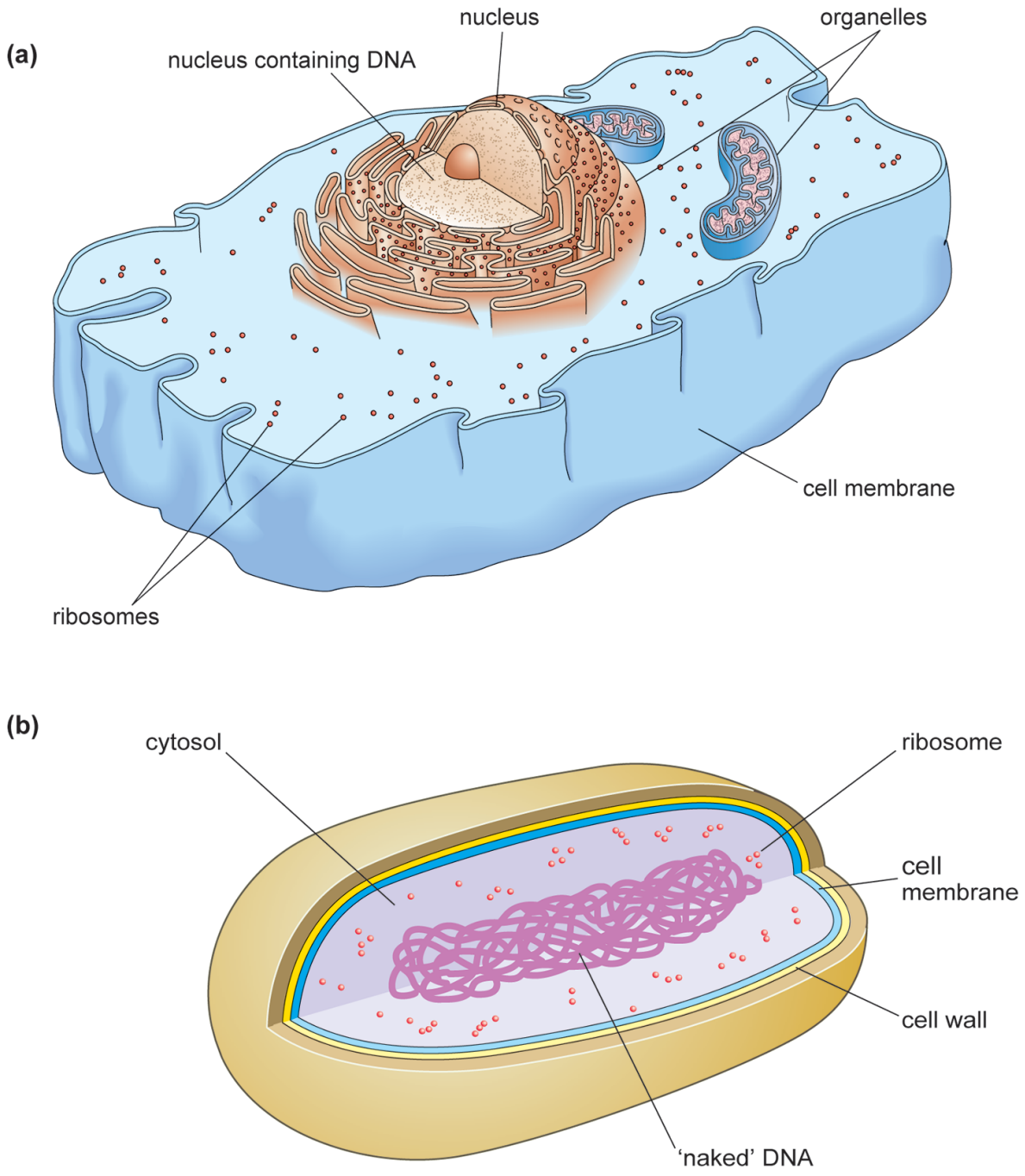


Figure 1 Schematic diagram of a typical (a) eukaryotic animal cell and (b) prokaryotic bacterial cell (not drawn to scale).

Cell membrane

A complex structure enclosing the cytosol of living cells which controls the passage of substances into and out of the cell.

Cell wall

A protective outer layer which provides mechanical support to the cell. It also prevents harmful surges of water moving into the cell by osmosis which could cause it to burst (lysis).

Cytosol

A watery fluid in which many chemical reactions take place.

Ribosome

A structure where proteins are made in the cell. Each ribosome consists of a large and a small subunit which have distinct roles in protein synthesis.

Mitochondrion

The place in a cell where chemical energy derived from nutrients is converted to a form that can be used by the cell (plural, mitochondria).

Endoplasmic reticulum

The place in a cell that sorts proteins and ensures they are transported to the correct part of the cell. The rough endoplasmic reticulum is studded with ribosomes.

Nucleus

A membrane-bound structure that encloses the genetic material (DNA).

DNA

Deoxyribonucleic acid is a large molecule containing the cell's genetic information. This is the complete set of instructions needed for an organism to grow, survive and reproduce.

(b) What structural differences can you see between the bacterial and the animal cell?

Answer

- The bacterial cell has a cell wall; the animal cell lacks one.
- The bacterial cell lacks membrane-bound **organelles** such as mitochondria and endoplasmic reticulum.
- DNA is free in the cytosol of the bacterial cell; DNA in the animal cell is in the nucleus.
- In the animal cell, ribosomes are both free in the cytosol and attached to the membrane of the rough endoplasmic reticulum.

Although there are similarities between the two cell types, eukaryotic cells are structurally much more complex. Prokaryotes and eukaryotes carry out the same essential processes necessary for survival, such as making new proteins, **metabolism** and reproduction, but these processes are not identical. For example, different proteins might be produced or different **enzymes** used to drive key chemical reactions.

Antibiotics are selectively toxic because they target structural features or cellular processes in the bacterial pathogen that are different or lacking in the host's cells.

1.2 Potential bacterial targets for antibiotics

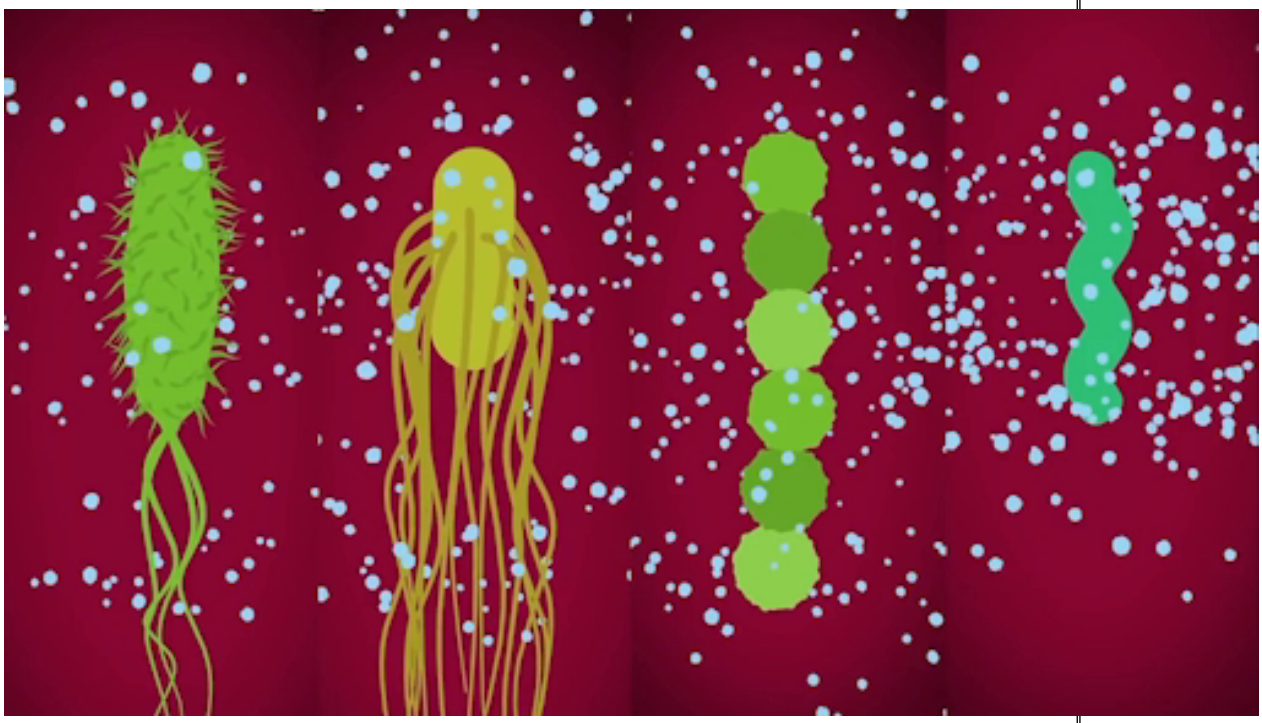
In Activity 2 you will discover which essential cell processes in the bacterial pathogen are potential targets for antibiotics.

Activity 2 When are bacteria vulnerable to antibiotics?

Allow about 20 minutes

Watch the video about key bacterial cell processes and answer the related questions. You can pause the video to work through this activity at your own pace.

Video content is not available in this format.
Video 2 How do antibiotics work?



(a) Suggest a likely consequence for the cell if DNA replication is blocked.

Answer

Blocking DNA replication would impair cell division and kill the bacterial cell.

(b) Which stage or stages of protein synthesis could be targeted by antibiotics?

Answer
Interference with either stage of protein synthesis could result in faulty enzymes and/or structural proteins.

(c) DNA replication, metabolic reactions and protein synthesis also occur in eukaryotic cells. Suggest why antibiotics that target these bacterial processes demonstrate selective toxicity.

Answer
Although cellular processes of prokaryotic and eukaryotic cells have many similarities, antibiotics are selected for clinical use that target those processes that are wholly or partly unique to the bacterial pathogen. This minimises the risk of side effects in the patient.

(d) What might happen to a cell that can no longer make a cell wall?

Answer
Bacterial cells that lack a cell wall are in danger of bursting if too much water moves into the cell by osmosis

(e) Why do antibiotics that target cell wall synthesis leave eukaryotic cells unharmed?

Answer
Eukaryotic cells lack a cell wall.

(f) A relatively small number of antibiotics target the bacterial cell membrane. Such antibiotics are often highly toxic to the host. Can you suggest a reason for this?

Answer
The membrane of animal and human cells has a very similar structure to that of bacteria. The potential for such antibiotics to adversely affect eukaryotic cells is therefore greater and these antibiotics generally demonstrate poor selective toxicity. This increases the risk of harmful side effects for the patient.

In Week 1 you learned that structurally similar antibiotics tend to have similar antibacterial activity and are grouped together in the same class. You should by now appreciate that each class of antibiotic has a specific mode of action, affecting susceptible bacterial cells in a way that depends on the drug's affinity for a specific target or process in the bacterial cell.

You will explore different modes of antibiotic action in Section 2.

2 Antibiotic modes of action

This section focuses on the four main modes of antibiotic action that lead to inhibition of one of the following:

- cell wall synthesis
- protein synthesis
- nucleic acid synthesis

- metabolic reactions.

Don’t worry if you don’t understand all of these terms, as they will be explained in the next sections.

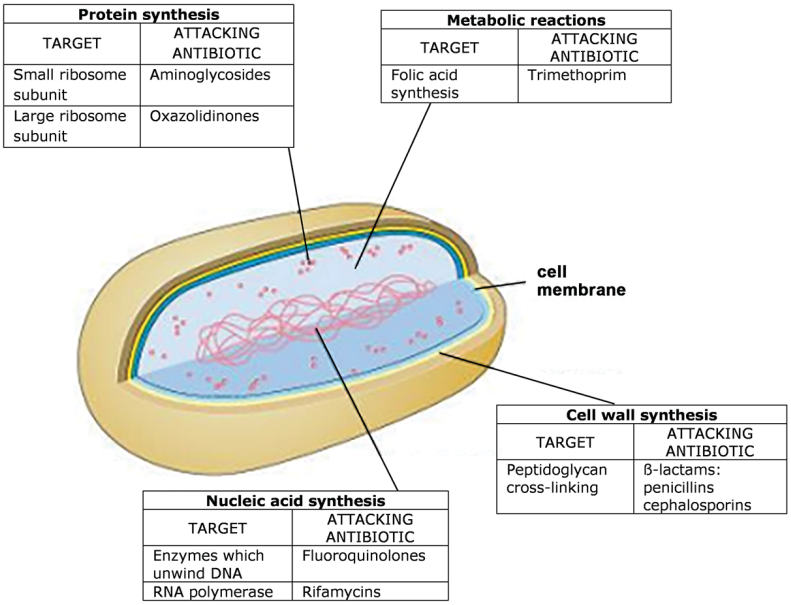


Figure 2 Main antibiotic modes of action.

Members of the same class of antibiotics share a characteristic structural feature that determines the drug’s affinity and specificity for target molecules in susceptible bacteria. You will now look in more detail at antibiotics that exemplify each of these four main modes of action.

2.1 Inhibitors of cell wall synthesis

As you saw in Activity 2, the cell wall is essential for normal functioning of the bacterial cell. Antibiotic inhibitors of cell wall synthesis block the production of **peptidoglycan**, the main component of the cell wall. Cross-linking between peptidoglycan chains forms a strong, mesh-like structure that gives the cell wall structure and rigidity, and protects the underlying cell membrane from osmotic damage when water moving into the cell by osmosis could cause it to burst, or lyse. Disruption of the peptidoglycan layer of the cell wall can therefore result in cell lysis (Figure 3).

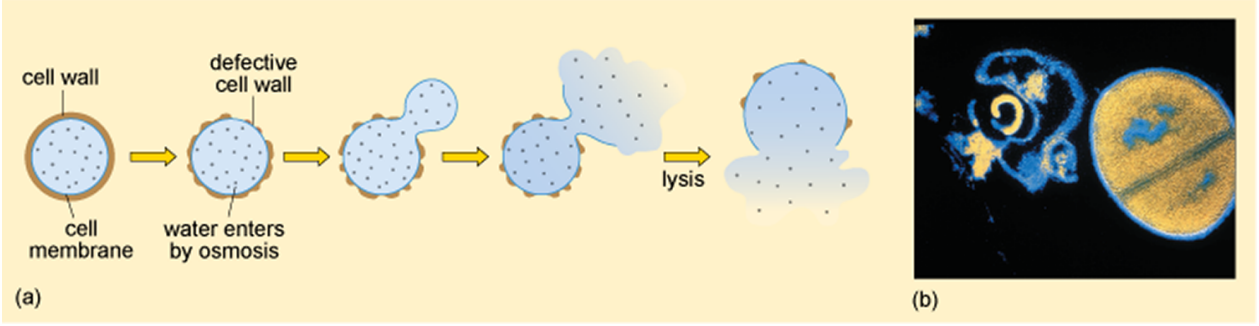


Figure 3 Lysis of a bacterium with a defective cell wall. (a) Diagram showing the

sequence of events that lead to lysis. (b) Light micrograph of *S. aureus*: a lysed cell on the left and an intact dividing cell on the right.

Examples of cell wall synthesis inhibitors are the ß-lactam antibiotics. These include penicillin and its derivatives, and the cephalosporins. All ß-lactam antibiotics contain a core chemical structure called a ß-lactam ring (Figure 4) which determines the mode of action of this class of antibiotics.

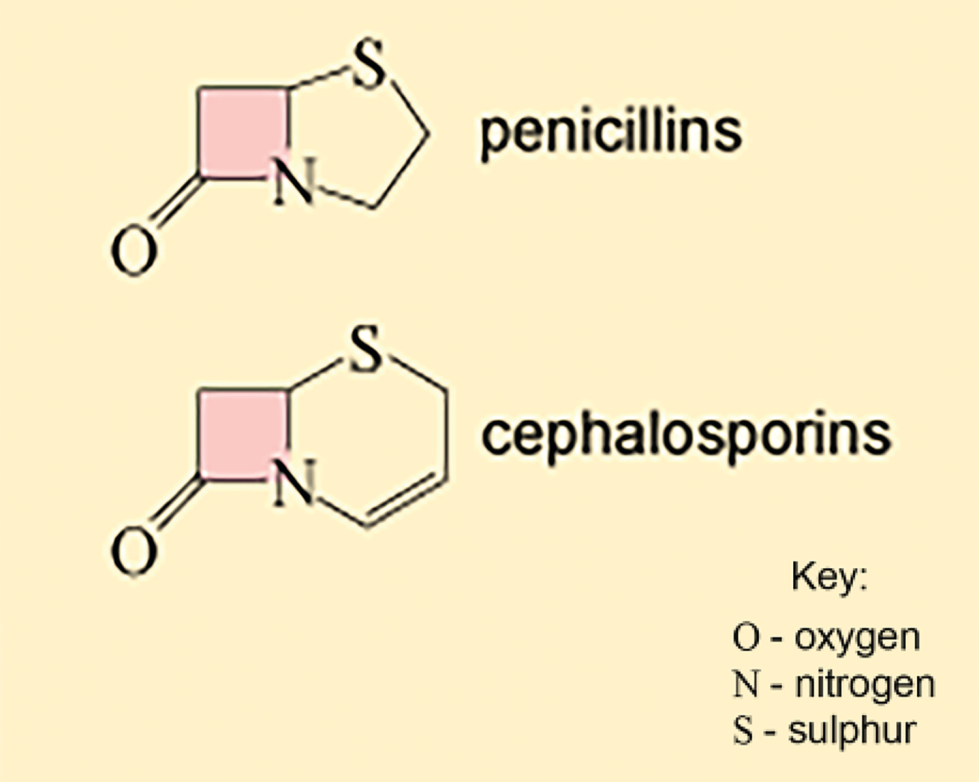


Figure 4 Core ring structures of two types of β-lactam antibiotics. The β-lactam ring is shaded pink in each case.

The ß-lactam antibiotics interfere with the formation of the peptidoglycan cross-links, thereby weakening the cell wall. You will learn more about the precise mechanism in this week's case study (Section 3). For now, you can see the effect of the disrupted cell wall on bacterial growth in Video 3.

Video content is not available in this format.
Video 3 A ß-lactam antibiotic in action.

2.2 Inhibitors of protein synthesis

You learned in Activity 1 that cells synthesise new proteins in ribosomes which are made up of one large and one small subunit. These subunits differ structurally and chemically between prokaryotic and eukaryotic ribosomes (Figure 5). This provides antibiotic targets in the bacterial pathogen which are not present in the host cells.

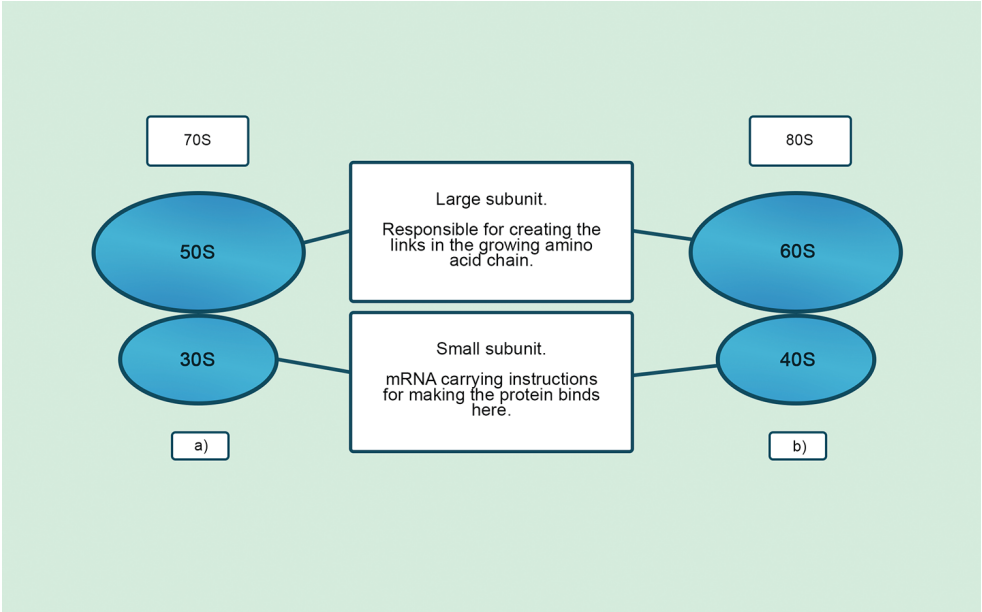
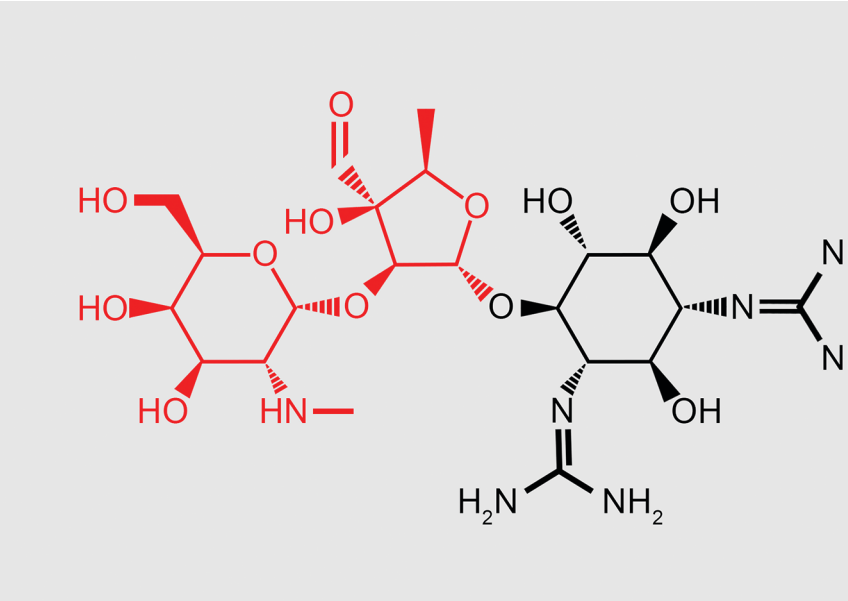
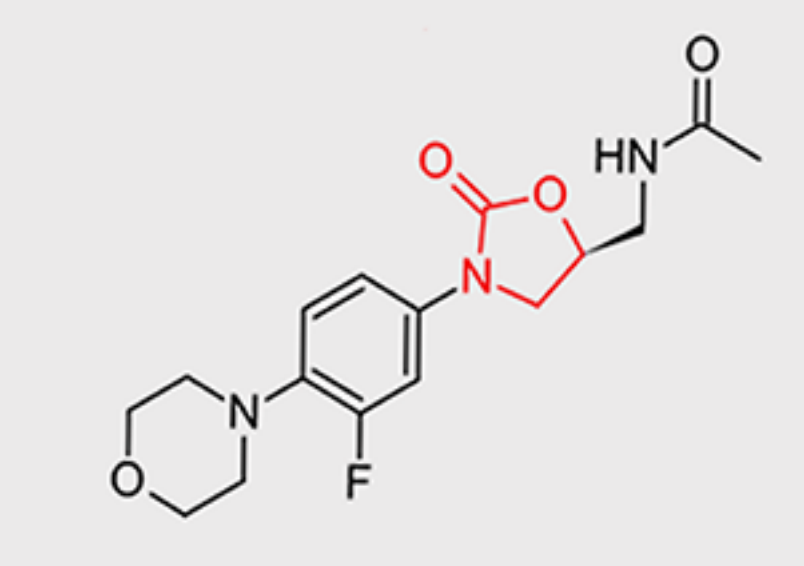


Figure 5 Ribosome structure in (a) prokaryotes and (b) eukaryotes. The Svedberg unit (S) indicates the size, shape and density of each subunit.

Table 1 Examples of protein synthesis inhibitor antibiotic classes

Ribosomal target	Outcome	Antibiotic class	Structure
Small (30S) subunit	Errors give rise to faulty proteins that disrupt the cell membrane	Aminoglycosides	All contain amino sugar substructures (red) 
Large (50S) subunit	First steps of protein synthesis (initiation) are impaired and bacteria cannot grow and divide	Oxazolidines	All contain 2-oxazolidone (red) somewhere in their structure 

(OpenStax College Microbiology, n.d.)

2.3 Inhibitors of nucleic acid synthesis

Differences between enzymes that carry out the synthesis of nucleic acids in eukaryotic and prokaryotic cells allow antibiotics to target these processes in bacterial pathogens.

For example, fluoroquinolones (Figure 6) specifically inhibit bacterial enzymes that unwind the DNA double helix, separating the two strands so that the DNA can make a copy of itself. If this process does not happen, **replication** is blocked.

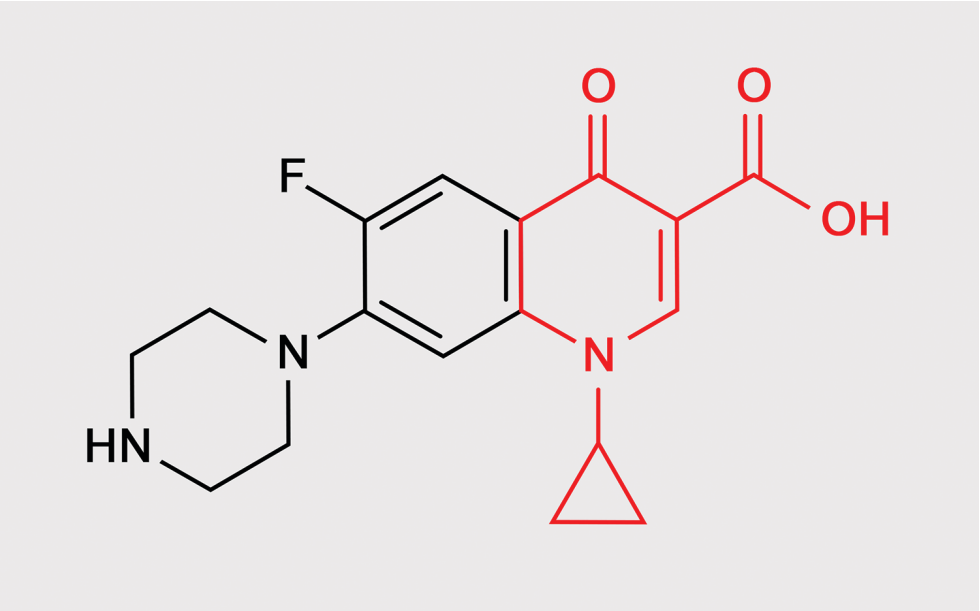


Figure 6 The fluoroquinolone called ciprofloxacin. Fluoroquinolones all contain the chemical structure highlighted in red.

Another class of antibiotics – rifamycins – inhibits RNA synthesis by binding to and inhibiting an enzyme called RNA polymerase. This enzyme transfers the instructions carried by genes to the intermediary molecule, mRNA. Interference in this process ultimately stops new proteins being made.

2.4 Inhibitors of metabolic reactions

Antibiotics that disrupt essential bacterial metabolic pathways are acting as **antimetabolites**. These chemicals are structurally similar to natural **metabolites** but just different enough to interfere with normal cell function.

For example, trimethoprim inhibits the synthesis of folic acid, a vitamin which bacteria, unlike humans, must make themselves. Trimethoprim is a **structural analogue** of dihydrofolic acid, an intermediate compound in the folic acid pathway. Trimethoprim outcompetes dihydrofolic acid to react with a specific bacterial enzyme in the pathway, thereby interrupting folic acid synthesis and inhibiting bacterial growth (Figure 7).

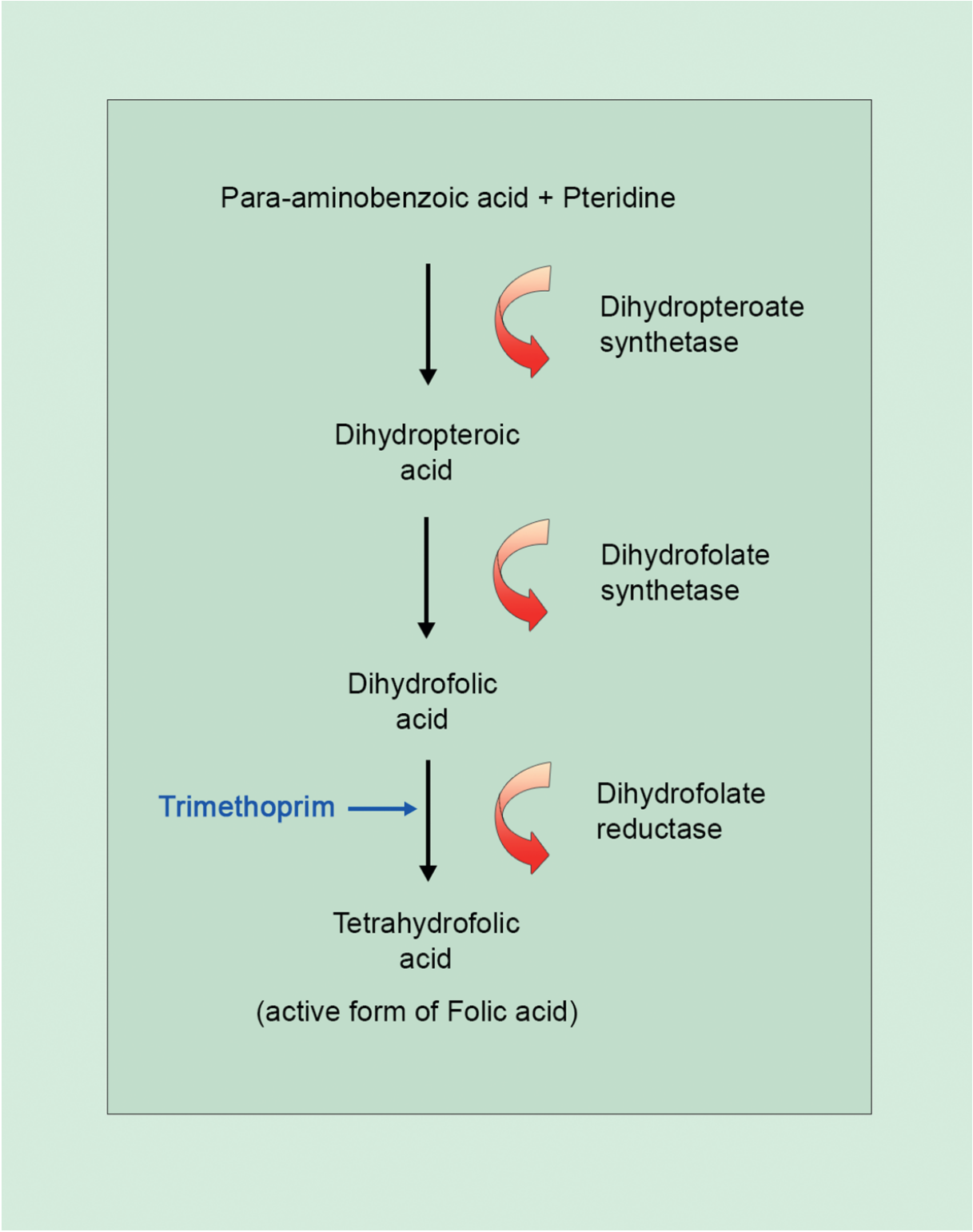


Figure 7a The folic acid pathway. Trimethoprim prevents the enzyme dihydrofolate reductase reacting with the intermediate compound dihydrofolic acid, thereby blocking the pathway at the point shown.

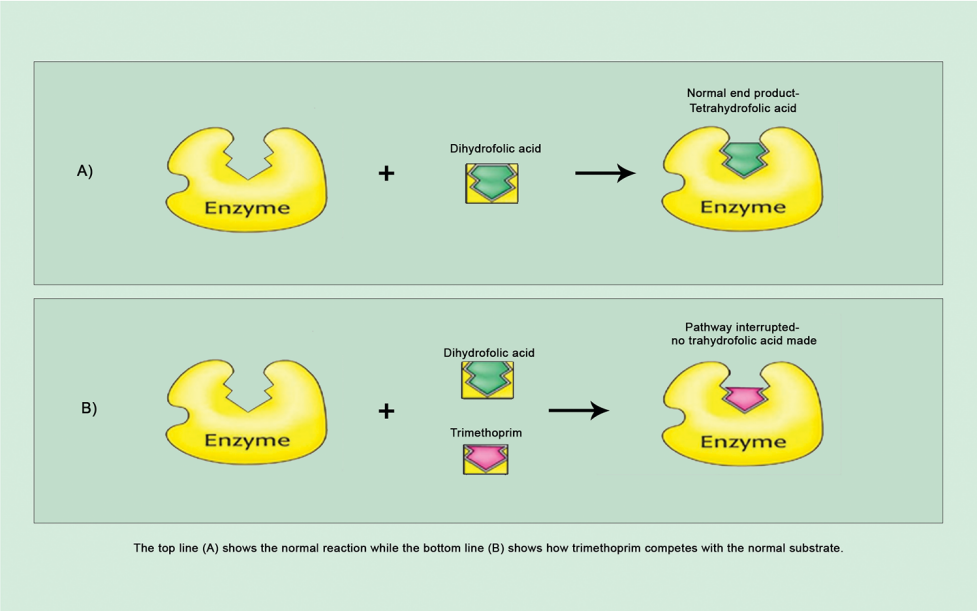


Figure 7b The underlying competitive mechanism.

The action of trimethoprim illustrated in Figure 7b exemplifies the specific interaction between antibiotic and bacterial target at a molecular level which disrupts a particular cellular process. You will return to this topic in Week 3 in relation to the development of antibiotic resistance.

In the next section, you will look in detail at the mechanism of ß-lactam antibiotics.

3 Case study: mechanism of ß-lactams

The β-lactam antibiotics target the bacterial cell wall (Figure 8) by inhibiting the enzymes responsible for cross-linking adjacent molecules in the peptidoglycan layer. The ß-lactam antibiotics bind to these enzymes, collectively known as **penicillin-binding proteins (PBPs)**, and prevent them from forming cross-links. As the bacterial cell grows, the effect of the antibiotic is to progressively weaken the cell wall until the cell lyses as a result of osmotic damage.

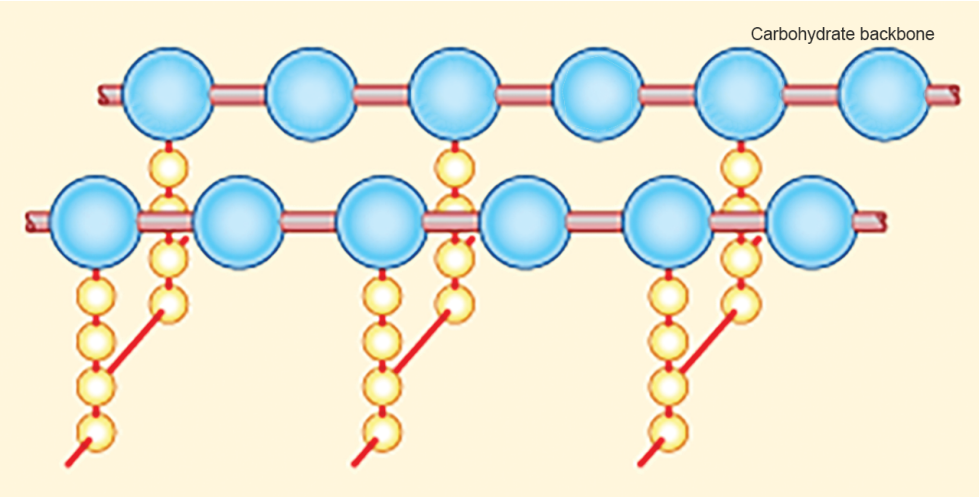


Figure 8 Structure and arrangement of peptidoglycan chains in the bacterial cell wall. Peptidoglycan molecules consist of a backbone of carbohydrate units with sets of amino-acid residues attached (yellow). They are cross-linked by bridges (red), providing structure and strength.

In Section 2 you learned that the activity of penicillins and cephalosporins resides in the ß-lactam ring. Activity 3 looks more closely at this.

Activity 3 Mechanism of ß-lactam antibiotics

Allow about 15 minutes

First, watch the short video below which describes the inherent instability of the ß-lactam ring structure which makes it highly reactive. The video refers to penicillin, but the same is true of the ß-lactam ring in cephalosporins and all other antibiotics of this class.

Video content is not available in this format.

Video 4 The inherent instability of the ß-lactam ring structure.

Figure 9 shows what happens when a ß-lactam antibiotic, in this case penicillin, binds to an active PBP.

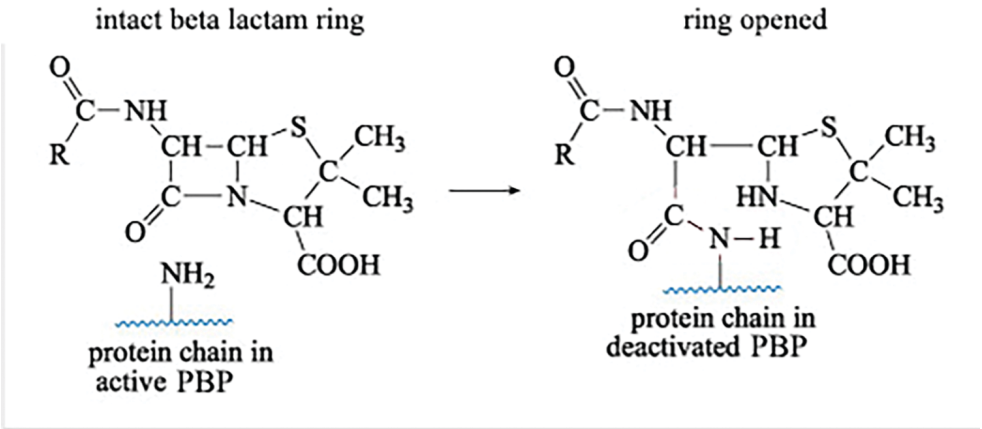


Figure 9 Reaction of penicillin with a PBP. The -NH_2 side chain of the PBP reacts with the ß-lactam ring of penicillin to form a new side chain. This reaction releases the strain in the ß-lactam ring which remains open.

The reaction shown in Figure 9 results in a new PBP side chain which is much larger than the original -NH_2 group and effectively deactivates the PBP. Can you suggest why?

Answer

The large side chain means that there is no longer sufficient space for the enzyme (PBP) to bind to its normal substrate during the peptidoglycan cross-linking process.

You will learn more about how disrupting the interaction between ß-lactam antibiotics and PBP contributes to antibiotic resistance mechanisms in Week 3. Next, however, you will

see how antibiotics of the same class, and with the same mode of action, can have a different spectrum of activity and exert different effects.

4 Types of antibiotic

So far in this course you have learned that antibiotics may be active against a wide range of bacteria (**broad-spectrum**) or just a few types (**narrow-spectrum**). You also know that antibiotics either kill bacterial cells (bactericidal) or stop them growing and dividing (bacteriostatic).

Factors that determine the spectrum of antibiotic activity include:

- ability to penetrate the bacterial cell – since most bacterial targets are located in the cell's interior
- how widespread the target is among different bacterial species
- bacterial resistance to the antibiotic (discussed in Weeks 3 and 4).

4.1 Gram-positive and Gram-negative bacteria

Bacteria are divided into two groups based on how the cell wall appears when they are stained using **Gram straining**. This procedure allows the composition of the wall to be visualised.

In **Gram-positive** bacteria, the cell wall has a thick peptidoglycan layer which is relatively porous, allowing substances to pass through it quite easily.

In **Gram-negative** bacteria, this peptidoglycan layer is greatly reduced and is further protected by a second, outer membrane (Figure 10).

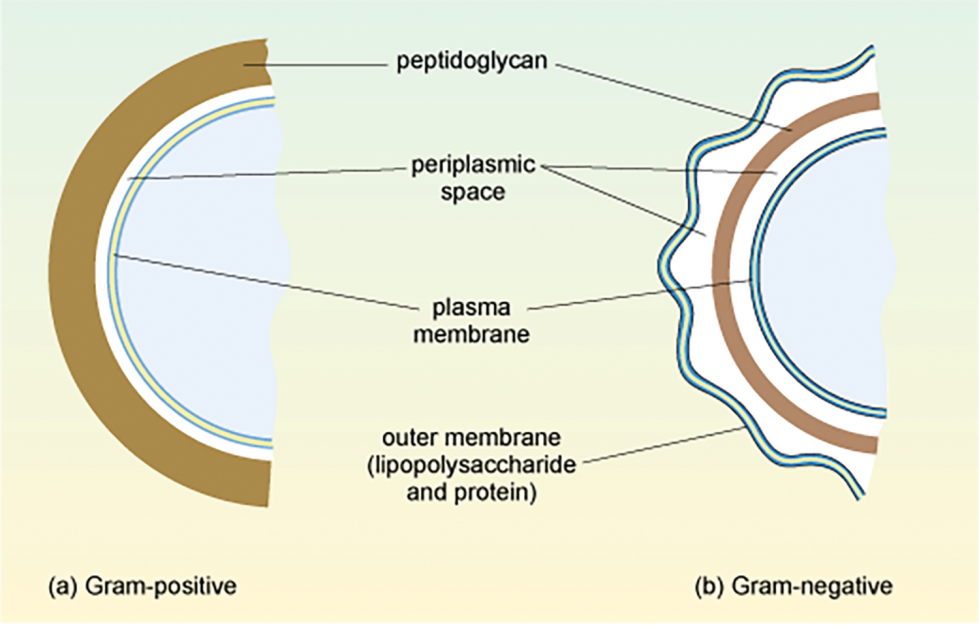


Figure 10 Arrangement of the cell wall in (a) Gram-positive and (b) Gram-negative bacteria.

This second, outer membrane of Gram-negative bacteria is an effective barrier, regulating the passage of large molecules such as antibiotics into the cell. In contrast, the thick, porous peptidoglycan layer in the cell wall of Gram-positive bacteria gives greater access to antibiotics, allowing them to more easily penetrate the cell and/or interact with the peptidoglycan itself.

You will learn more about the strategies antibiotics use to cross the cell wall in Week 3.

4.2 Activity against Gram-positive and Gram-negative bacteria

Narrow-spectrum antibiotics are effective against *either* Gram-positive or Gram-negative bacteria, whereas broad-spectrum antibiotics are effective against both types.

- Not all Gram-positive and/or Gram-negative bacteria are affected by a single antibiotic. Why is this?
- This is because of the specificity of the antibiotic/bacterial target interaction, whether the bacterial species has the target in question and whether the bacteria are resistant to the antibiotic.

4.3 Bactericidal versus bacteriostatic antibiotics

While some antibiotic classes have consistent antibacterial effects, such as ß-lactams which are nearly always bactericidal, the activity of other classes may depend on the dose of antibiotic prescribed or how long the treatment lasts. For example, fluoroquinolones and aminoglycosides, while usually bactericidal, may be bacteriostatic when used at low concentration.

You should by now have a good idea of how antibiotics interact with bacterial cells. Activity 4 looks at what happens to the bacterial population as a whole when antibiotics are administered.

Activity 4 Effect of antibiotics on bacterial growth

Allow about 10 minutes

In Week 1 you learned that bacteria are at their most susceptible to antibiotic attack when they are actively growing. In this activity you consider what happens to a bacterial culture when antibiotics are introduced during this exponential phase of growth.

Bacteriostatic antibiotics

(a) Figure 11a shows the normal growth curve of a bacterium which is sensitive to the bacteriostatic antibiotic ‘A’. Explain what you would expect to happen to the rate of bacterial growth when A is added to the culture in high concentration. You should assume that growth conditions are otherwise optimal.

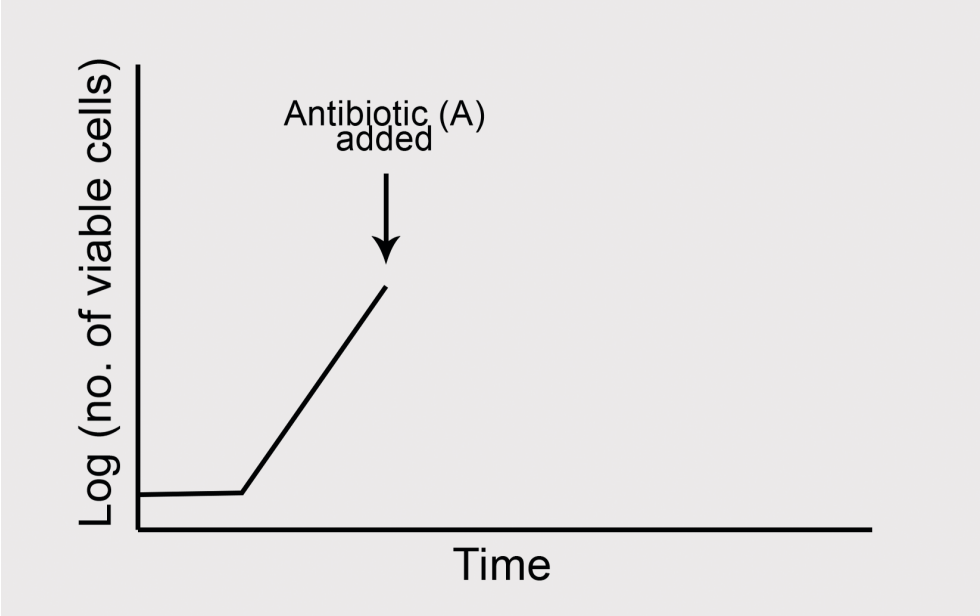


Figure 11a Normal growth curve of bacterium in the absence of antibiotic A.

Answer

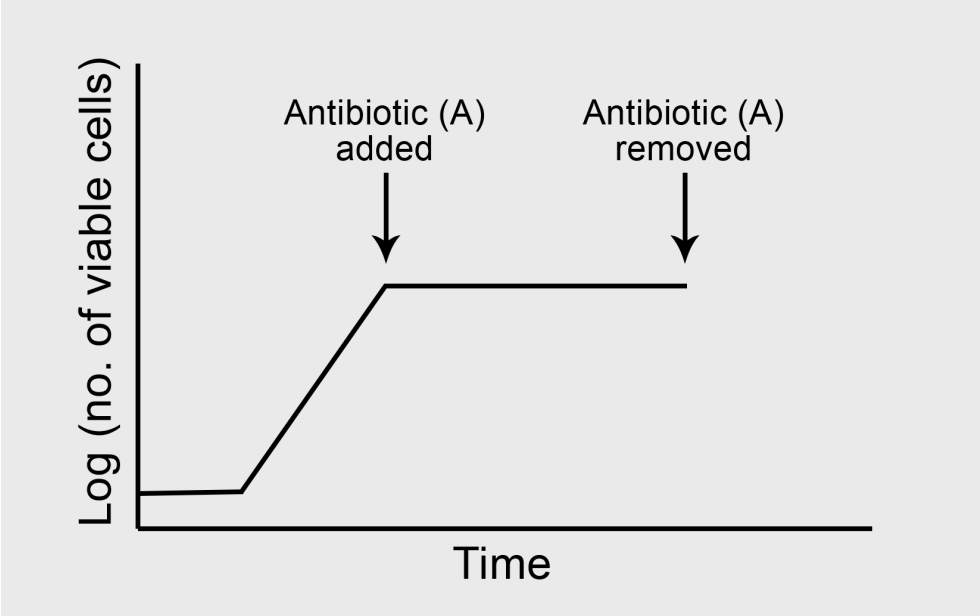


Figure 11b The bacterial population remains constant as the cells are prevented from growing and dividing.

(b) Predict what will happen to bacterial growth if antibiotic A is removed from the culture at the point indicated on the graph.

Answer

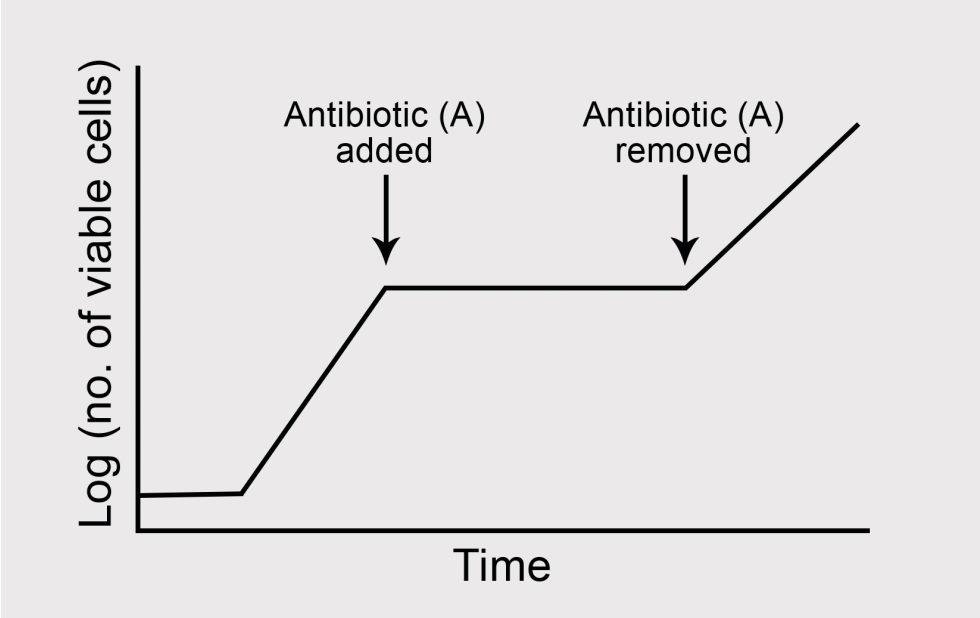


Figure 11c As the bacteria are still alive and nutrients are plentiful, the cells can now divide and growth restarts.

Bactericidal antibiotics

Figure 12a shows the normal growth curve of a bacterium which is sensitive to the bactericidal antibiotic 'B'. Explain what you would expect to happen to the rate of bacterial growth when B is added to the culture in high concentration. You should assume that growth conditions are otherwise optimal.

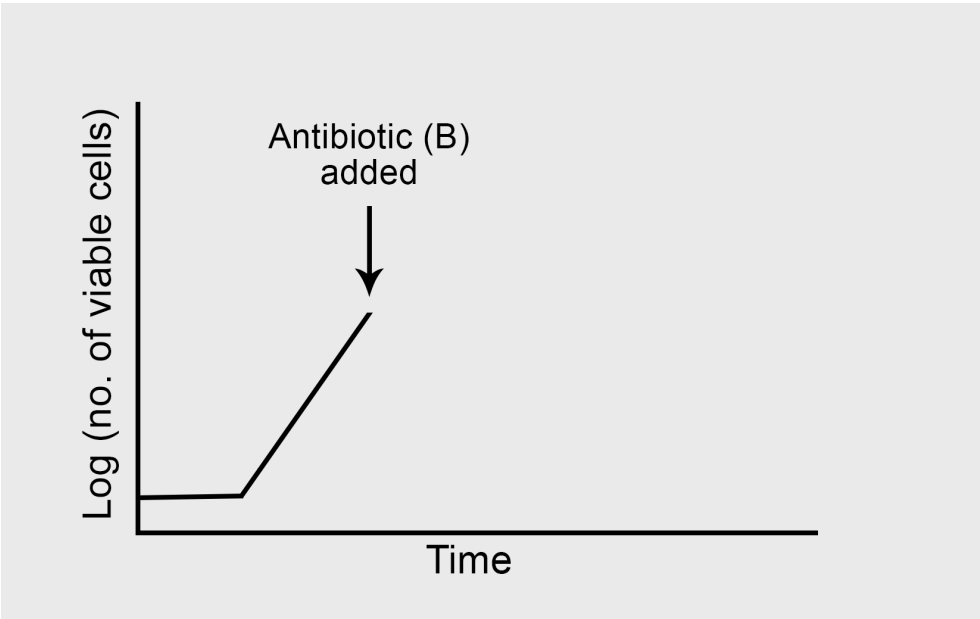


Figure 12a Normal growth curve of the bacterium in the absence of antibiotic B.

Answer

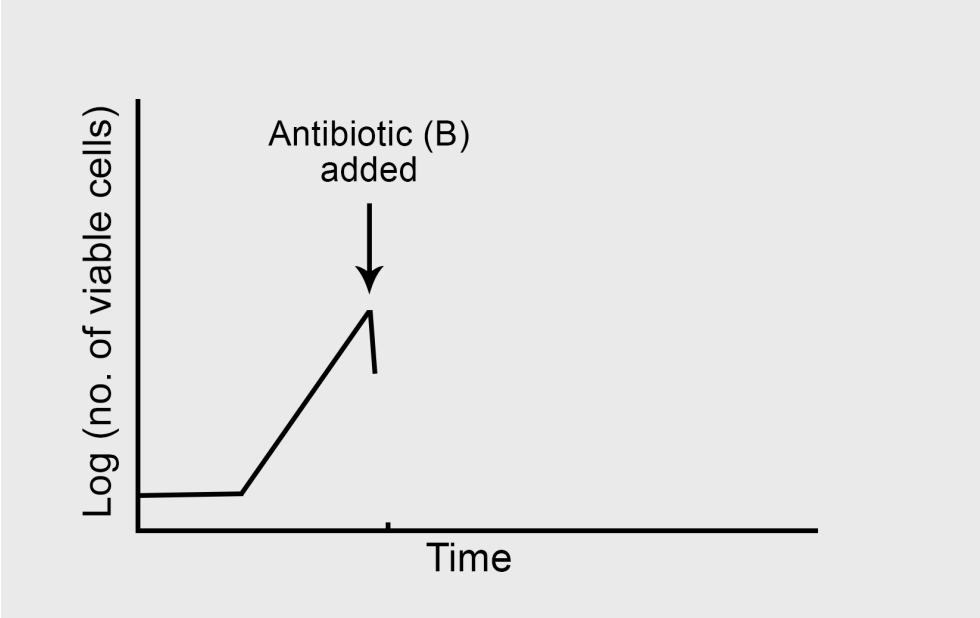


Figure 12b The number of bacterial cells falls rapidly as the cells are killed.

Bactericidal antibiotics kill susceptible bacteria during the exponential phase of growth and cure the infection.

Bacteriostatic antibiotics stop bacterial growth even though the cells remain viable. This allows time for the host's immune system to be activated and target the bacterial pathogen – again effecting a cure.

5 This week's quiz

Well done – you have reached the end of Week 2 and can now do the quiz to test your learning.

Week 2 practice quiz

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link. Return here when you have finished it.

6 Summary

This week introduced some of the basic biology and chemistry that underpins antibiotic activity. You looked at the main modes of antibiotic action and learned why these drugs demonstrate selective toxicity.

You should now be able to:

- recognise different types of commonly used antibiotics

- recall the characteristic features of bacterial and human or animal cells
- explain why antibiotics have selective toxicity
- demonstrate how commonly used antibiotics affect bacterial growth
- summarise the main mechanisms by which antibiotics stop infections from spreading and kill bacteria.

Having explored different types of antibiotic in some detail, you should now be well prepared to move on to Week 3 which discusses antibiotic resistance mechanisms.

You can now go to Week 3.

Week 3: How do bacteria become resistant to antibiotics?

Introduction

In Week 2 you looked at how antibiotics target bacteria, either killing them or preventing their growth. But bacteria are constantly fighting back against this threat to their survival. Antibiotic resistance is the ability of pathogenic bacteria to resist the action of antibiotics so that they survive exposure to antibiotics that would normally kill them or stop their growth (CDC, 2017; PHE, 2017).

You could be forgiven for thinking that antibiotic resistance has been caused by our use, and misuse, of antibiotics. However, as you will see in the following video, bacteria that have not interacted with humans have acquired resistance to many of the antibiotic medicines we use to treat infections.

Watch the Video at YouTube.com

Video 1 Antibiotic resistance is a natural bacterial defence mechanism.

You will return to look at how resistance has evolved and spread in Week 4. In this week, you will focus on how bacteria develop resistance in order to protect themselves from antibiotics. You will start by considering several mechanisms of antibiotic resistance before moving on to look at the differences between intrinsic and acquired antibiotic resistance. You will end the week by returning to the case study to explore the mechanisms responsible for resistance to third generation cephalosporins.

By the end of this week, you should be able to:

- state what is meant by the term ‘antibiotic resistance’
- recognise that antibiotic resistance evolved to protect bacteria
- describe the three main mechanisms of resistance that bacteria have developed to counteract the action of antibiotics
- give examples of these resistance mechanisms
- distinguish between intrinsic and acquired antibiotic resistance.

1 Antibiotic resistance mechanisms

Bacteria have evolved several sophisticated antibiotic resistance mechanisms. Figure 1 gives an overview of the major mechanisms by which bacteria become resistant to the action of antibiotics. Don't worry if you don't understand all of these terms, as they will be explained in the following sections.

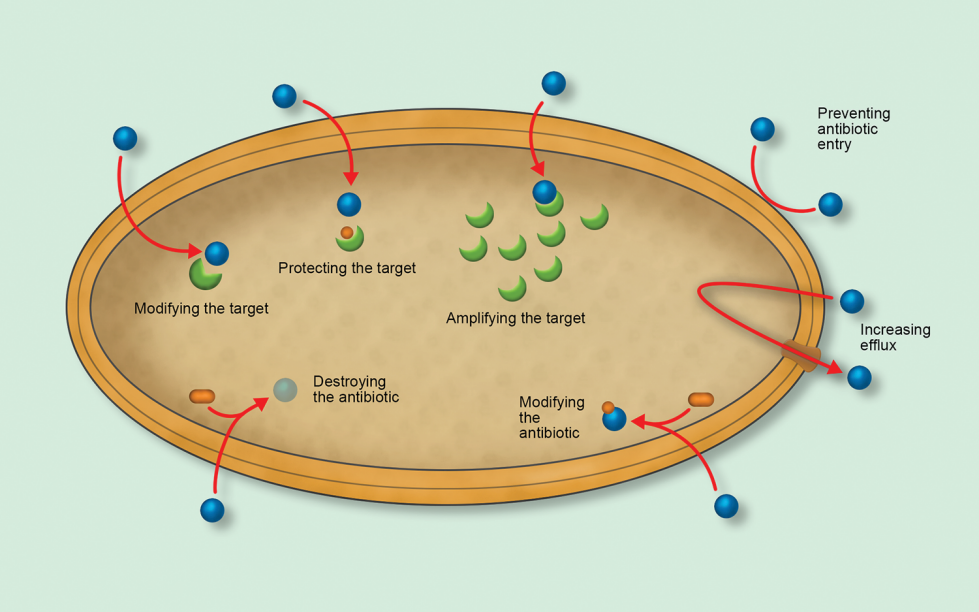


Figure 1 An overview of the mechanisms of antibiotic resistance.

In this section you will look at the three main mechanisms of antibiotic resistance:

- modifying the antibiotic target
- destroying or modifying the antibiotic
- preventing the antibiotic from reaching its target.

Although you will look at each of these mechanisms in turn, it is worth remembering that bacteria may use multiple resistance strategies simultaneously to survive exposure to antibiotics.

1.1 Modifying the antibiotic target

As you saw in Week 2, antibiotics are selectively toxic because they target structural features or cellular processes in the bacterial pathogen that are different or lacking in the host's cells. Recall how penicillin and other related β-lactam antibiotics work by binding to penicillin-binding proteins (PBPs), preventing them from binding to their normal target, peptidoglycan. Or how trimethoprim prevents dihydrofolate reductase reacting with dihydrofolic acid.

Changes to the structure of the target that prevent efficient antibiotic binding but still enable the target to carry out its normal function will confer antibiotic resistance (Figure 2).

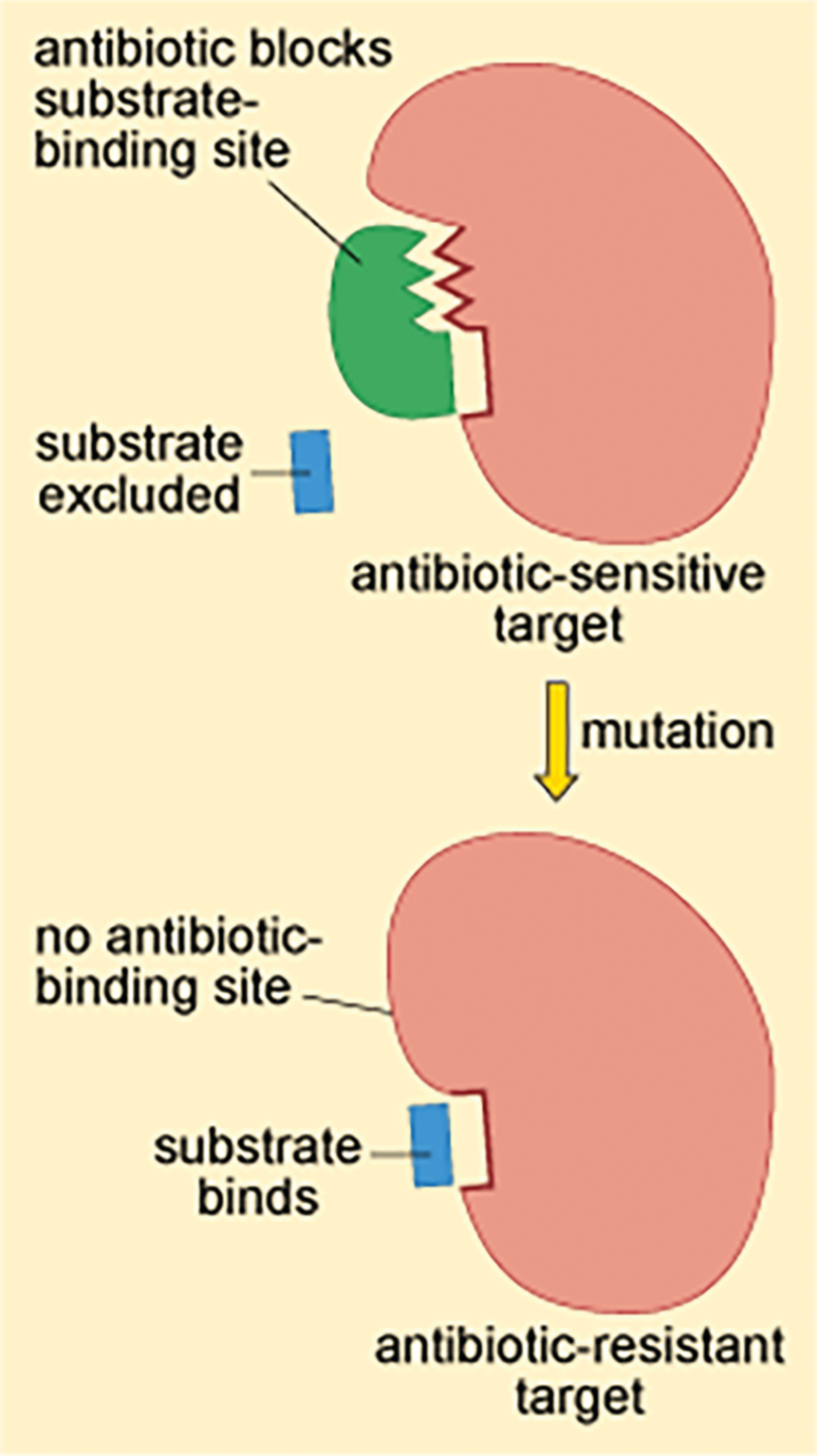


Figure 2 Schematic diagram showing how structural changes in a target enzyme can lead to antibiotic resistance. The substrate is the chemical on which the target enzyme reacts. It binds to the enzyme and is converted into a product or products through the action of the enzyme.

This resistance strategy is widespread among bacteria. For example, the oxazolidinone class antibiotic linezolid disrupts bacterial growth by preventing the initiation of protein synthesis. The target of linezolid is the bacterial large (50S) ribosomal subunit. Changes

to the 50S ribosomal subunit structure have been identified in clinical isolates of *S. aureus* and *S. pneumoniae* that are resistant to linezolid (Woodford and Ellington, 2007).

As you will see in Week 4, changes to the structure of antibiotic targets are often caused by genetic mutations. However, the structure of antibiotic targets can also be modified to prevent antibiotic binding by adding chemical groups. For example, resistance to linezolid can be caused by either genetic mutations (see Week 4) or the addition of chemical groups to the bacterial 50S ribosomal subunit, both of which prevent or reduce linezolid binding (Long et al., 2006).

You will return to look at how changes to the structure of penicillin-binding protein (PBP) contributes to resistance to cephalosporins in the case study at the end of this week.

1.2 Destroying or modifying the antibiotic molecule

The second mechanism of antibiotic resistance you will look at is the destruction or modification of the antibiotic by bacterial enzymes. Probably the most well studied example of enzymes that destroy antibiotics are the β-lactamases.

As you may recall from Week 2, β-lactamases deactivate the β-lactam ring of β-lactam antibiotics, preventing them from binding to their target (Figure 3).

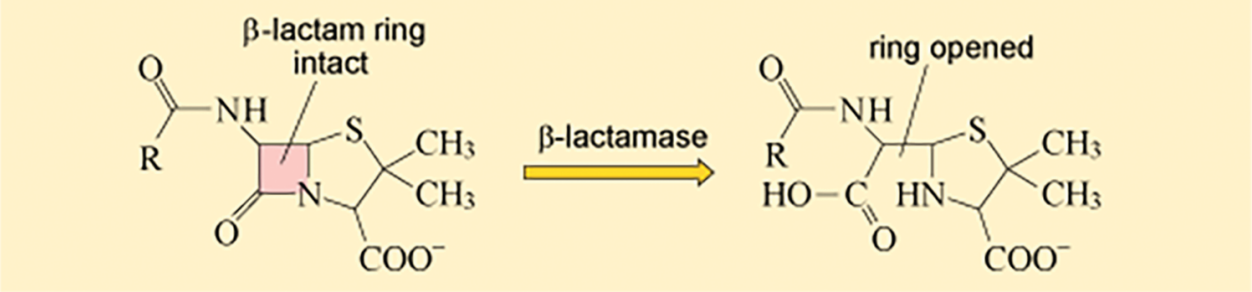


Figure 3 Inactivation of a β-lactam antibiotic by β-lactamase.

The β-lactamases can deactivate almost all of the β-lactam antibiotics currently in therapeutic use. As you will see in the case study at the end of this week, this includes cephalosporins. Consequently, their presence significantly reduces the available treatment options for infections caused by bacteria expressing **β-lactamase**. One successful strategy for treating these infections is to combine antibiotic treatment with a **β-lactamase inhibitor**.

- How might a β-lactamase inhibitor help the treatment of infections caused by β-lactamase-expressing bacteria?
- The β-lactamase inhibitor will block the ability of the β-lactamase to deactivate the β-lactam antibiotic so that it can bind to its target molecule.

Other antibiotic-modifying enzymes do not destroy or target the core chemical structure that confers antibacterial activity. Instead they modify the antibiotic's structure by adding chemical groups to prevent it from binding to its target. One group of antibiotics that are particularly susceptible to modification are the aminoglycoside antibiotics which include streptomycin (Figure 4).

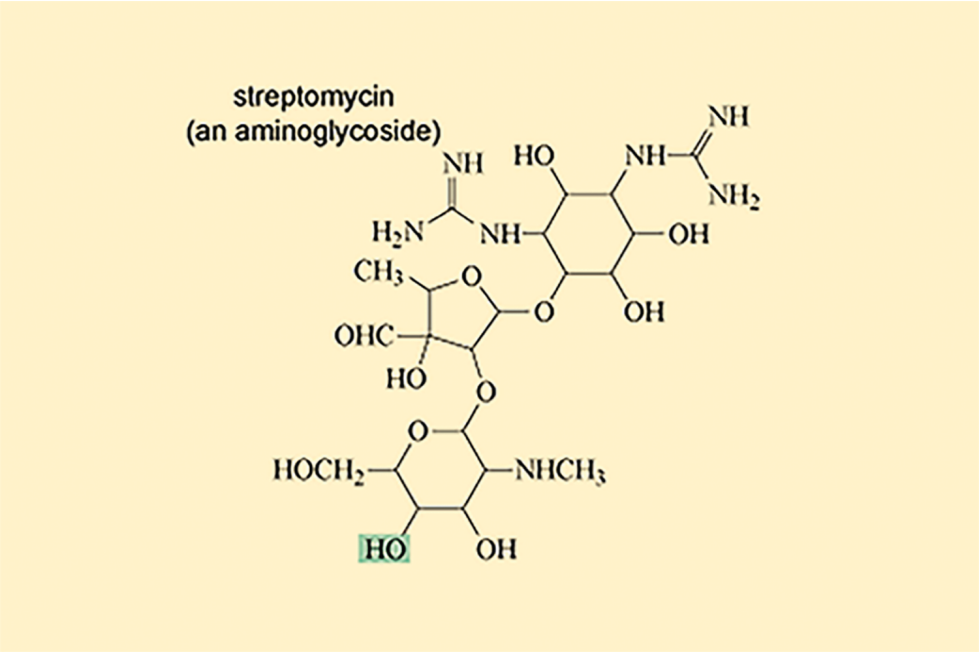


Figure 4 Structure of streptomycin. An exposed hydroxyl (-OH) group that can be modified by aminoglycoside-modifying enzymes is highlighted in green (in the figure the hydroxyl group is shown as -HO – this is the same as -OH).

Aminoglycoside-modifying enzymes add bulky chemical groups to the exposed hydroxyl (-OH) and amino ($-NH_2$) groups of the antibiotic, which prevent it from binding to its target.

1.3 Preventing entry, increasing exit

Antibiotics are only effective if they can reach their target. Preventing antibiotics from reaching their target is the final mechanism of antibiotic resistance that you will look at this week.

As you should recall from Week 2, the cell wall protects bacteria from osmotic and mechanical damage. To reach their targets inside the cell, antibiotics must cross this cell wall. In Activity 1 you will look at the mechanisms that antibiotics use to cross this bacterial cell wall.

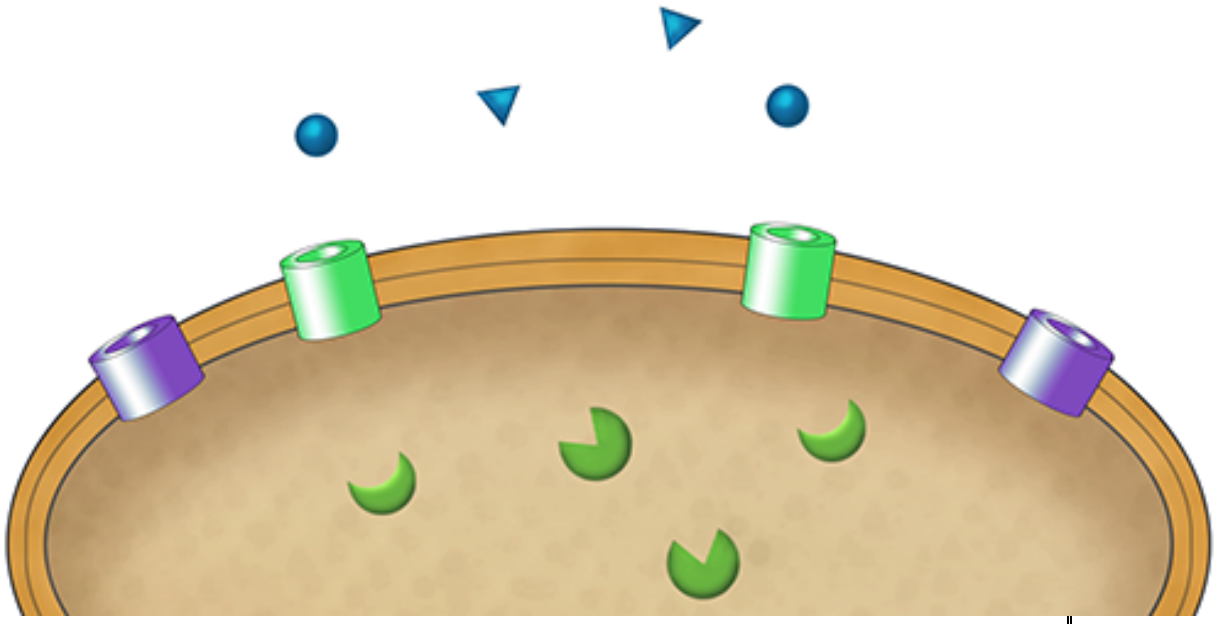
Activity 1 Transporting antibiotics across the bacterial cell wall

Allow 15 minutes

First, watch the following animation which describes how antibiotics are transported across the bacterial cell wall.

Video content is not available in this format.

Video 1 Animation of the mechanisms of transport of antibiotics across the membrane.



Now answer the following questions.

1 Decreasing the number of **porin** channels on the outer membrane:

○ (a) decreases the amount of antibiotic entering Gram-negative bacteria

Your answer is correct. Most antibiotics cannot cross the outer membrane of Gram-negative bacteria and therefore enter the cell via porin channels. Decreasing the number of porin channels will decrease the amount of antibiotic entering the bacteria.

○ (b) increases the amount of antibiotic entering Gram-negative bacteria

Your answer is incorrect. Most antibiotics cannot cross the outer membrane of Gram-negative bacteria and therefore enter the cell via porin channels. Decreasing the number of porin channels will decrease the amount of antibiotic entering the bacteria.

○ (c) has no effect on the amount of antibiotic entering Gram-negative bacteria.

Your answer is incorrect. Most antibiotics cannot cross the outer membrane of Gram-negative bacteria and therefore enter the cell via porin channels. Decreasing the number of porin channels will decrease the amount of antibiotic entering the bacteria.

2 Bacteria that are resistant to penicillin are likely to have:

○ (a) very few porin channels on their outer membrane or have replaced their porin channels with channels that exclude penicillin

Your answer is correct. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Decreasing the expression of porins, or replacing them with channels that cannot transport the antibiotic, will prevent the antibiotic from crossing the outer membrane and reaching its target, therefore these bacteria will be resistant.

○ (b) numerous porin channels on their outer membrane

Your answer is incorrect. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Decreasing the expression of porins, or replacing them with channels that cannot transport the antibiotic, will prevent the antibiotic from crossing the outer membrane and reaching its target, therefore these bacteria will be resistant.

○ (c) replaced their porin channels with channels that selectively transport penicillin.

Your answer is incorrect. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Decreasing the expression of porins, or replacing them with channels that cannot transport the antibiotic, will prevent the antibiotic from crossing the outer membrane and reaching its target, therefore these bacteria will be resistant.

3 Increasing the rate of active transport of penicillin through the **efflux pump** would:

○ (a) increase the amount of penicillin in the bacterial cell

Your answer is incorrect. Efflux pumps actively transport antibiotics out of the bacterial cell. Therefore, increasing transport through these channels will decrease the amount of antibiotic inside the cell.

○ (b) decrease the amount of penicillin in the bacterial cell

Your answer is correct. Efflux pumps actively transport antibiotics out of the bacterial cell. Therefore, increasing transport through these channels will decrease the amount of antibiotic inside the cell.

○ (c) have no effect on the amount of penicillin in the bacterial cell.

Your answer is incorrect. Efflux pumps actively transport antibiotics out of the bacterial cell. Therefore, increasing transport through these channels will decrease the amount of antibiotic inside the cell.

4 Bacteria that are resistant to penicillin are likely to have:

○ (a) efflux pumps that are unable to transport penicillin

Your answer is incorrect. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Actively transporting antibiotics out of the cell decreases their concentration inside the cell, so that they cannot build up to a high enough concentration to exert the effect on their target.

Increasing active transport by expressing more efflux pumps that can actively transport the antibiotic out of the cell decreases the amount of antibiotic inside the cell and prevents it from acting on its target.

○ (b) efflux pumps that transport penicillin

Your answer is correct. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Actively transporting antibiotics out of the cell decreases their concentration inside the cell, so that they cannot build up to a high enough concentration to exert the effect on their target.

Increasing active transport by expressing more efflux pumps that can actively transport the antibiotic out of the cell decreases the amount of antibiotic inside the cell and prevents it from acting on its target.

○ (c) no efflux pumps.

Your answer is incorrect. If an antibiotic cannot reach its target, bacteria will be resistant to its action. Actively transporting antibiotics out of the cell decreases their concentration inside the cell, so that they cannot build up to a high enough concentration to exert the effect on their target.

Increasing active transport by expressing more efflux pumps that can actively transport the antibiotic out of the cell decreases the amount of antibiotic inside the cell and prevents it from acting on its target.

As you should now appreciate, bacteria can prevent antibiotics from reaching their target by decreasing the permeability of their outer membrane or by actively transporting antibiotics out of the cell (Activity 1). Both decreased porin expression and increased efflux pump expression have been reported in antibiotic-resistant clinical **isolate**s. For

example, *S. aureus* that overexpresses multidrug-resistant efflux pumps, which transport a wide range of antibiotics, have been isolated from patients (Kosmidis et al., 2012).

You will look at an example of how altering porin expression contributes to antibiotic resistance in the case study at the end of this week.

2 Intrinsic and acquired resistance

There are two types of antibiotic resistance:

- intrinsic (or inherent) resistance
- acquired resistance.

In this section, you will look at each type in turn.

2.1 Intrinsic resistance

Intrinsic resistance is the innate ability of a type of bacteria species to resist the action of an antibiotic as a consequence of the bacteria's structural or functional characteristics. In contrast to acquired resistance, which you will look at next, intrinsic resistance is 'normal' for bacteria of a given type.

Intrinsic resistance may occur because bacteria lack the target for a particular antibiotic or because the drug can't get to its target. It reduces the pool of antibiotics available to treat infections. In addition, as you will see in Week 4, resistance elements that are intrinsic to one bacterial type can be transferred to another one. In this way, intrinsic antibiotic resistance in non-pathogenic bacteria (like the ones you saw in Video 1) can be transferred to a pathogenic bacterium where it can restrict the treatment options for infections caused by these bacteria.

2.2 Introducing acquired resistance

As its name suggests, **acquired resistance** is not innate to a bacterial type. It occurs when a bacterium acquires the ability to resist the actions of a particular antibiotic.

Unlike intrinsic resistance, acquired resistance is only found in some populations of a bacterial type. This makes acquired resistance harder to track since each new outbreak or isolate may have acquired resistance to a different spectrum of antibiotics.

Acquired resistance is a very significant healthcare concern. Infections caused by bacteria that have acquired resistance to an antibiotic can no longer be treated with that antibiotic. Consequently, identifying the type of pathogenic bacteria causing an infection may not always be sufficient to determine which antibiotics will be effective treatments. Resistant isolates must be tested to determine which antibiotics are effective before treatment can be prescribed.

Activity 2 Acquiring multidrug resistance

Allow 15 minutes

The treatment options for infections caused by bacteria with acquired resistance can be further limited because bacteria can accumulate resistance to a variety of antibiotics over time. This is known as **multidrug resistance** (MDR).

Perhaps the most often cited example of intrinsic resistance is the multidrug resistance of Gram-negative bacteria.

Can you suggest why Gram-negative bacteria might be intrinsically resistant to many antibiotics?

Answer

Unlike Gram-positive bacteria, Gram-negative bacteria have an outer membrane which is impermeable to many antibiotics.

Now read the following BBC news article which highlights that, although multidrug resistance is rare, it can have a devastating impact.

Article 1 Bug resistant to all antibiotics kills woman

While you read the article, note down the answers to the following questions.

1 Which bacterium caused the patient's infection?

Answer

The patient's infection was caused by the Gram-negative bacterium *Klebsiella pneumoniae.*

2 How many antibiotics was the infection resistant to?

Answer

It was resistant to 26 different antibiotics, including the 'drug of last resort' – colistin.

3 Is resistance to all antibiotics a common occurrence?

Answer

No, infections that are resistant to all antibiotics are uncommon.

Acquired resistance can occur as a result of genetic mutations or the transfer of resistance elements from other bacteria through a process called horizontal gene transfer. Don't worry if you don't understand these terms yet. You will return to these processes in Week 4.

Activity 3 Comparing intrinsic and acquired resistance

Allow 15 minutes

Look at the following statements in the table. Decide whether they are about intrinsic or acquired resistance or both and type your answer into the right-hand column.

Statement	Intrinsic resistance, acquired resistance, or both?
Mechanism only present in a subpopulation of bacteria of a given type	*Provide your answer...*

Difficult to track	*Provide your answer...*
Can be identified if the bacterial type is known	*Provide your answer...*
Normal for bacteria of that type	*Provide your answer...*
Limits treatment options	*Provide your answer...*
Mechanism present in all bacteria of a given type	*Provide your answer...*
Occurs as a result of genetic mutation or horizontal gene transfer	*Provide your answer...*

Answer

Statement	**Intrinsic resistance, acquired resistance, or both?**
Mechanism only present in a subpopulation of bacteria of a given species	Acquired resistance
Difficult to track	Acquired resistance
Can be identified if the bacterial species is known	Intrinsic resistance
Normal for bacteria of that species	Intrinsic resistance
Limits treatment options	Both
Mechanism present in all bacteria of a given species	Intrinsic resistance
Occurs as a result of genetic mutation or horizontal gene transfer	Acquired resistance

3 Case study: resistance to third-generation cephalosporins

In Weeks 1 and 2 you learned about the cephalosporin antibiotics and their mechanism of action. You may recall from Week 1 that the proportion of *E. coli* isolates that are resistant to cephalosporins has been increasing in the UK.

In this case study, you will look at some the molecular mechanisms underlying this resistance.

3.1 Intrinsic resistance to cephalosporins

Several bacteria are intrinsically resistant to cephalosporins. As a result, infections caused by these bacteria cannot be treated with cephalosporins. Some of these intrinsically resistant bacteria are summarised in Table 1.

Table 1 Bacteria intrinsically resistant to cephalosporins

Type	Infectious disease	Resistance mechanism (Cox and Wright, 2013)	Resistance
Pseudomonas aeruginosa	**Nosocomial infections** including pneumonia, urinary tract infections and **bacteraemia**	Expresses cephalosporinase which deactivates cephalosporins	Resistant to 1st and 2nd generation cephalosporins*
Enterococci spp.	Urinary tract infections, bacteraemia, **bacterial endocarditis**, **diverticulitis** and meningitis	Expresses a modified antibiotic target (PBP) that binds to β-lactams poorly	Resistant to 1st and 2nd generation cephalosporins. Some resistance to 3rd generation cephalosporins*
Listeria monocytogenes	**Listeriosis**	Expresses a modified antibiotic target (PBP) that binds to cephalosporins poorly	Resistant to 1st, 2nd and 3rd generation cephalosporins*

* you will learn more about different generations of cephalosporins in Week 6

While intrinsic resistance limits the treatment options for infections caused by these pathogens, a greater concern is cephalosporin resistance being acquired by other **intrinsically susceptible** bacterial types. Some of these bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are of huge clinical importance.

The massive use of cephalosporin antibiotics to treat infections has led to the emergence of these bacteria, as you will see in the case studies in Weeks 4 and 5. But next you will look at the mechanisms of resistance to cephalosporins.

3.2 Mechanisms of cephalosporin resistance

Bacteria use multiple different mechanisms to resist the effects of cephalosporin antibiotics. In the final section of this week, you will look at three examples that illustrate the resistance mechanisms described in Section 2:

- modifying the target
- destroying the antibiotic
- preventing the antibiotic from reaching its target.

3.2.1 PBP2a – a PBP that doesn't bind cephalosporins

Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to most β-lactam antibiotics, including cephalosporins. This is one of the reasons why infections caused by

MRSA are extremely challenging to treat. This resistance results from the expression of **penicillin-binding protein 2a** (**PBP2a)**. PBP2a binds β-lactams more poorly than other PBPs because differences in its structure prevent β-lactam antibiotics from reaching the binding site (Figure 5).

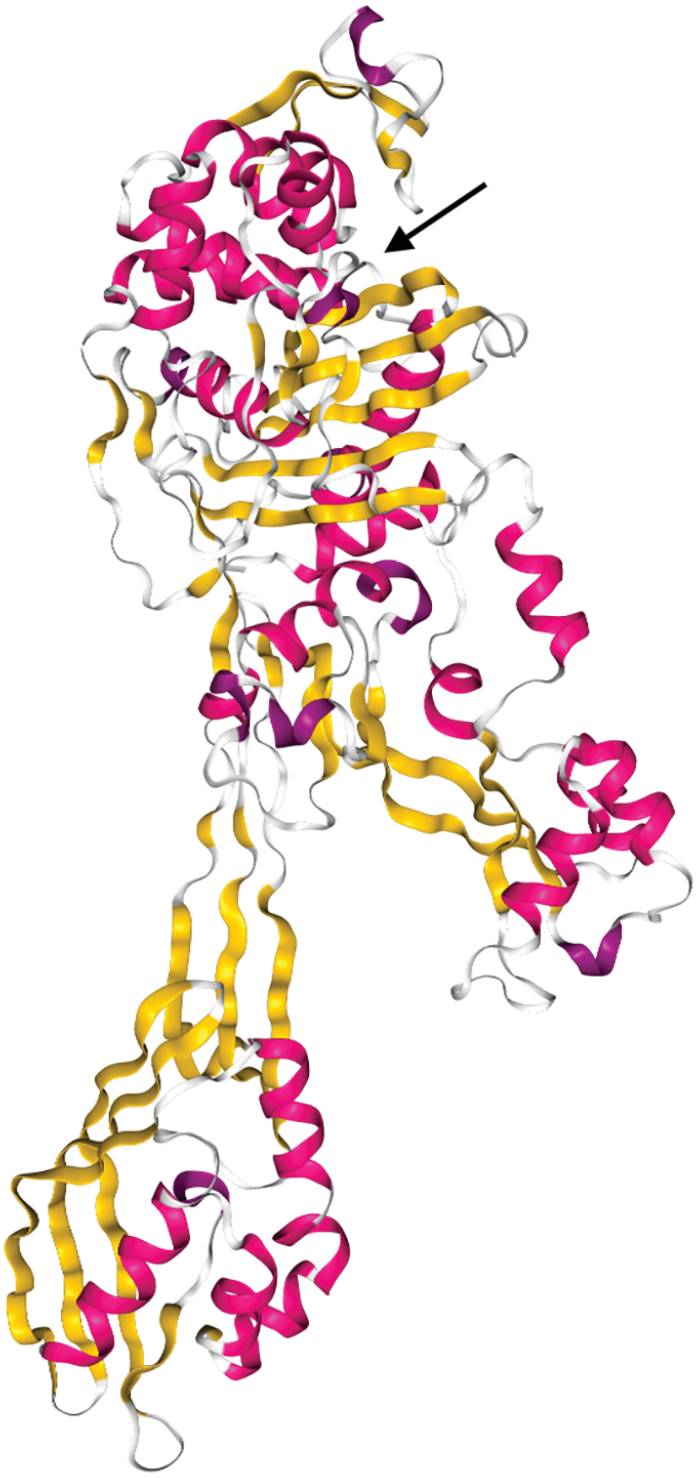


Figure 5 The protein structure of PBP2a. The figure shows a ribbon diagram of the PBP2a protein structure. The ribbon shows the overall organisation of the protein giving a representation of the overall protein shape. The ß-lactam binding site (indicated with an

arrow) is inaccessible to ß-lactam antibiotics because of changes to the structure of PBP2a (see Figure 2 in Section 1.1) (Lim and Strynadka, 2002). You do not need to study this structure in detail.

You may recall from Week 2 that cephalosporins exert their bactericidal action by binding to penicillin-binding proteins and preventing them from cross-linking the bacterial cell wall. Since cephalosporins do not bind to PBP2a, its presence in MRSA allows cell wall biosynthesis to occur in the presence of most cephalosporins.

Fortunately, more recently developed cephalosporins, including ceftaroline (Duplessis and Crum-Cianflone, 2011) and ceftobiprole (Kisgen and Whitney, 2008) can bind to and inhibit the activity of PBP2a. These cephalosporins have been licensed for the treatment of community- and hospital-acquired pneumonia and complicated skin and soft tissue infections (NICE, 2017).

You will learn more about the development of cephalosporin antibiotics in Week 6.

3.2.2 Extended spectrum β-lactamases

In Section 1.2 you saw how β-lactamases can hydrolyse β-lactam antibiotics in order to destroy them. The first β-lactamase to be identified was **penicillinase**. As its name suggests, penicillinase can hydrolyse penicillin but not cephalosporins. In the 1980s, a new group of β-lactamase enzymes were detected in Europe that hydrolyse cephalosporins. Because of their ability to hydrolyse a wider range of β-lactams, the name for these enzymes is **extended spectrum β-lactamase (ESBL)**.

In the next activity, you will look at how the presence of ESBLs in *E. coli* is associated with cephalosporin resistance.

Activity 4 Cephalosporin resistance and ESBLs

Allow 20 minutes

The data in this activity are from Pfizer's antimicrobial testing leadership and surveillance (ATLAS) (Pfizer, 2017).

E. coli bacteria were isolated from infections and tested to determine whether they produced ESBLs and whether they were resistant to cephalosporins. Figure 6 shows the percentage of ESBL- and non-ESBL-producing *E. coli* isolates that were resistant to the cephalosporin cefepime between 2004 and 2016.

Note that this figure compares ESBL-producing and non-ESBL-producing isolates for resistance to cefepime. However, it does not give any information on the number of *E. coli* isolates that produce ESBLs. As you will see in the case study in Week 4, the percentage of ESBL-producing *E. coli* isolates in the UK during this period remained below 15% (BSAC UK, 2014).

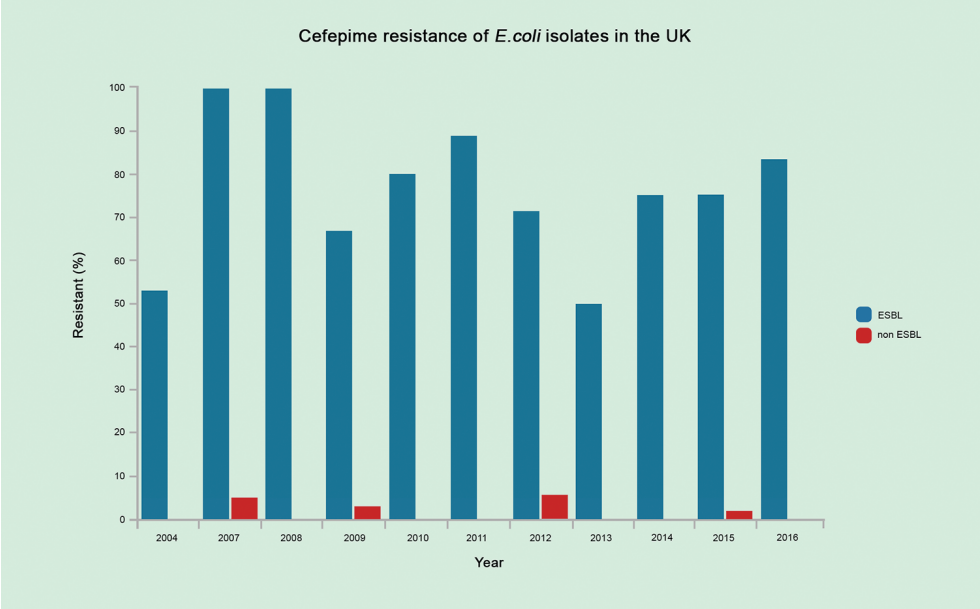


Figure 6 Cefepime resistance of *E. coli* isolates in the UK between 2004 and 2016 (Data from Pfizer, 2017).

Now answer the following questions based on the data in Figure 6.

1 How has the proportion of (a) ESBLs and (b) non-ESBLs resistant to cefepime changed over time?

Answer

(a) ESBL-producing *E. coli* have higher levels of resistance to cefepime than non-ESBL-producing *E. coli* isolates over the entire period. In 2004, approximately 50% of ESBL isolates were resistant. This increased to a peak of approximately 100% in 2007 and 2008. Resistance decreased between 2008 and 2009 and then rose again until 2011. Resistance reached its lowest level in 2013 before increasing again. Resistance never fell below 50% with the lowest levels in 2004 and 2013.

(b) non-ESBL producing bacteria display hardly any resistance to cefepime with low levels of resistance (less than 10%) only being observed in 2007, 2009, 2012 and 2015.

2 Explain the difference in resistance between ESBL- and non-ESBL-producing *E. coli*?

Answer

The presence of an ESBL in ESBL-producing *E. coli* results in the hydrolysis, and therefore destruction, of cefepime. Since cefepime can no longer inhibit PBP, these bacteria are resistant. Non-ESBL-producing *E. coli* lack the ESBL and cannot hydrolyse cefepime, therefore it can exert its bactericidal effects by binding to and inhibiting its target PBP.

3 Do you think the expression of ESBLs is a major determinant of resistance to cephalosporins in *E. coli*?

Answer

Resistance to cefepime remains between 50 and 100% in ESBL-producing *E. coli* whereas almost all non-ESBL-producing bacteria are susceptible to cefepime. This

suggests that the presence of an ESBL is a major determinant of cephalosporin resistance.

Since they were first described in the early 1980s, the frequency of infections caused by ESBL-producing bacteria has been increasing (Figure 7). Resistance to cephalosporins limits the treatment options for these infections. Consequently, ESBLs represent an ever-growing healthcare challenge.

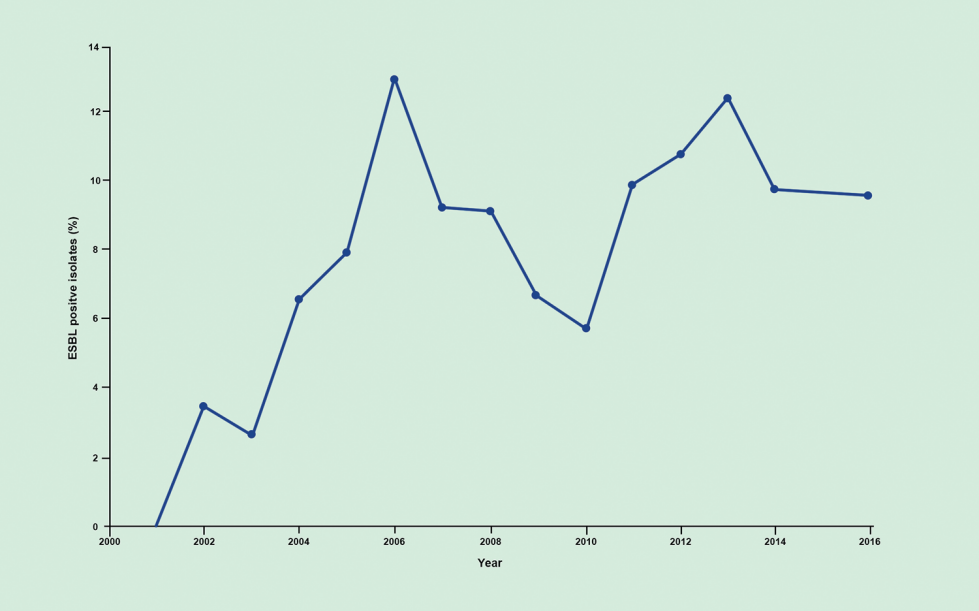


Figure 7 Frequency of ESBL-positive *E. coli* isolates in the UK from 2001 to 2016 (Data from BSAC UK, 2014).

Several ESBL classes have been identified. Of them, the CTX-M class of ESBLs, has become the most common worldwide. You will learn more about the origin and spread of CTX-M ESBLs in the case study in Week 4.

3.2.3 Porin expression and cephalosporin resistance in *K. pneumoniae*

K. pneumoniae bacteria express two major porins called OmpK35 and OmpK36. Expression of either of them is sufficient for the transport of β-lactam antibiotics across the cell membrane.

You may remember from Section 1.3 that reducing the number of porins in the cell wall can confer antibiotic resistance by preventing the antibiotic from crossing the membrane to reach its target. Therefore, you might expect that loss of either OmpK35 or OmpK36 from *K. pneumoniae* would result in resistance to cephalosporins. However, multiple studies have suggested that the loss of porins from the cell wall of *K. pneumoniae* does not result in clinically relevant resistance (Hernández-Allés et al., 2000). Therefore, infections caused by *K. pneumoniae* lacking porins can still be treated using β-lactam antibiotics.

Porin loss can contribute to cephalosporin resistance in bacteria with additional mechanisms of resistance. For example, the loss of OmpK35 and OmpK36 from the cell

wall of ESBL-producing *K. pneumoniae* results in resistance to cefoxitin, a cephalosporin which is a poor ESBL substrate.

- How might this affect the treatment of ESBL-producing *K. pneumoniae*?
- Cefoxitin could be used to treat ESBL-producing *K. pneumoniae* because it is a poor substrate for ESBLs. However, if these *K. pneumoniae* strains do not express OmpK35 or OmpK36, cefoxitin will not be able to cross the outer membrane to reach its target.

Although you have largely considered each resistance mechanism separately this week, this example illustrates how bacteria may rely on multiple resistance mechanisms to protect themselves.

4 This week's quiz

Well done – you have reached the end of Week 3 and can now do the quiz to test your learning.

Week 3 practice quiz

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link. Return here when you have finished it.

5 Summary

This week introduced the mechanisms of antibiotic resistance. You should now be able to explain how antibiotic resistance protects bacteria from both natural and synthetic antibiotics and give examples of the main mechanisms of antibiotic resistance.

You should now be able to:

- state what is meant by the term 'antibiotic resistance'
- recognise that antibiotic resistance evolved to protect bacteria
- describe the three main mechanisms of resistance that bacteria have developed to counteract the action of antibiotics
- give examples of these resistance mechanisms
- distinguish between intrinsic and acquired antibiotic resistance.

Having seen how antibiotic resistance can be either intrinsic or acquired, next week you will look in more detail at the processes of mutation and gene transfer that lead to acquired resistance.

You can now go to Week 4.

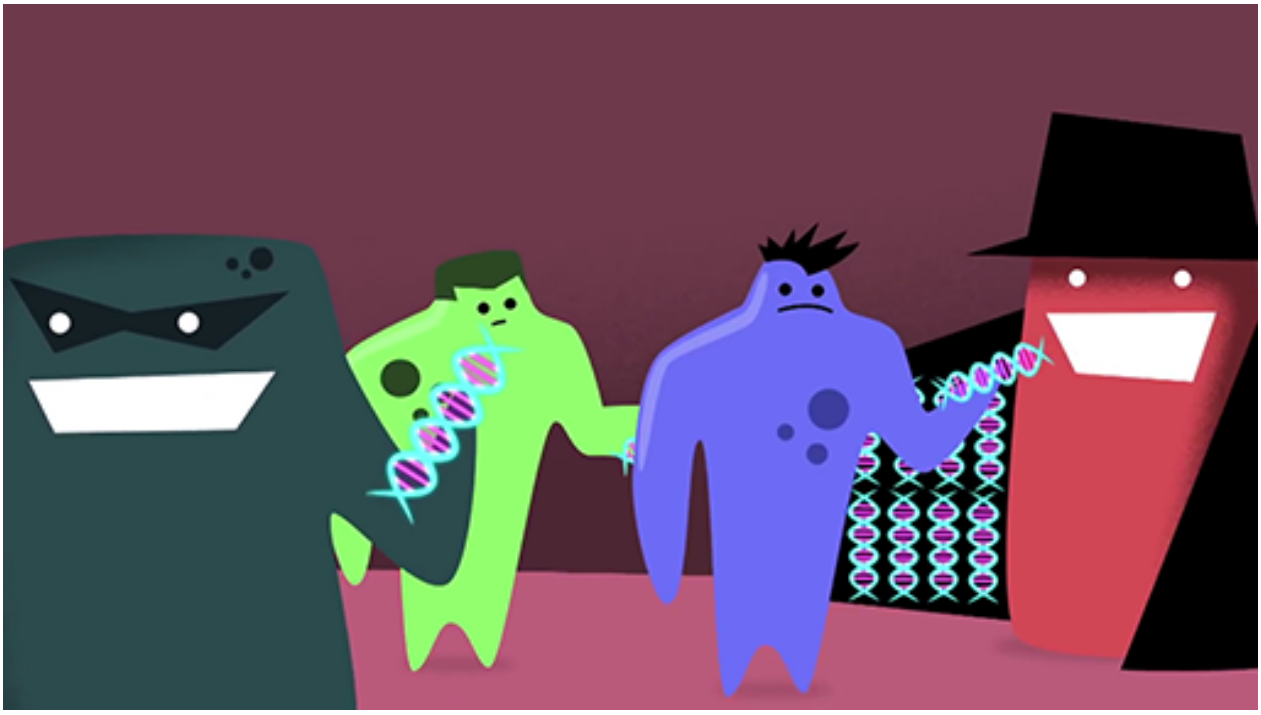
Week 4: Why are so many bacteria resistant to antibiotics?

Introduction

Last week you learned that acquired resistance can result from mutation or **horizontal gene transfer**. This week you will learn more about both of these processes before considering why antibiotic resistance arises and spreads so rapidly.

Begin this week by watching the first 2.40 minutes of the following Ted Talks video which shows how bacteria can acquire and spread antibiotic resistance.

Video content is not available in this format.
Video 1 An introduction to the acquisition and spread of antibiotic resistance.



By the end of this week, you should be able to:

- explain how genetic mutations can give rise to antibiotic resistance that can be inherited
- describe the horizontal gene transfer mechanisms that allow antibiotic resistance to be transferred between bacteria
- discuss how evolution and natural selection maintain antibiotic resistance in bacteria.

1 How do mutations lead to resistance?

A bacterium can acquire antibiotic resistance through **genetic mutations** which are permanent changes in the **deoxyribonucleic acid (DNA)** sequence that makes up a **gene**. Perhaps the best example of acquisition of resistance by mutation is *Mycobacterium tuberculosis* where resistance to all therapeutic agents is caused by mutation.

So how does altering the sequence of a bacteria's DNA result in antibiotic resistance? The answer lies in how genetic information, encoded by DNA, is converted into proteins which are required for the structure and function of bacteria.

Optional activity: What do genes do?

If you are unfamiliar with the terms DNA, RNA, base pair, gene, amino acid or protein, you may want to try our free OpenLearn course *What do genes do?* before you begin the following sections.

1.1 From genetic information to protein function

Almost every process in a cell requires proteins. As you saw in Week 2, antibiotics often exert their bactericidal and bacteriostatic effects by binding to proteins that are crucial to the structure or function of the bacterial cell.

The function of a protein is largely determined by its structure. Proteins are comprised of building blocks called amino acids. The sequence of these amino acids determines the structure of a protein. The **amino acid** sequence of a protein is specified by the DNA sequence of a gene (Figure 1). So, there is a direct relationship between DNA and the structure and function of a protein.

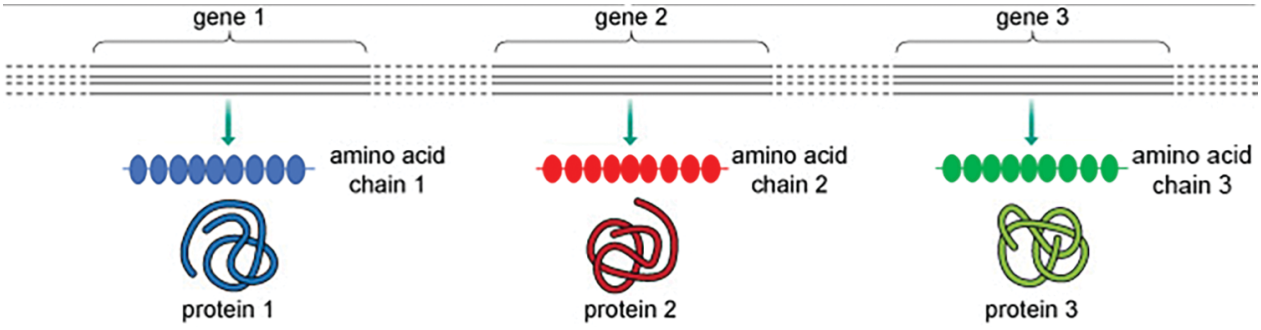
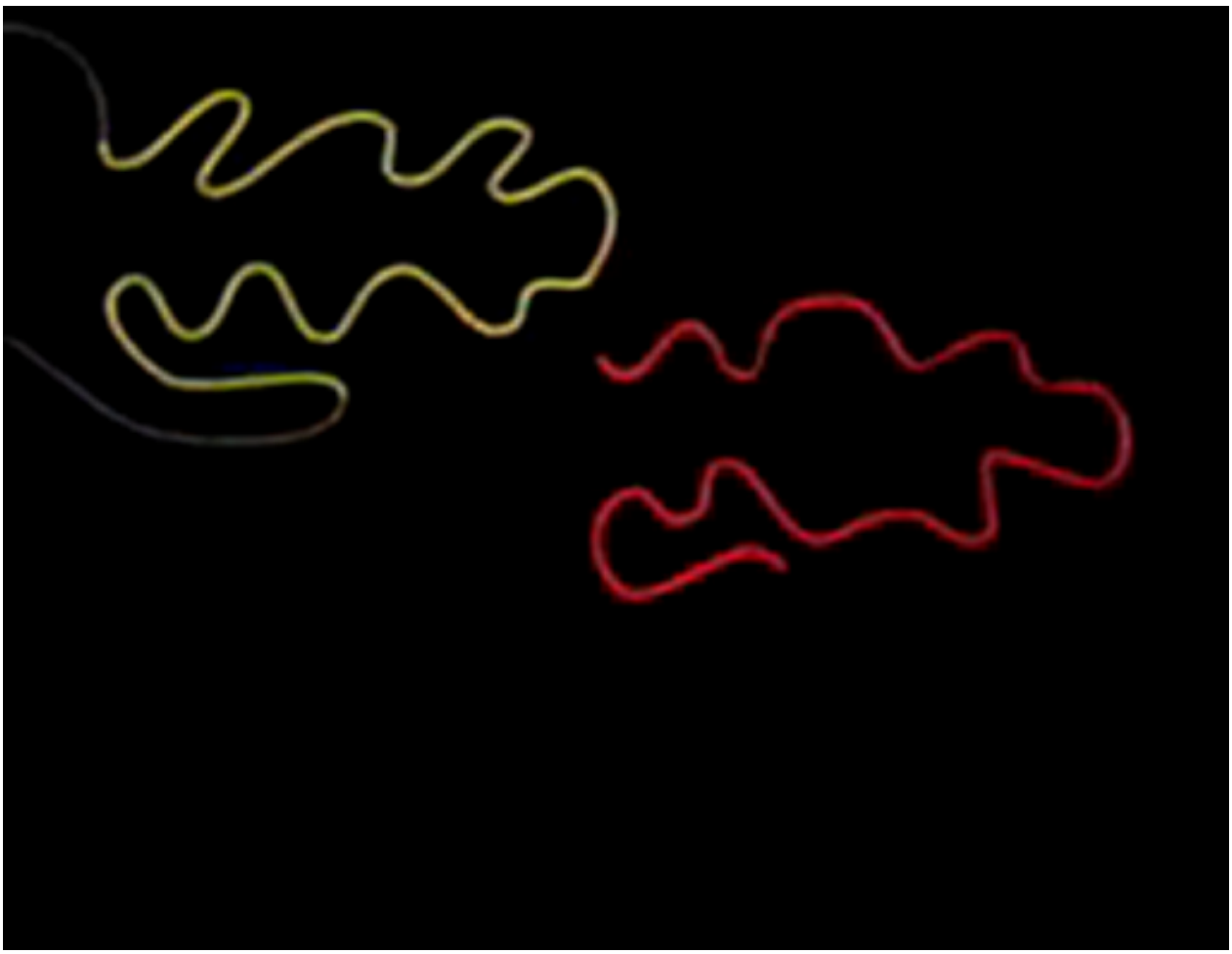


Figure 1 The DNA sequence of a gene encodes the sequence of amino acids in a protein.

In 1958, Francis Crick, who helped discover the structure of DNA, proposed the central dogma to explain how genetic information, encoded in DNA, can be converted into a functional product, a protein. The following short video gives an overview of this central dogma. Note that the conversion of information, encoded in DNA, into a protein occurs via an intermediate molecule called **RNA (ribonucleic acid)**.

Video content is not available in this format.
Video 2 An overview of the flow of information from DNA to protein.



1.2 Genetic mutations and protein structure

As you saw in Week 3, changes in the structure of bacterial proteins can result in antibiotic resistance.

- Can you think of a specific example of how changing protein structure could lead to antibiotic resistance?
- Structural changes to an antibiotic target protein could prevent the antibiotic from binding. This would make the target insensitive to the antibiotic and bacteria containing this protein would be resistant to the effects of the antibiotic. For example, linezolid exerts its antibiotic effects by binding to ribosomes and preventing the

initiation of protein synthesis. Structural changes to the ribosome can prevent the binding of linezolid. Consequently, protein synthesis initiation is no longer blocked in the presence of linezolid and resistant bacteria can grow.

Recall from Section 1.1 that the amino acid sequence, and therefore the structure of a protein, is encoded in the DNA sequence of a gene. Small changes, or mutations, in the DNA sequence within a gene can alter the amino acid sequence of the protein it encodes (Figure 2).

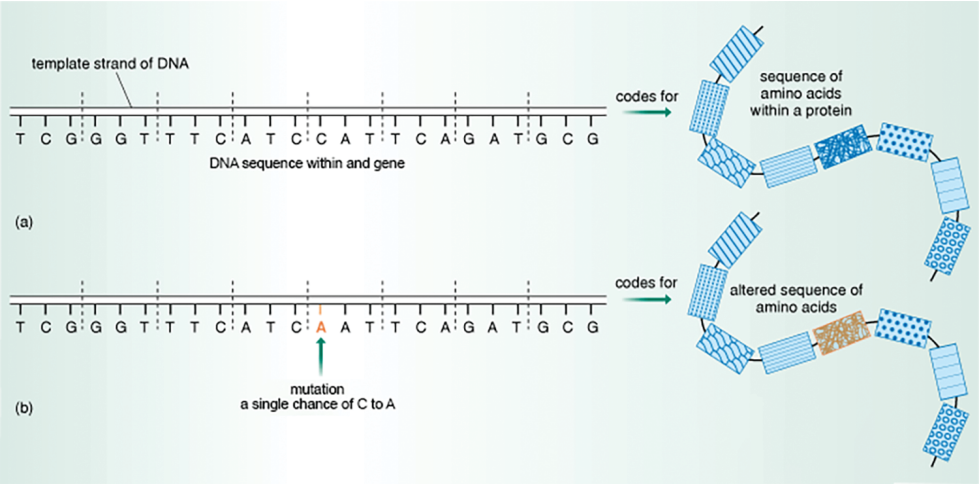


Figure 2 Genetic mutations can alter the amino acid sequence of a protein.

It only requires a very small change in the bacteria's DNA sequence to alter the amino acid sequence and, therefore, the structure of proteins that are targeted by antibiotics. As you have seen, these changes in the structure of proteins targeted by antibiotics can have important consequences for their function.

Recall from Week 3 how changing the structure of the ribosome to prevent linezolid binding results in resistance to this antibiotic. These structural changes are caused by several genetic mutations that alter the amino acid sequence, and therefore the structure, of the ribosome.

In the case study later this week, you will look at how genetic mutations can cause resistance to cephalosporin antibiotics.

1.3 Transmission of mutations by vertical gene transfer

Vertical gene transfer is the transfer of genetic information, including any genetic mutations, from a parent to its offspring. As you briefly saw in Week 1, bacteria reproduce by binary fission, where the cell divides into two identical daughter cells. As in humans, the genetic information in bacteria is encoded in DNA, which is packed into **chromosomes**. During binary fission, the chromosomal DNA is copied, so that each new daughter cell inherits an exact copy of the parent cell's chromosomes (Figure 3).

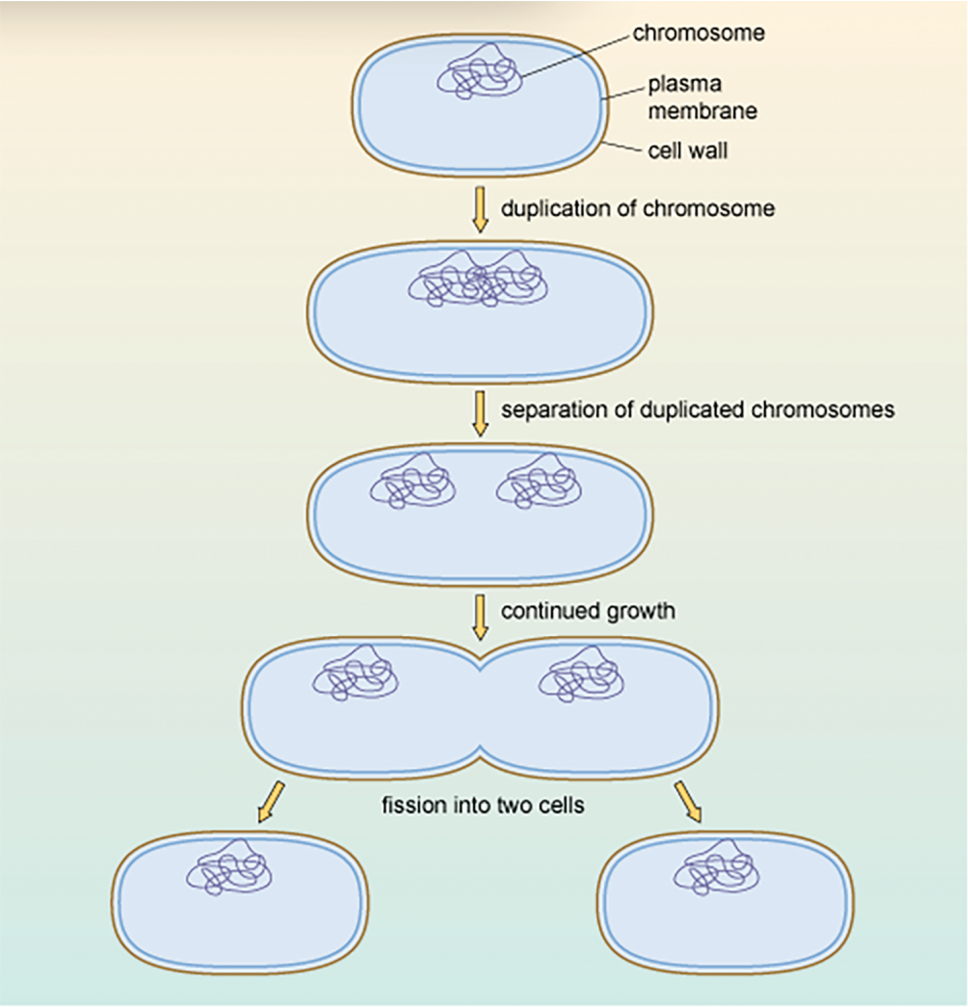


Figure 3 The stages of binary fission.

Activity 1 Exploring vertical transmission

Allow about 10 minutes

Begin by watching the following animation which illustrates the process of binary fission in *E. coli*. Then complete the activity below.

Video content is not available in this format.
Video 3 Binary fission in *E. coli*.

Apply what you have learned and the information about binary fission in the animation to complete the following sentences. Select the appropriate word from the list.

(a) The DNA in both of the daughter cells is [identical/similar/different] to the DNA in the parent cell.

- ○ identical
- ○ similar
- ○ different

Answer

During binary fission, the genetic material (DNA) is copied so that each new daughter cell inherits an exact copy of the parent cell's DNA.

(b) If an *E. coli* bacterium contains a genetic mutation in a chromosomal *pbp* gene, both of its daughters will [always/sometimes/never] contain a mutation in the *pbp* gene.

- ○ sometimes
- ○ never
- ○ always

Answer

During binary fission, the genetic material (DNA) is copied, so that each new daughter cell inherits an exact copy of the parent cell's DNA. When the parent DNA is copied during binary fission, any genetic mutations will also be copied, and consequently inherited, by both of the daughter cells.

(c) If the parent bacterial cell contains a genetic mutation that results in resistance to β-lactam antibiotics, both of the daughter cells will [always/sometimes/never] be resistant to β-lactam antibiotics.

- ○ sometimes
- ○ always

- never

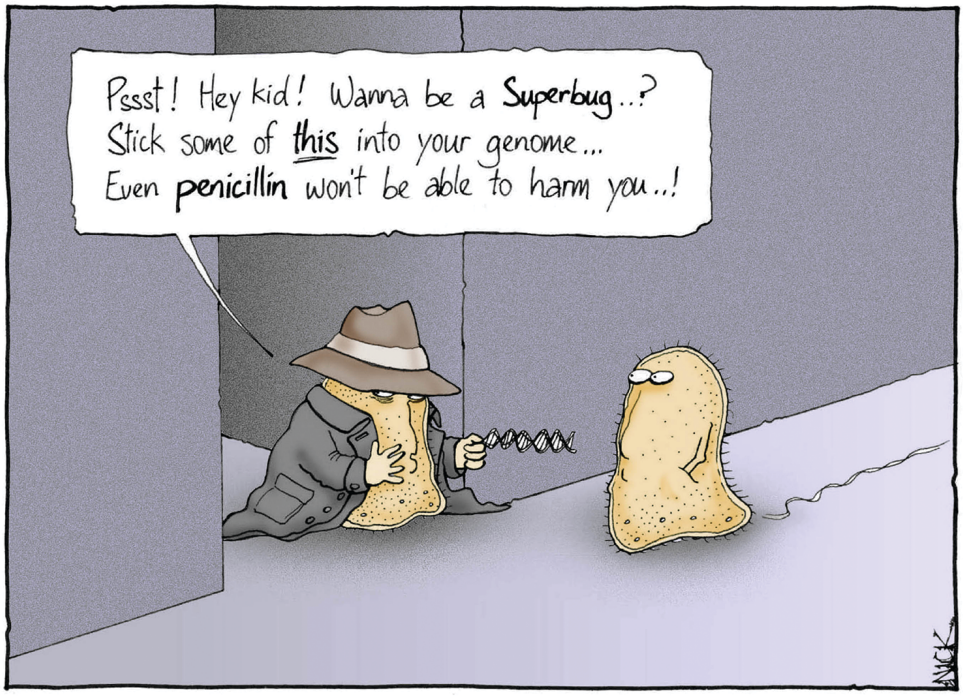
Answer

During binary fission, the genetic material (DNA) is copied, so that each new daughter cell inherits an exact copy of the parent cell's DNA. When the parent DNA is copied during binary fission, any genetic mutations will also be copied, and consequently inherited, by both of the daughter cells. If these genetic mutations give rise to antibiotic resistance in the parent bacteria, they will also result in antibiotic resistance in both of the daughters.

Vertical gene transfer is only one of the ways in which bacteria can spread antibiotic resistance genes. In the next section you will look at another – horizontal transfer.

2 Horizontal transfer

Horizontal gene transfer, or horizontal transfer, is the primary mechanism of spread of antibiotic resistance that allows bacteria to spread antibiotic resistance genes rapidly between different bacterial types. As you should be starting to appreciate, the acquisition of antibiotic resistance by new bacterial types is particularly concerning because it can result in multidrug-resistant bacterial strains such as MRSA.



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

CartoonStock.com

Figure 4 Antibiotic resistance.

2.1 Plasmids

In Section 1.3, you saw how chromosomal DNA can be copied and transmitted to the next generation via vertical gene transfer. Unlike humans, bacteria contain additional, non-chromosomal DNA which can be replicated independently of the genomic chromosomal DNA. These non-chromosomal genetic elements are called plasmids.

Plasmids are small, circular pieces of DNA which often carry genes associated with a specific function: for example, antibiotic resistance (Figure 5).

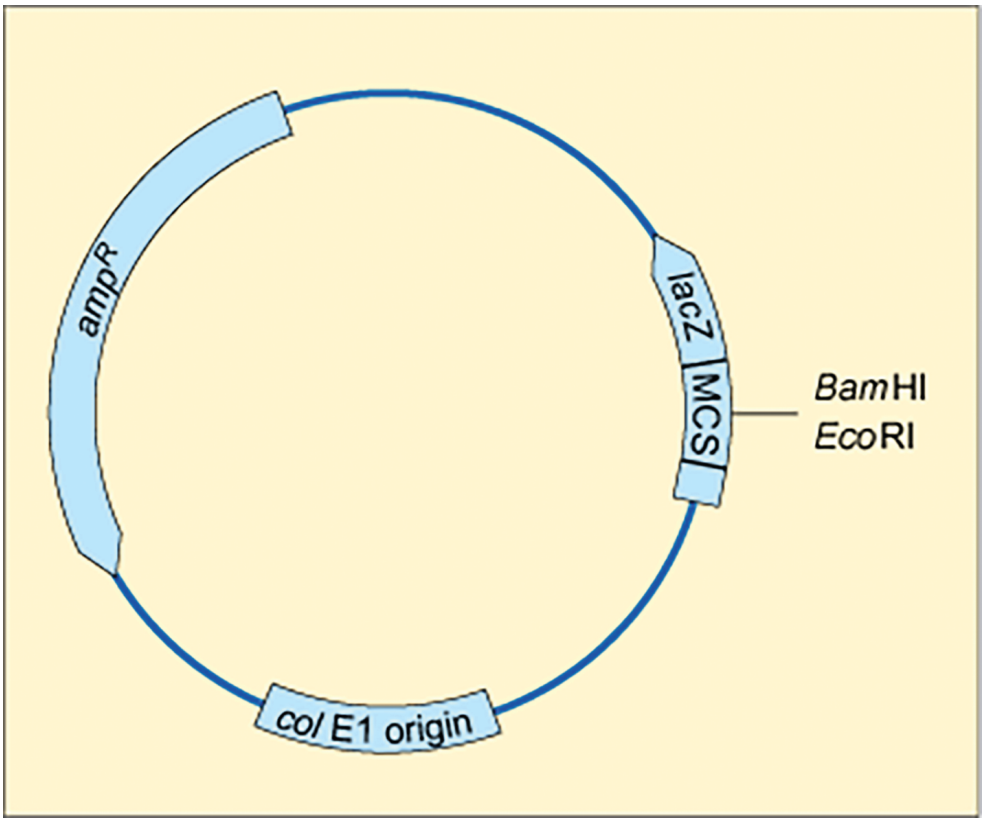


Figure 5 A simple **plasmid** containing one antibiotic resistance gene (ampR). This plasmid also contains an origin of replication (colE1 origin); where DNA replication begins when the plasmid is replicated, a multiple cloning site (MCS); a short section of DNA present in engineered plasmids used for research that allows molecular biologists to easily insert additional DNA sequences into the plasmid; and the sequence of the lacZ gene that encodes the β-galactosidase enzyme.

Unlike vertical gene transmission, where chromosomal DNA is replicated and then transferred from parent cells to daughter cells through binary fission, plasmids are usually transferred by horizontal gene transfer. This is the process of swapping genetic information between two unrelated cells. In contrast to vertical gene transmission, it does not require binary fission and can occur between bacteria of the same generation, not just between parents and daughters, and even between bacteria of different types (Figure 6).

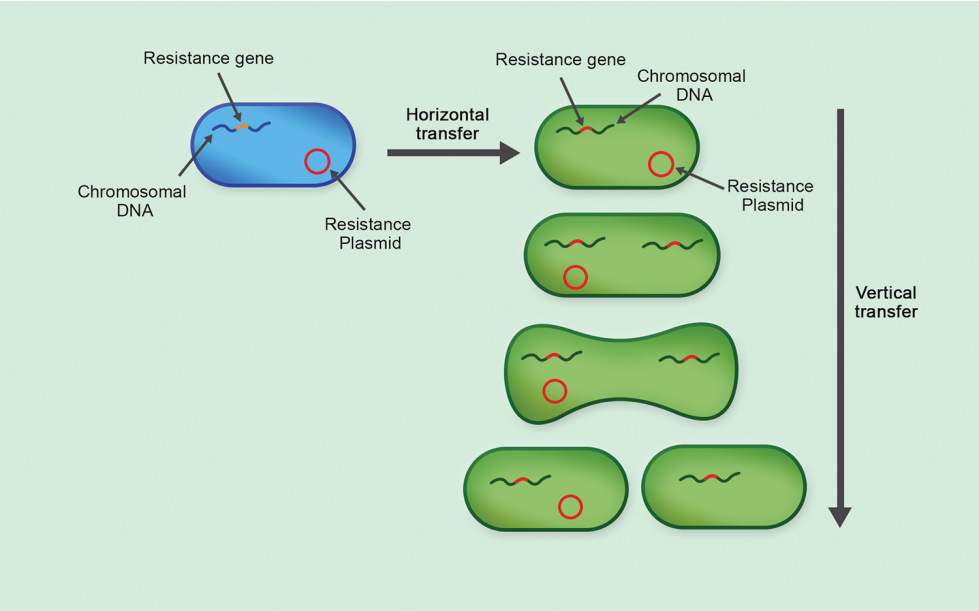


Figure 6 The differences between horizontal and vertical gene transmission.

- Can you suggest why horizontal gene transfer is the primary mechanism of spreading antibiotic resistance?
- Horizontal gene transfer allows plasmids carrying antibiotic resistance genes to spread rapidly between different types of bacteria. Thus species of bacteria that are intrinsically sensitive to a given antibiotic rapidly acquire resistance genes, making them insensitive to treatment with that antibiotic.

There are three mechanisms of horizontal gene transfer:

- conjugation
- transformation
- transduction.

You will now look at each mechanism in more detail.

2.2 Conjugation

In the process of conjugation, plasmids are transferred between two contacting bacteria via a hollow tube or pilus (Figure 7).

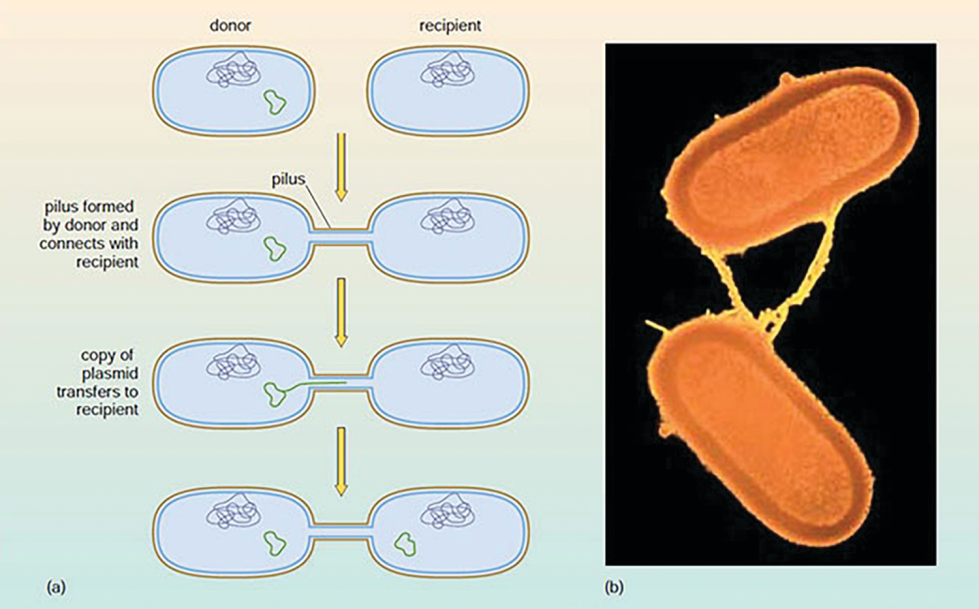


Figure 7 The process of conjugation. (a) A hollow pilus connects two bacteria and plasmid DNA is transferred from the donor bacterium to the recipient. (b) Scanning-electron micrograph of two bacteria attached by pili.

Since antibiotic resistance genes are often located on plasmids, conjugation can result in the transfer of antibiotic resistance from one bacterium to another.

2.3 Transformation

In contrast to conjugation, the process of transformation allows bacteria to take up DNA from their environment (for example, from a lysed bacterium) across the cell wall. This DNA can then be incorporated into the genome of the bacterium (Figure 8).

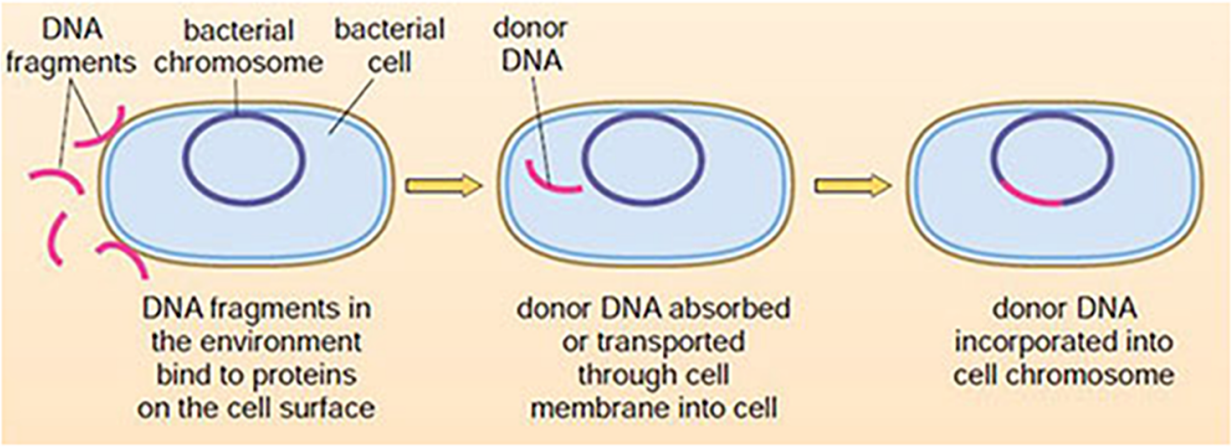


Figure 8 Schematic diagram of a bacterium taking up DNA from the environment by transformation.

Transformation occurs naturally between some bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenza*. When antibiotic resistance genes in the environment are transformed into a new bacterial type, they can be incorporated into that

bacterium's genome. They are then transmitted to the next generation by binary fission, establishing a newly resistant population of bacteria.

2.4 Transduction

The final mechanism of horizontal gene transfer you will look at is **transduction**. In this process, transfer of DNA from one bacterial cell to another is mediated by a **virus**.

Viruses that infect bacteria are called bacteriophages. When bacteriophages infect a bacterial cell, they insert their DNA into the bacterial cell genome. When it is time for the virus to replicate, it excises its DNA from the bacterial genome. However, this excision is imperfect and some bacterial DNA is accidentally excised and incorporated into the newly made virus. When these newly made viruses infect a different bacterial species, they carry this bacterial DNA, which may contain antibiotic resistance genes, and insert it into the genome of the new host bacterium (Figure 9).

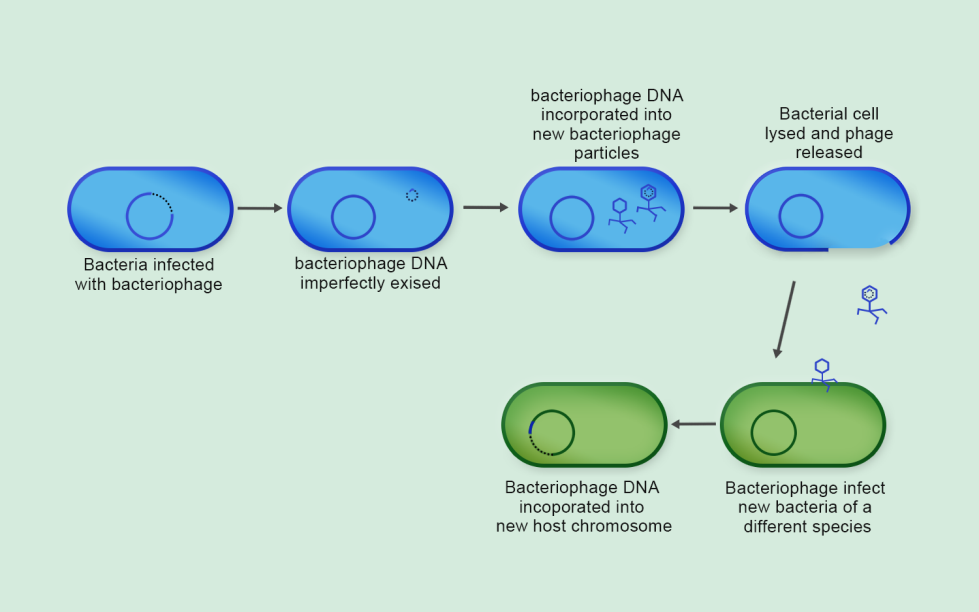


Figure 9 Schematic diagram of transduction. When **bacteriophage** DNA, shown by a black dotted line, is excised from the bacterial genome it carries with it some bacterial DNA, shown in blue, from the infected bacteria. This DNA is incorporated into new bacteriophage particles which are released and infect new bacteria of a different species. The bacterial DNA from the original bacteria, in blue, is incorporated into the genome of the newly infected bacteria.

Activity 2 Comparing horizontal transfer mechanisms

Allow about 10 minutes

Below are some incomplete sentences. Type in the missing words using the following list of words:

horizontal, binary fission, vertical, conjugation, transformation, transduction, plasmid, chromosome, vertical gene transfer.

___ gene transfer can occur between bacteria of the same generation but vertical gene transfer requires ___.

Answer

Horizontal gene transfer can occur between bacteria of the same generation but vertical gene transfer requires binary fission.

___ is the only mechanism of horizontal gene transfer that requires direct contact between the donor and recipient bacteria.

Answer

Conjugation is the only mechanism of horizontal gene transfer that requires direct contact between the donor and recipient bacteria.

___, ___ and ___ can occur between bacteria of different types.

Answer

Conjugation, transduction and transformation can occur between bacteria of different types.

___ is the only mechanism of horizontal gene transfer which requires a virus known as a bacteriophage.

Answer

Transduction is the only mechanism of horizontal gene transfer which requires a virus known as a bacteriophage.

The bacterial genetic element transmitted by horizontal gene transfer is called a ___.

Answer

The bacterial genetic element transmitted by horizontal gene transfer is called a plasmid.

You will return to look at some specific examples of how genetic mutation and horizontal gene transfer can result in acquired resistance in the case study of cephalosporin antibiotics at the end of this week. Next you will look at how antibiotic resistance has developed through evolution and natural selection.

3 Why are so many bacteria resistant to antibiotics?

So far this week, you have looked at how bacteria acquire antibiotic resistance through genetic mutation or horizontal gene transfer. But why are so many bacteria resistant to antibiotics? In this section, you will look at how antibiotic resistance spreads so quickly.

3.1 Evolution and natural selection

In 1858, the British naturalists Charles Darwin and Alfred Russel Wallace both independently proposed the theory of evolution through **natural selection** to explain how organisms change over time.

Evolution is a change over time in the inherited characteristics or traits in a population. This change is largely brought about by natural selection. This is the process by which a particular **trait** that confers a survival advantage for an individual becomes more frequent in the population.

Although Darwin and Wallace were unaware of the existence of DNA, we now know that natural selection is the process by which genetic mutations that increase the ability of an organism to survive are selectively passed on to subsequent generations.

Now listen to Audio 1 in which Professor Steve Jones from University College London explains Darwin's theories of evolution and natural selection.

Audio content is not available in this format.
Audio 1 Darwin's theories of evolution and natural selection.

In the next section, you will see how our use of antibiotics contributes to the evolution of resistance.

3.2 Evolving resistance to antibiotics

How do bacteria evolve resistance to antibiotics? Activity 3 will help you to think about how evolution and natural selection contribute to the spread of antibiotic resistance.

Activity 3 Evolution, natural selection and antibiotic resistance

Allow about 10 minutes

Darwin's theory was that evolution by natural selection would occur if the following conditions were met:

- There is a struggle for existence. Survival is limited by environmental constraints, so that there is competition, and not all individuals will survive to produce offspring.

- There is variation between individuals. Individuals with advantageous traits will have a greater probability of survival under these conditions and are therefore more likely to reproduce.
- The characteristics, or traits, of an individual are inherited. Advantageous traits that promote survival will be inherited by the next generation so that these traits become increasingly common in the population.

Now answer the following questions about the evolution of antibiotic resistance.

1 Which of the environmental conditions below might lead to the evolution of antibiotic resistance?

○ (a) low nutrient supply

Your answer is partially correct. Any of these could conditions could create a struggle for existence that could lead to the evolution of antibiotic resistance.

○ (b) presence of antibiotics

Your answer is partially correct. Any of these could conditions could create a struggle for existence that could lead to the evolution of antibiotic resistance.

○ (c) low oxygen availability

Your answer is partially correct. Any of these could conditions could create a struggle for existence that could lead to the evolution of antibiotic resistance.

○ (d) all of the above

Your answer is correct. Any of these could conditions could create a struggle for existence that could lead to the evolution of antibiotic resistance.

2 Would antibiotic resistance be an advantageous, or a disadvantageous, trait for bacteria growing in the presence of antibiotics?

○ (a) Antibiotic resistance would be advantageous.

Your answer is correct. Antibiotic resistance would be an advantageous trait in the presence of antibiotics because resistant bacteria in the population will have a survival advantage over sensitive bacteria. However, in the absence of antibiotics, resistance can sometimes be disadvantageous because it can result in slower growth.

○ (b) Antibiotic resistance would be disadvantageous.

Your answer is incorrect. Antibiotic resistance would be an advantageous trait in the presence of antibiotics because resistant bacteria in the population will have a survival advantage over sensitive bacteria. However, in the absence of antibiotics, resistance can sometimes be disadvantageous because it can result in slower growth.

○ (c) Antibiotic resistance would have no effect on the survival of bacteria growing in the presence of antibiotics.

Your answer is incorrect. Antibiotic resistance would be an advantageous trait in the presence of antibiotics because resistant bacteria in the population will have a survival advantage over sensitive bacteria. However, in the absence of antibiotics, resistance can sometimes be disadvantageous because it can result in slower growth.

3 How would the trait of antibiotic resistance be inherited by the next generation?

○ (a) horizontal gene transfer

Your answer is incorrect. Antibiotic resistance genes, acquired via genetic mutation or horizontal gene transfer, can be inherited by subsequent generations through binary fission.

○ (b) transformation

Your answer is incorrect. Antibiotic resistance genes, acquired via genetic mutation or horizontal gene transfer, can be inherited by subsequent generations through binary fission.

○ (c) binary fission

Your answer is correct. Antibiotic resistance genes, acquired via genetic mutation or horizontal gene transfer, can be inherited by subsequent generations through binary fission.

○ (d) genetic mutation

Your answer is incorrect. Antibiotic resistance genes, acquired via genetic mutation or horizontal gene transfer, can be inherited by subsequent generations through binary fission.

Within a bacterial population, some bacteria will be sensitive to antibiotic treatment while others will have acquired resistance to antibiotics, via either genetic mutation or horizontal gene transfer. In the presence of antibiotics, the resistant bacteria have a survival advantage over the sensitive bacteria and are more likely to survive and reproduce. Because bacteria reproduce so quickly, resistant bacteria can quickly dominate the population (Figure 10).

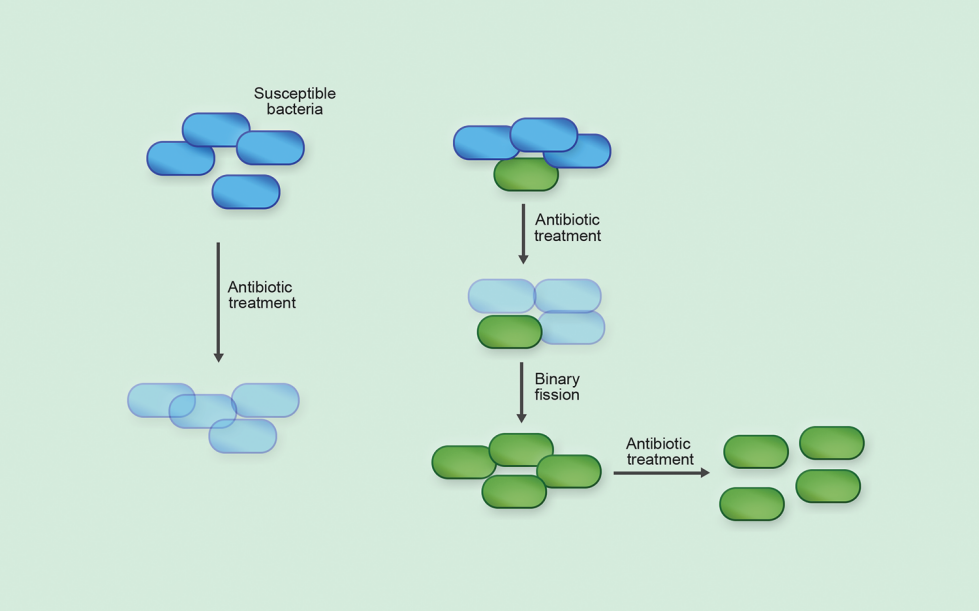


Figure 10 Natural selection for antibiotic resistance. When susceptible bacteria, shown in blue, are treated with antibiotics they all die. However, in the presence of antibiotics resistant bacteria, shown in green, survive and replicate by binary fission. This new bacterial population is now completely insensitive to treatment with the same antibiotic.

Of course, changes to the bacteria's environment made by us can affect the evolution of antibiotic resistance. You will return to this theme when you look at how our use of antibiotics contributes to the rise of antibiotic resistance bacteria in Week 5.

3.3 Experimentally evolving antibiotic resistance

Most animals evolve over millions of years. However, because bacteria grow and evolve so rapidly, scientists can study the evolution of antibiotic resistance in the laboratory. You will now look at an experiment which shows how bacteria adapt to survive increasingly higher doses of antibiotic (Baym et al., 2016).

Activity 4 Evolution in action

Allow about 30 minutes

Watch the following video taken from an episode of the BBC's *Horizon* programme. Here, researchers from Harvard University and Technion-Israel Institute of Technology describe an experiment to evolve antibiotic-resistant bacteria in the laboratory.

Video content is not available in this format.
Video 4 Experimental evolution of antibiotic resistance.

In the next video you will watch what happens when bacteria grown on a plate containing increasing concentrations of antibiotics like the one described in Video 4. This plate is known as a Microbial-Evolution and Growth Area (MEGA) plate. Before you watch the next video, note down what you think will happen to the bacteria as they grow on the MEGA plate.

Provide your answer...

Discussion

As bacteria grow to fill the area of the MEGA plate, with no antibiotic they begin to compete for resources, meeting one of Darwin's conditions for evolution – a struggle for existence.

At this point, mutations occur which allow some bacteria to survive in the area of the plate containing antibiotic. These bacteria have a survival advantage over the antibiotic-sensitive bacteria and grow and reproduce to cover the area of the plate containing a low antibiotic dose. As they fill this area of the plate, they also begin to compete for resources and the cycle of mutation, selection and growth repeats.

Now click on the following link to watch a video showing a time-lapse recording of bacteria growing on the MEGA plate. Then answer the questions below.

1 How many different mutants have reached the 1000× antibiotic concentration at the end of the experiment? (Hint: you will need to watch until the end of the video.)

Answer

Using the coloured tree diagram at the end of the video, we counted 16 different mutants that reached the 1000× antibiotic concentration at the end of the experiment.

2 Would you expect the first mutant bacteria that appear (those that occur at the no antibiotic:1× antibiotic boundary) to grow on the 1000× antibiotic region on the plate?

Answer

It is unlikely that the resistance mutations that allowed bacteria to survive on the 1× dose of antibiotic would be sufficient for bacteria to survive on the 1000× dose. It is more likely that bacteria would require multiple antibiotic resistance mutations to survive on the 1000× dose.

3 Did your predictions from the first part of this activity match the experimental results?

Discussion

You may not have exactly predicted what would happen in the experiment but you may have been able to make some suggestions about how bacteria acquire mutations in order to cross the no antibiotic:1× antibiotic boundary.

Now that you have watched the experiment, you may want to reread the discussion from the first part of this activity.

4 Case study: resistance to cephalosporins

In Week 3's case study, you looked at the molecular mechanisms of resistance to cephalosporins and were introduced to ESBLs. The most common class of ESBLs in Europe is the **CTX-M-type ESBL**.

In this case study, you will explore how bacteria acquire resistance to cephalosporin antibiotics through horizontal gene transfer and the mutation of CTX-M-type ESBLs. You will begin by looking at how the presence of CTX-M-type ESBLs has changed in the UK over recent years.

Activity 5 The rise of CTX-M-type ESBLs

Allow about 20 minutes

The data in this activity are from The British Society for Antimicrobial Chemotherapy's Resistance Surveillance Project (www.bsacsurv.org) which collects annual data on antibiotic resistance rates.

First, look at Figure 11 which shows the percentage of *E. coli* isolate producing CTX-M-type, or other, ESBLs between 2002 and 2016. Then answer the questions below.

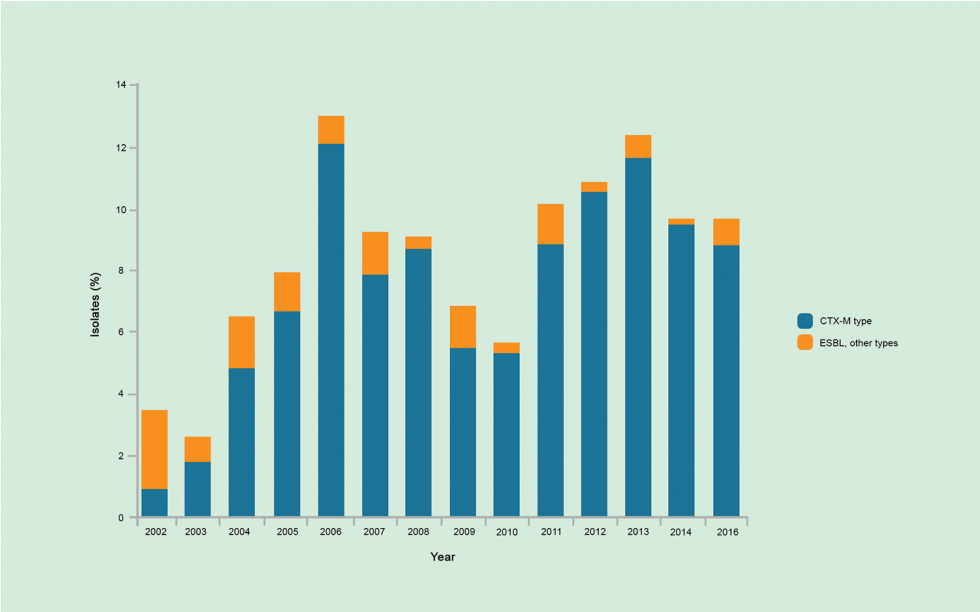


Figure 11 BSAC UK bacteraemia susceptibility survey data for *E. coli* exhibiting an ESBL phenotype. Data from www.bsacsurv.org/ (accessed 13 November 2017).

(a) Using the data in Figure 11, how has the proportion of isolates producing CTX-M-type ESBLs changed over time?

Discussion

The proportion of isolates producing CTX-M-type ESBLs was low in 2002 and increased to a peak in 2006. The percentage of resistant isolates decreased between 2007 and 2010 and then began to increase again, peaking in 2013.

(b) CTX-M-type ESBLs emerged in the late 1990s and were first reported in the UK in 2002. Suggest one possible reason for the change in frequency of these ESBLs in the UK over time.

Discussion

The increasing use of cephalosporin antibiotics could create conditions where resistance to cephalosporin antibiotics through the acquisition of CTX-M-type ESBLs is advantageous for the bacteria. Hence these conditions would satisfy Darwin's conditions for evolution through natural selection.

(c) In Activity 7 in Week 1, you looked at how resistance to cephalosporins had changed in the UK over time (Figure 12). By comparing the data in Figures 11 and 12 do you think that the occurrence of CTX-M-type ESBLs is a good indicator of the rate of resistance to cephalosporins?

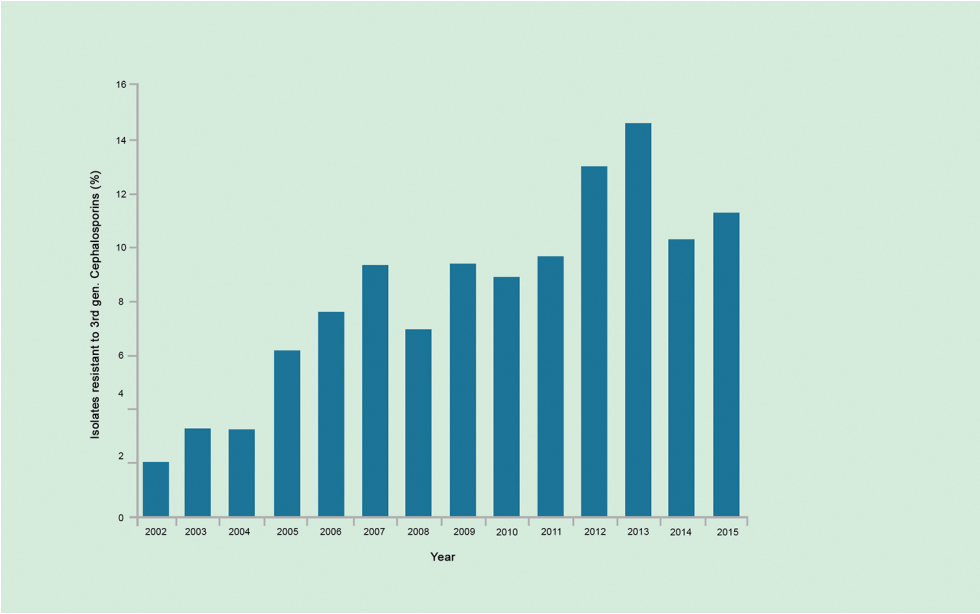


Figure 12 Resistance to cephalosporins in the UK between 2002 and 2015. Data from https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc (accessed 13 November 2017).

Discussion

Yes. Patterns of resistance to cephalosporins and the occurrence of CTX-M-type ESBLs were broadly similar between 2002 and 2016. This suggests that CTX-M occurrence is a good indicator of cephalosporin resistance and that the presence of CTX-M-type ESBLs in *E. coli* is the major cause of cephalosporin resistance.

(d) What challenges might these changes in the prevalence of CTX-M-type ESBLs present to health care?

Answer

The increasing frequency of cephalosporin-resistant bacteria and CTX-M-type ESBLs restricts the treatment options for infections caused by these bacteria.

4.1 The origin of CTX-M-type ESBLs

Unlike most acquired β-lactamases, for which the source remains unknown, the source of CTX-M-type ESBLs has been identified as members of the bacterial **genus** *Kluyvera*.

***Kluyvera* spp.** are soil bacteria which are associated with plant roots and are non-pathogenic to humans. Precursors of the CTX-M genes found in *E. coli* have been identified as chromosomal genes in *Kluyvera* spp. where they can confer resistance to third-generation cephalosporins (Humeniuk et al., 2002).

- The resistance of *Kluyvera* spp. to third generation cephalosporins is an example of what type of resistance?
- It is an example of intrinsic resistance.

These chromosomal CTX-M precursor genes have been captured and incorporated into plasmids through mechanisms that you do not need to know about in this course.

In the next section, you will look at how these plasmid-encoded CTX-M genes have been rapidly spread by horizontal gene transfer to other bacterial types, including *E. coli* and *Klebsiella pneumoniae*.

4.2 The rapid spread of CTX-M genes

Plasmids carrying CTX-M genes have been reported in several **enterobacteria** types (Figure 13). They are most commonly found in *E. coli* and *K. pneumoniae* but have also been isolated from other pathogenic bacteria.

Plasmids that are found in many genetically diverse bacterial strains are termed 'epidemic plasmids' and can help to explain the rapid global spread of CTX-Ms. This is sometimes referred to as the 'CTX-M pandemic' (Cantón and Coque, 2006). However, the reasons for this CTX-M pandemic are complex. The horizontal gene transfer of plasmids containing CTX-M genes occurs in the human gut and in the environment and is fundamental to their global spread.

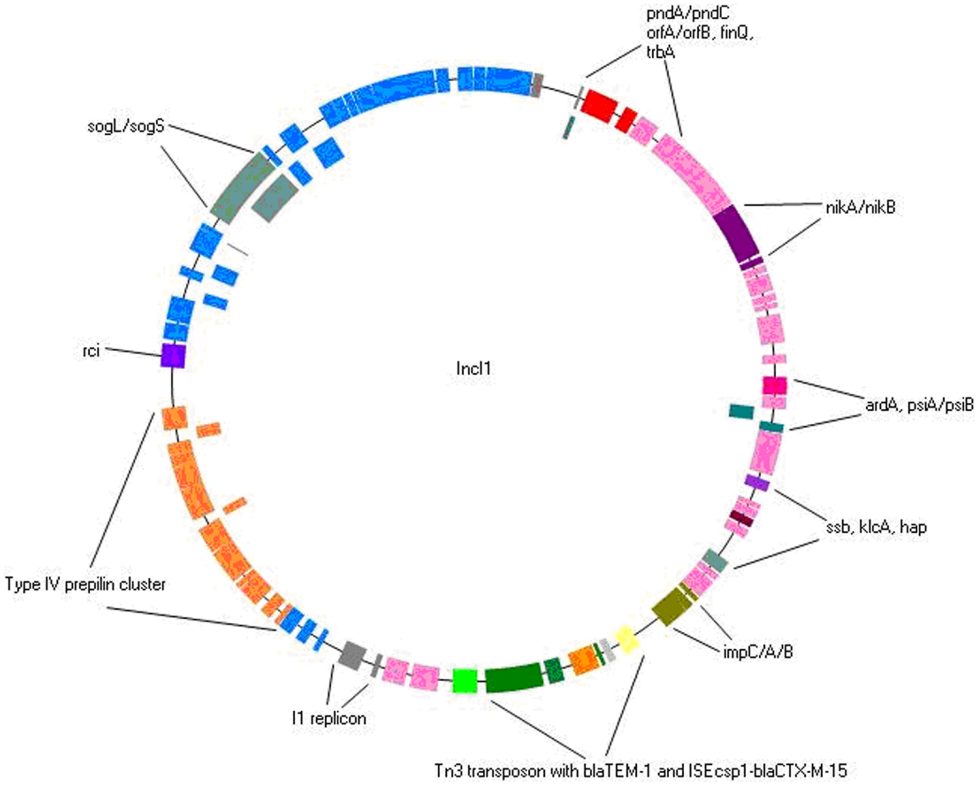


Figure 13 Plasmid map of a CTX-M-containing plasmid isolated from *E. coli*. The CTX-M gene is shown in dark green (Smet et al., 2010). You do not need to study this figure in detail.

Plasmids carrying CTX-M genes often carry bacteriophage-related sequences (Falgenhauer et al., 2014) or genes that are required for the formation of pili (Carattoli, 2013).

- What horizontal gene transfer mechanisms do the presence of bacteriophage-related sequences and pili formation genes suggest?
- The presence of bacteriophage-related sequences in some CTX-M-containing plasmids suggests horizontal gene transfer by transduction (see Section 2.4). Alternatively, gene transfer via conjugation requires a pilus linking the donor and

recipient bacteria, therefore the presence of genes required for the formation of pili suggests horizontal gene transfer via this mechanism (see Section 2.1).

Perhaps the most concerning feature of these CTX-M-containing plasmids is their ability to acquire additional antibiotic resistance genes (Potron et al., 2013). If 'epidemic plasmids' acquire resistance to antibiotics such as carbapenems, which are frequently used to treat cephalosporin-resistant infections, the rapid spread of multidrug resistance could seriously challenge the treatment of infections.

4.3 Mutations in CTX-M-type ESBLs

CTX-M-type ESBLs preferentially act on certain cephalosporin antibiotics. **Cefotaxime** is easily recognised and inactivated by CTX-M-type ESBLs while the bulkier cephalosporin **ceftazidime** is poorly recognised by CTX-M-type ESBLs (Bonnet, 2004). As a consequence, infections caused by bacteria that produce CTX-M-type ESBLs can be treated with ceftazidime. This specificity is based on the structure of the CTX-M β-lactam binding site which only allows the efficient recognition of penicillins, first-generation cephalosporins and cefotaxime (Figure 14) (Chen et al., 2005).

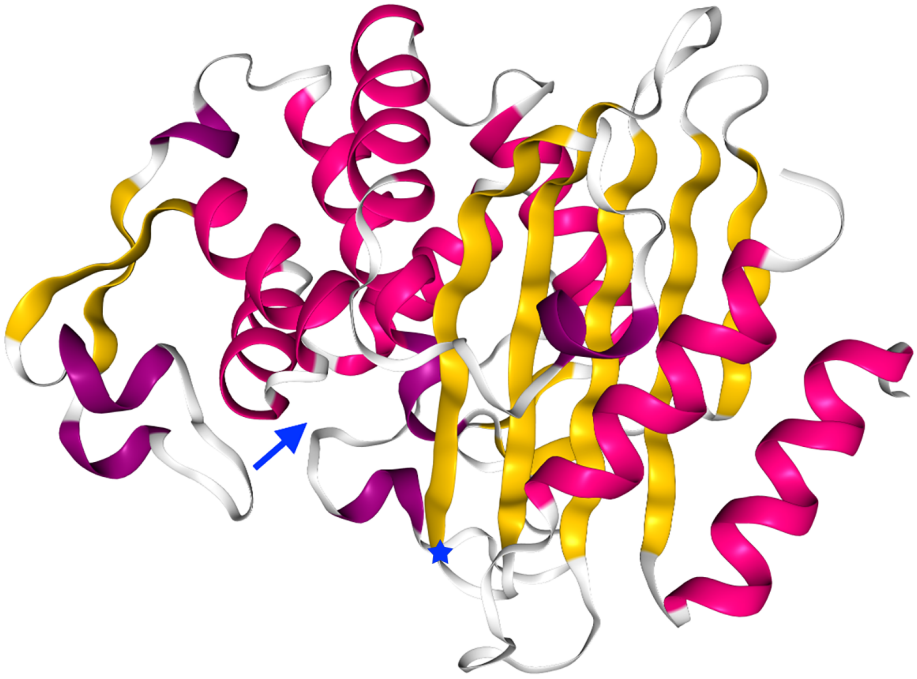


Figure 14 The structure of a CTX-M-type ESBL (Chen et al., 2005). The figure shows a ribbon diagram of a CTX-M-type ESBL protein structure. The ribbon shows the overall organisation of the protein giving a representation of the overall protein shape. The β-lactam binding site is indicated by the blue arrow. The amino acid mutation that increases the ceftazidimase activity of CTX-M is indicated by the blue star. You do not need to study this structure in detail.

The specificity of CTX-M-type ESBLs can be modified by point mutations which improve the specificity of CTX-M-type ESBLs for ceftazidime. One of these mutations is indicated on Figure 14 (Cartelle et al., 2004). Altering this amino acid allows the bulkier ceftazidime

to be more easily accommodated in the β-lactam binding site (Chen et al., 2005). Infections caused by bacteria producing this mutated version of the CTX-M-type ESBL are not treatable with ceftazidime. This CTX-M variant has been isolated from clinical strains of *E. coli* (Cartelle et al., 2004) and has probably been selected for the increasing use of ceftazidime in clinical practice.

5 This week's quiz

It's time to complete the Week 4 badged quiz. It is similar to the previous quizzes but this time, instead of answering 5 questions, there will be 15, covering Weeks 1 to 4.

Week 4 compulsory badge quiz

Remember that the quiz counts towards your badge. If you're not successful the first time, you can attempt the quiz again in 24 hours.

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link.

6 Summary

In this week you learned how bacteria acquire antibiotic resistance and how this resistance can rapidly spread, or evolve, in a population. You should now be able to explain how genetic mutations cause acquired antibiotic resistance and how these mutations can be inherited through binary fission.

You have also seen how horizontal gene transfer has an important role in transmitting antibiotic resistance to different bacterial types. Having seen how antibiotic resistance evolves to protect bacteria, you can now begin to speculate on how our use of antibiotics contributes to the rise of antibiotic resistance.

You should now be able to:

- explain how genetic mutations can give rise to antibiotic resistance that can be inherited
- describe the horizontal gene transfer mechanisms that allow antibiotic resistance to be transferred between bacteria
- discuss how evolution and natural selection maintain antibiotic resistance in bacteria.

Next week you will discover how the mismanagement of antibiotics has increased the rate of resistance.

You can now go to Week 5.

Week 5: How antibiotic resistance has become such a big problem

Introduction

In Weeks 3 and 4, you learned how some bacteria have an innate ability to resist the action of a particular antibiotic. Other bacteria acquire the ability to resist one or more antibiotics through genetic mutation or horizontal gene transfer. You also learned how evolution and natural selection contribute to the rapid spread of acquired antibiotic resistance both within and between bacterial types.

This week, you will discover how the mismanagement of antibiotics, coupled with behaviours that promote the spread of infections, has increased the rate of antibiotic resistance.

Drug-resistant bacteria lead to infections which are difficult to treat and are a significant and growing healthcare concern. By the end of this week, it should be clear that the current global health crisis, with record levels of antibiotic resistance, has been fuelled by human activity.

By the end of this week, you should be able to:

- describe the scale and nature of antibiotic resistance worldwide
- summarise how antibiotic resistance spreads
- explain how the overuse and misuse of antibiotics contribute to bacterial resistance
- list the factors which have prevented new antibiotics coming onto the market
- recognise how a lack of laboratory capacity and inadequate surveillance contribute to the development and spread of antibiotic resistance.

1 The antibiotic resistance crisis

Start this week by completing the activity below. This will give you a sense of how serious the problem is and an introduction to the factors that drive resistance.

Activity 1 The antibiotic resistance crisis

Allow about 10 minutes

First, watch the following video.

Video content is not available in this format.
Video 1 The antibiotic resistance crisis.

Consider the following statements and decide if they are true or false. Write your answer in the right-hand column.

Statement	True or false?
1 All antibiotics are antimicrobials but not all antimicrobials are antibiotics.	*Provide your answer...*
2 Drug resistance is only a problem in Europe, the USA and other **high-income countries (HICs)**.	*Provide your answer...*
3 Ten million people each year die from antimicrobial resistance (AMR) infection.	*Provide your answer...*
4 AMR causes significant economic damage.	*Provide your answer...*
5 Using fewer antibiotics will not help reduce antibiotic resistance.	*Provide your answer...*
6 It is acceptable to give antibiotics to healthy animals to promote growth.	*Provide your answer...*

7 Few new antibiotics are being developed to replace those to which bacteria have become resistant.	*Provide your answer...*
8 Antibiotic resistance surveillance data is necessary to inform clinical decision making.	*Provide your answer...*

Answer

1 TRUE Antibiotics are just one type of antimicrobial drug. Antivirals, antifungals and antiprotozoans are also antimicrobials.

2 FALSE AMR is a global problem.

3 FALSE An estimated 700,000 people die every year from AMR infections. This number is expected to rise to 10 million deaths per year by 2050 if resistance is not tackled.

4 TRUE For example, the estimated cost to the European Union of AMR infections is €1.5 billion per year.

5 FALSE The more antibiotics that are used, the greater the antibiotic resistance.

6 FALSE Using antibiotics for reasons other than to treat bacterial infection has been shown to increase antibiotic resistance. You will learn more later about why this happens.

7 TRUE Pharmaceutical companies find the cost and regulatory challenge of developing new antibiotics prohibitive.

8 TRUE The impact of inadequate AMR surveillance systems on the spread of antibiotic resistance is discussed in Section 6.

2 How antibiotic resistance spreads

In Week 4, you learned that, in the presence of antibiotics, resistant bacteria have a survival advantage over sensitive bacteria and can quickly dominate a bacterial population. Resistance is an inevitable consequence of using antibiotics. The more that antibiotics are used, the more widespread resistance becomes.

You have also learned that antibiotic resistance spreads in a bacterial population by resistance genes passing from one bacterium to another. In Activity 2, you will discover that antibiotic resistance also spreads when resistant bacteria move from one human or animal host to another.

Activity 2 How does antibiotic resistance spread?

Allow about 10 minutes

First, watch the video below which shows how antibiotic resistance spreads in different communities.

Video content is not available in this format.
Video 2 How does antibiotic resistance spread?

Now, answer the following questions:

1 In which ways can people be infected by antibiotic-resistant bacteria?

Provide your answer...

2 What roles do people moving from one geographical region to another play in spreading antibiotic resistance?

Provide your answer...

Answer

1 Antibiotic-resistant bacteria can spread to humans through food and through direct contact with animals or other people (for example, via unclean hands or contaminated objects). Resistance may also develop naturally if a person takes antibiotics to treat a bacterial infection. You will learn more about how infections are spread between people in Week 7.

2 The numbers of people travelling abroad for work or holidays is rising. This increases the likelihood that resistant bacteria, acquired from food or the environment, will be brought home and spread to other people.

Antibiotics eventually end up in the environment. Contaminated soil and waterways become reservoirs of antibiotics and antibiotic-resistant bacteria. This creates **selective pressure** that encourage the development and spread of resistance and the transfer of antibiotic-resistant bacteria to people and animals (Figure 1).

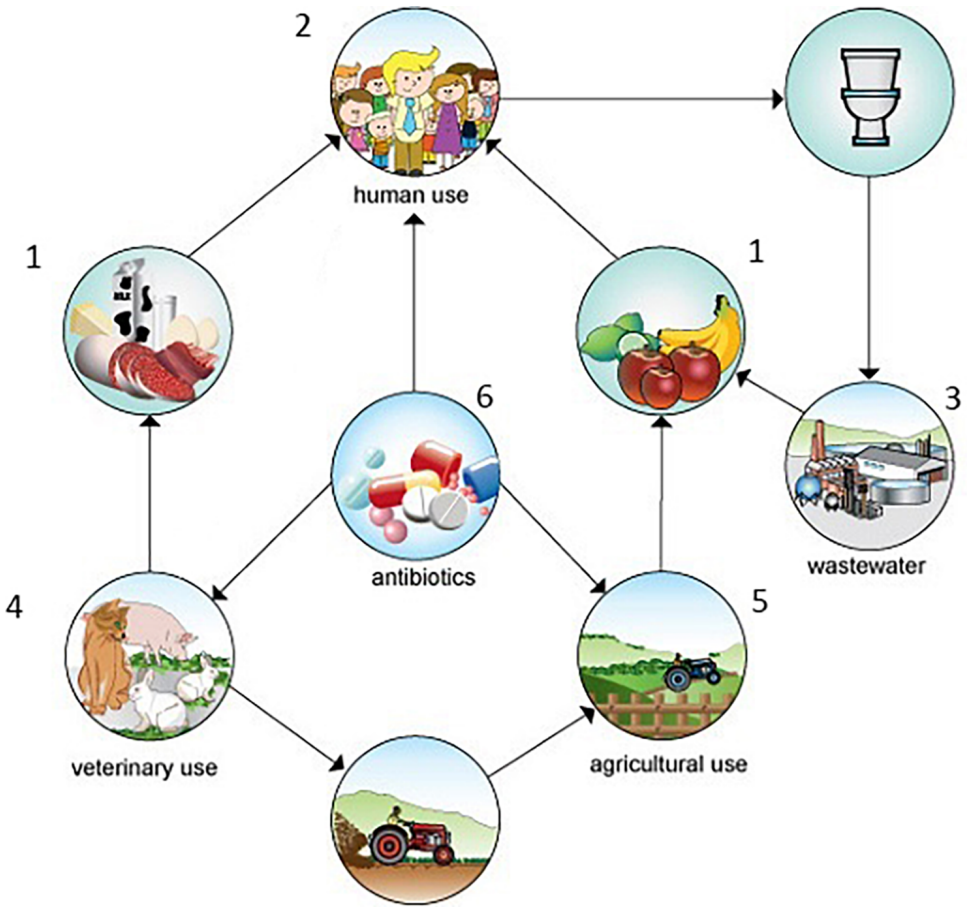


Figure 1 Main antibiotic routes into the soil and waterways. 1. Uptake of resistant bacteria in the food chain 2. Excreted antibiotics and their metabolites enter the sewage system 3. Water treatment facilities are not completely effective at removing bacteria which then enter waterways 4. Animal waste containing resistant bacteria and unmetabolised antibiotics contaminates soil and water directly and also used to fertilise crops 5. Antibiotics in crop sprays contaminate soil and waterways directly 6. Pharmaceutical waste containing antibiotics may be released directly into the environment.

Two interrelated factors contribute to the spread of antibiotic resistance. An increased rate of resistance, which results in higher numbers of antibiotic-resistant bacteria, and a greater number of cases of infectious diseases. Both factors increase the use of antibiotics which, in turn, drives the antibiotic resistance rate.

In the following sections, you will look at the main drivers of antibiotic resistance:

- poor hygiene and infection control
- the overuse of antibiotics
- the misuse of antibiotics.

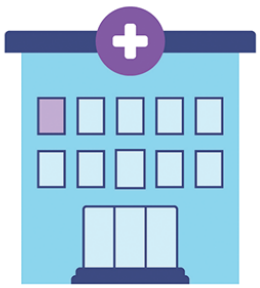
You will also consider how the lack of new antibiotics and gaps in global infection and resistance data exacerbate the problem.

3 Poor hygiene and infection control

Healthcare settings are hot spots for infectious diseases, including those caused by antibiotic-resistant bacteria (Figure 2).

Infections are spread through failures in hygiene, such as poor hand-washing technique, and because measures to prevent and control infections are inadequate or not followed consistently. Failure to wear protective clothing, to dispose of waste safely and to maintain a clean working environment all contribute to the spread of bacteria. You will learn more about the role of hygiene in preventing the spread of infections in Week 7.

A high number of cases of infectious diseases not only increases the demand for antibiotics and drives resistance but also increases mortality and has a negative impact on quality of life (Figure 3).

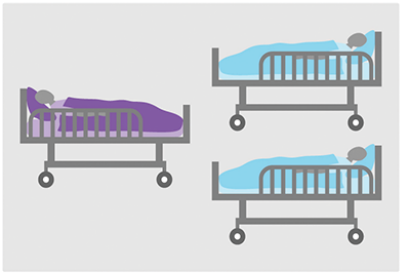


7 to 10%

Of every 100 hospitalised patients, 7 in high-income and 10 in low and middle-income countries, will acquire at least one healthcare-associated infection.

1 in 3

A third of patients in intensive care units (ICUs) in high-income countries are affected by at least 1 healthcare-associated infection.



1 in 4

A quarter of healthcare-associated infections in long-term acute care settings are caused by antibiotic-resistant bacteria.

Sources: WHO Healthcare-Associated Infections, Fact Sheet, 2014, WHO, The Burden of Health Care-Associated Infection Worldwide: A Summary, 2010, and CDC, Vital Signs Report, March 2016.

Review on Antimicrobial Resistance

Figure 2 The number of patients contracting infections within healthcare settings (O'Neill, 2016).

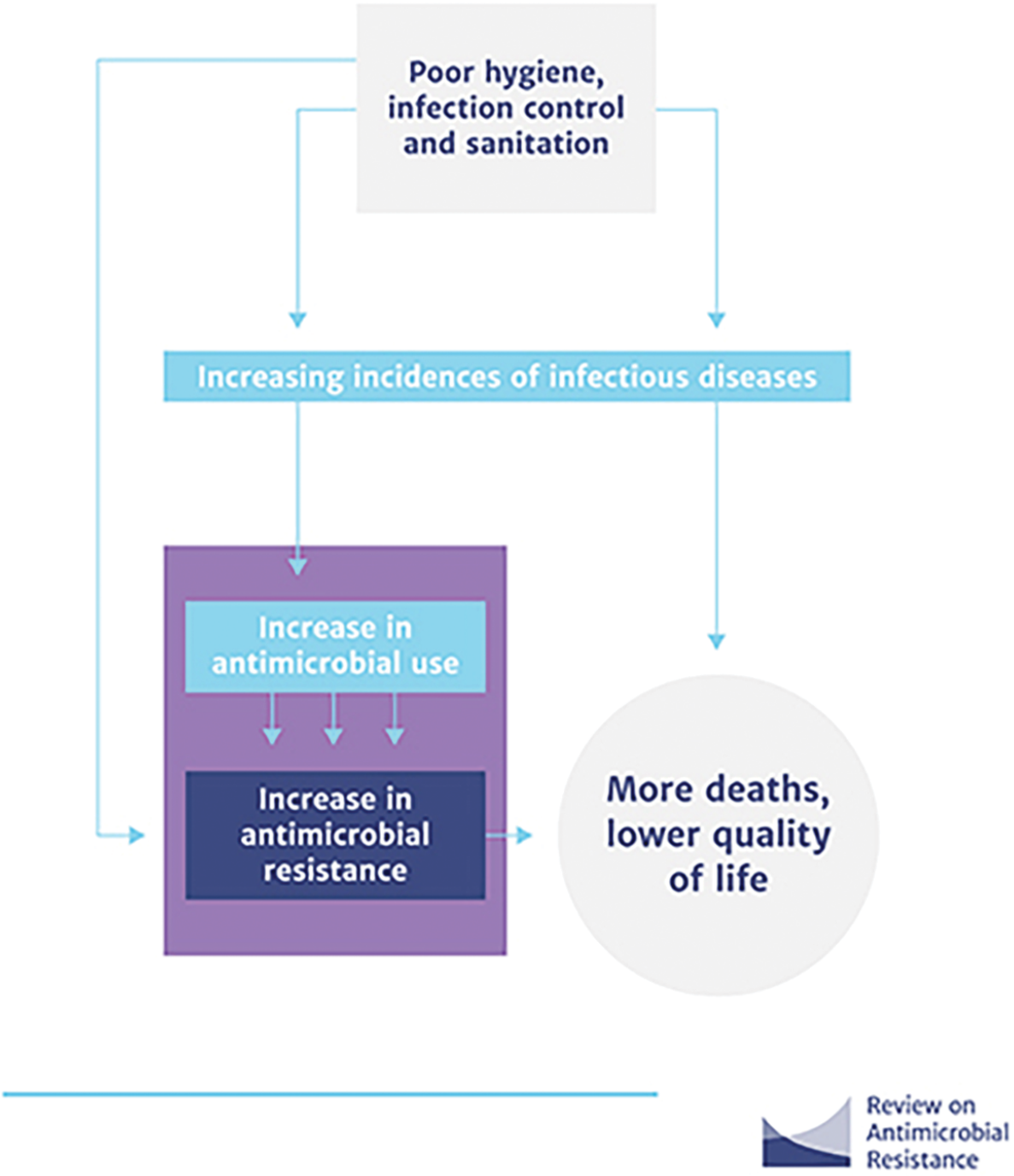


Figure 3 How poor infection control contributes to resistance and loss of life (O'Neill, 2016).

In the next section, you will explore the link between the overuse of antibiotics and resistance.

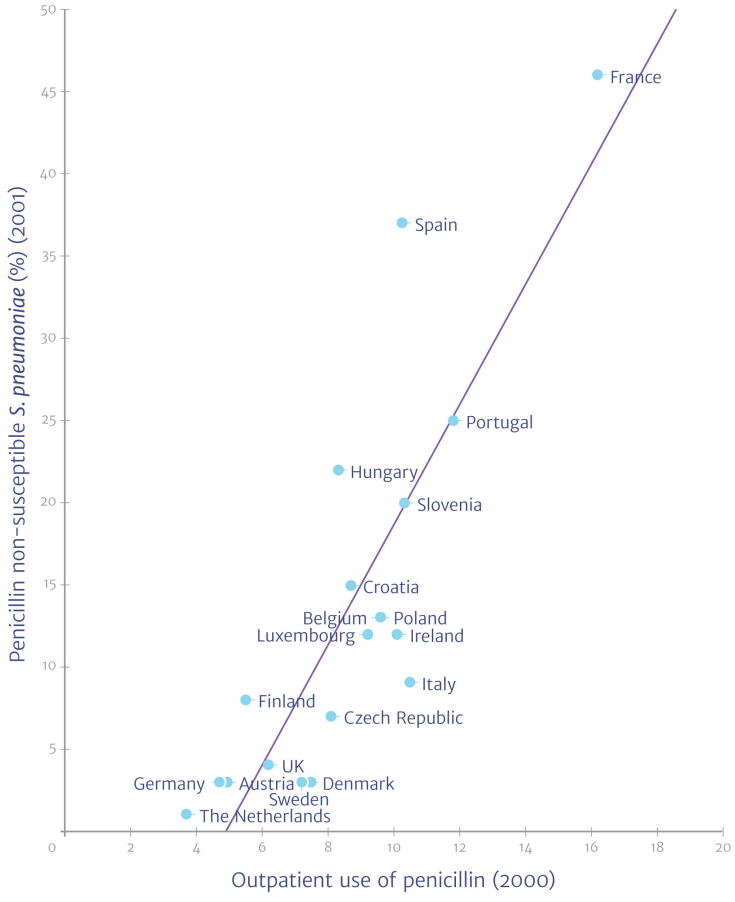
4 Overuse of antibiotics

Central to the growing problem of antibiotic resistance is the increasing demand for antibiotics. In the next activity, you will look at the relationship between antibiotic use and antibiotic resistance across Europe.

Activity 3 Antibiotic use and antibiotic resistance in Europe

Allow about 10 minutes

First, look at Figure 4. The *x*-axis (horizontal) shows a measure of penicillin use in the year 2000 (given as the defined dose per 1000 inhabitants daily – DID. You do not need to know how this is calculated). The *y*-axis (vertical) shows the proportion of *Streptococcus pneumoniae* infections that were penicillin-resistant in the year 2001. Each point on the graph represents a country.



Source: Goossens H, Ferech M, Vander Stichele R, et al. *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet 2005; 365(9459): 579–87.

Review on Antimicrobial Resistance

Figure 4 The relationship between antibiotic use and antibiotic resistance (O'Neill, 2016).

Now answer the following questions, based on the data in Figure 4.

1 Which country had the lowest antibiotic use?

2 Which country had the highest antibiotic resistance?

Provide your answer...

Answer

1 The Netherlands (furthest to the left of the *x*-axis).

2 France (highest on the *y*-axis).

3 Does the graph show a correlation between antibiotic use and antibiotic resistance? A correlation simply means that there is a relationship between two sets of data (i.e. the antibiotic use on the *x*-axis and the antibiotic resistance on the *y*-axis). For example, as the value of X, increases, the value of Y also increases.

Provide your answer...

Answer

Yes, there is a positive correlation between antibiotic use and antibiotic resistance. As antibiotic use increases, so does the proportion of antibiotic-resistant infections.

Next, you will consider the factors that promote the overuse of antibiotics and encourage the development and spread of antibiotic resistance.

4.1 Factors leading to the overuse of antibiotics

In the UK, antibiotics can only be obtained on prescription from a doctor. However, overprescription is a problem and online sales of antibiotics can circumvent regulation. In other countries, the unregulated, over-the-counter sales of cheap antibiotics allow people to **self-medicate**. Public attitudes and behaviours towards using antibiotics are a key factor in both the overuse and the misuse of antibiotics.

In agriculture, antibiotics are mainly used to keep animals healthy and to promote growth (Figure 5). The rising global demand for a meat-based diet has led to more intensive, large-scale farming with animals reared in confined spaces where they are at greater risk of infection. Under these conditions, the demand for antibiotics is high. In some countries, more antibiotics are consumed by animals than by people. For example, in the USA, 70% of medically important antibiotics are consumed by animals.

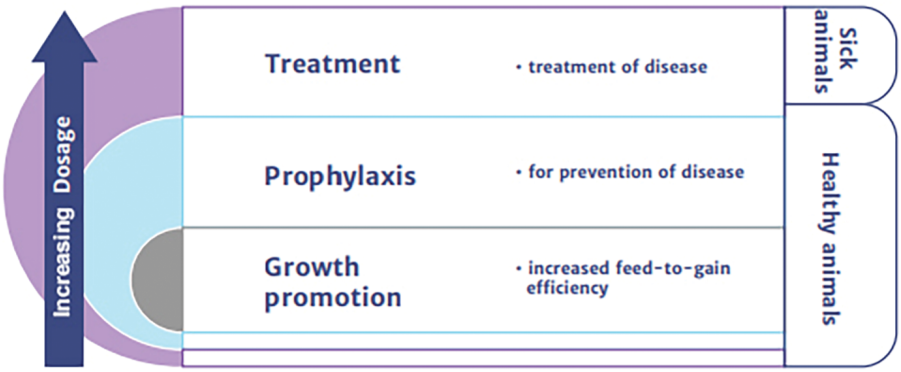


Figure 5 Uses of antibiotics in animals (O'Neill, 2015).

In the next activity, you will consider how these factors might influence the consumption of antibiotics in different countries.

Activity 4 Comparing antibiotic consumption in different countries

Allow about 25 minutes

In this activity, you will compare antibiotic consumption in two HICs – the UK and the USA – and two **low-middle-income countries (LMICs)** – China and India.

Part A

Figure 6 shows the consumption of antibiotics by country.

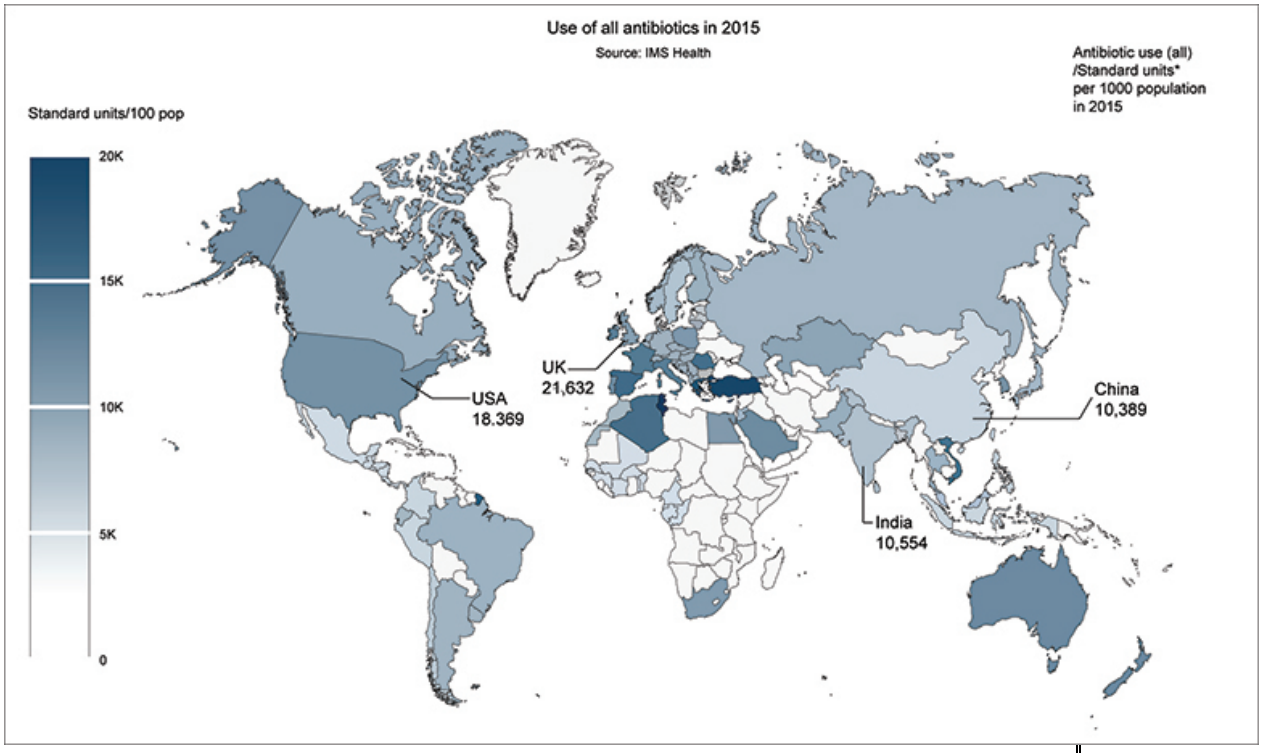


Figure 6 Worldwide consumption of antibiotics by people in 2015. Data from the Center for Disease Dynamics, Economics and Policy (CDDEP) (2017).

Complete the table of antibiotic use using the information given on the map in Figure 6. If you want to use the larger version of the figure, open it in a new browser tab or window so you can look at it alongside the activity.

Country	Antibiotic use (all) /standard units* per 1000 population in 2015
China	*Provide your answer...*
India	*Provide your answer...*
UK	*Provide your answer...*
USA	*Provide your answer...*

*A standard unit is defined as the equivalent of one pill, capsule or ampoule.

1 Which of these countries had the highest consumption of antibiotics per 1000 population in 2015 and which country had the lowest consumption?

Provide your answer...

Answer

1 The UK used the most antibiotics at 21 632 standard units per 1000 population. China used the least antibiotics at 10 389 standard units per 1000 population.

Country	Antibiotic use (all) /standard units per 1000 population in 2015
China	10 389
India	10 554
UK	21 632
USA	18 389

2 Were you surprised by which of the four countries had the highest antibiotic consumption per 1000 population in 2015? Why or why not?

Provide your answer...

Answer

2 Many different factors affect antibiotic consumption at a country level. For example, access to healthcare, availability and cost of drugs and public attitudes. In LMICs, poor access is probably a significant factor in antibiotic use. Although the UK and the USA have comparable levels of antibiotic use per 1000 population, the UK possibly has fewer barriers to health care and antibiotics are readily prescribed.Note that, although the UK has the highest antibiotic use per 1000 population, it has the lowest *total* antibiotic use. Both India and China used ten times more antibiotics in 2015 than the UK. This is due to their larger population size.

Part B

Figures 7a and 7b show the consumption of antibiotics in the four countries between 2000 and 2015.

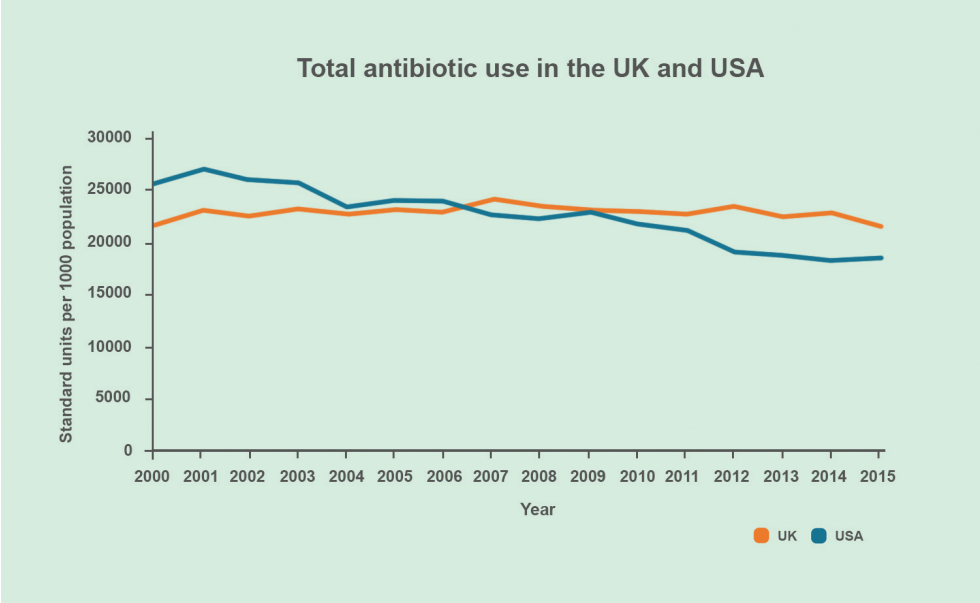


Figure 7a Total antibiotic use by people between 2000 and 2015 in UK and USA.

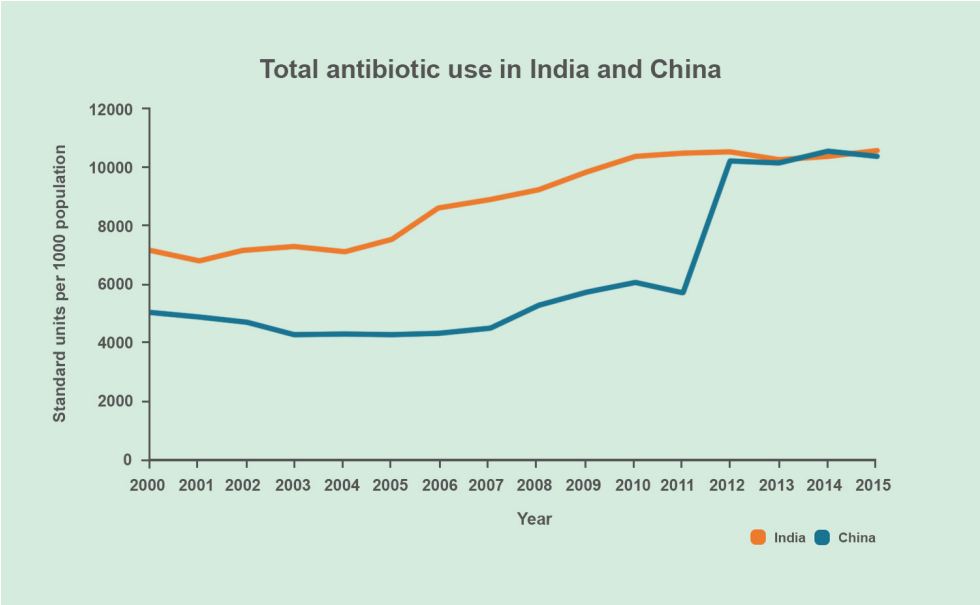


Figure 7b Total antibiotic use by people between 2000 and 2015 in China and India.

Answer the following questions about antibiotic use over this time period.

3 In which of these countries did antibiotic use rise?

Provide your answer...

4 In which country did antibiotic use fall?

Provide your answer...

5 Which country maintained similar levels of antibiotic use?

Provide your answer...

Answer

3 India and China

4 USA

5 UK

6 Can you make a general observation about the use of antibiotics in different countries?

Provide your answer...

Answer

6 Antibiotic use varies between countries and within a country as demand rises or falls.

Part C

The table below shows projected change in antimicrobial consumption in China, India, the UK and the USA by 2030.

Table 1 Projected change in antimicrobial consumption in China, India, the UK and the USA by 2030

Country	Projected change in antimicrobial consumption by 2030 (%)
China	13
India	18
UK	1
USA	2

* The mg/PCU is a standard unit of measurement based on the animal population and the weight of the animal at the time of treatment with antibiotics. Data from CDDEP, 2013.

7 Which country is projected to have the greatest increase in antimicrobial consumption for animal use by 2030? What might be driving the increase?

Provide your answer...

Answer

7 India is expected to increase its antimicrobial consumption by 18% over this period. Five LMICs, including India and China, are expected to account for one-third of increased antibiotic consumption in animals by 2030.This will be driven by consumer demand for meat products and hence more intensive farming practices which rely heavily on antibiotics. The potential consequences for antibiotic resistance are considerable (van Boeckel et al., 2015).

Activity 4 revealed the extent to which antibiotics are used by people and for animals. The agricultural use of antibiotics is of particular concern because studies have shown that the **sub-therapeutic** doses of antibiotics used in intensive farming can encourage the development of resistant bacteria (O'Neill, 2015).

5 Misuse of antibiotics

Begin this section by completing Activity 5 in which you reflect on your personal experience of using antibiotics.

Activity 5 Taking antibiotics

Allow about 5 minutes

Answer the questions below, based on either a recent experience or according to how you would probably behave.

1 The last time you felt ill, were you hoping or expecting the doctor to prescribe antibiotics?

Provide your answer...

2 If you were given antibiotics, did you (a) take the correct number of tablets at the correct time and (b) complete the full course of treatment?

Provide your answer...

3 Have you ever taken someone else's 'leftover' antibiotics?

Provide your answer...

Discussion

Being prescribed unnecessary antibiotics, failing to complete the full antibiotic course or taking antibiotics that have not been prescribed to you all increase the risk of antibiotic resistance developing and spreading.

The emergence and spread of antibiotic resistance is promoted when antibiotics are wrongly prescribed and/or taken, or when they are used indiscriminately. Self-medication is very common. For example, it accounts for over 30% of antibiotic use in LMICs (Ocan et al., 2015).

The indiscriminate use of antibiotics leads directly to overuse. This is a global problem. It is common to use antibiotics to treat mild bacterial infections that could resolve spontaneously, and for viral or non-infectious diseases. There is an over-reliance on broad-spectrum antibiotics that target a wide range of bacteria because **rapid diagnostics**, which could identify the resistance profile of the pathogen, are lacking (Ventola, 2015). You will look more closely at rapid diagnostics in Week 7.

Using antibiotics for non-therapeutic purposes, such as for animal husbandry (see Section 4), provides further opportunities to spread antibiotic resistance (Meek et al., 2015).

You will look in more detail at some of these factors in the following sections.

5.1 Treatment of non-bacterial infections

One-third of people in the UK believe that antibiotics will treat coughs and colds. But these conditions are caused by viruses which antibiotics are not effective against (Public Health England, 2015). Watch the following videos which explain why.

Video content is not available in this format.
Video 3 Bacteria and viruses are very different.

Video content is not available in this format.
Video 4 Why different drugs are needed to treat bacterial and viral infections.

5.2 Wrong therapeutic use

Antibiotic resistance is more likely to develop when antibiotics are used at too low a dose or taken for too short a time. In the next activity, you will explore the effect of treatment duration on gut bacteria.

Activity 6 Effect of antibiotics on gut bacteria

Allow about 20 minutes

You might recall from Week 1 the typical growth pattern of a bacterial population (Figure 8 below). The death phase does not occur in the gut. This is because of the steady flow of material from mouth to anus, so that new food is always added and waste products are always removed. In the gut, the only time a population will decline like this is if something – for example, an antibiotic taken by mouth – kills it.

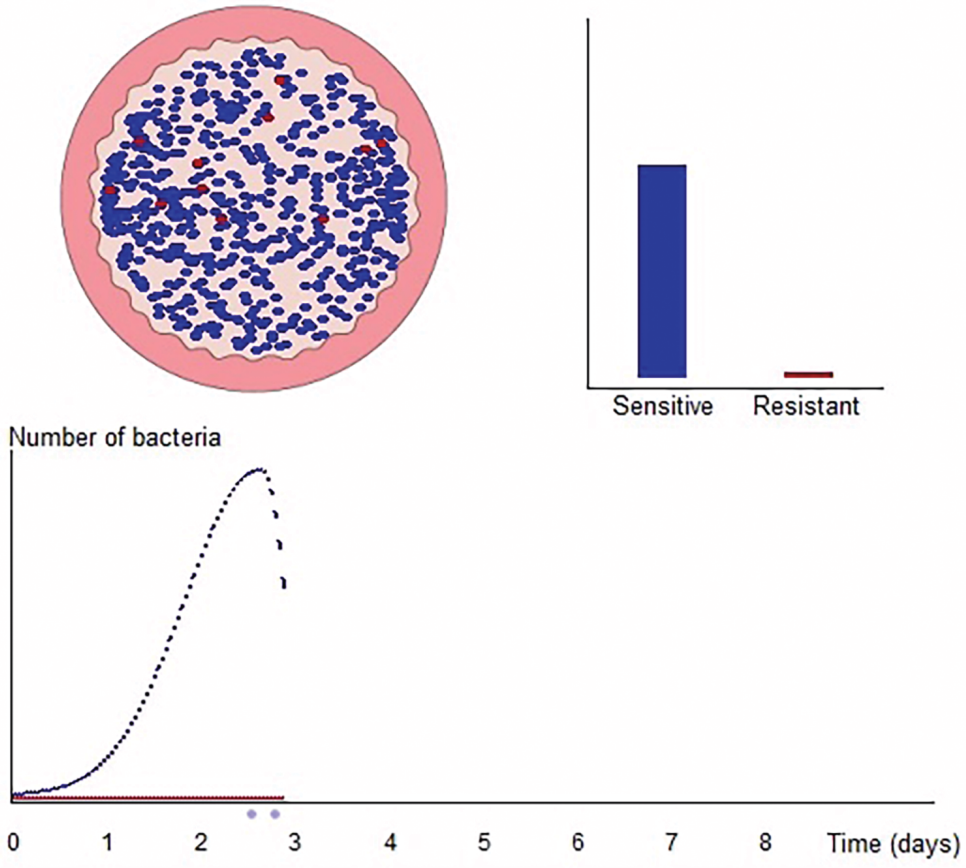


Figure 8 Bacterial growth in a closed system.

When a person swallows pathogenic bacteria, whether they become ill depends on the type of bacterium. For some types, only a few bacteria will cause illness. For other bacteria, millions must be taken in to cause any harm. The number of bacteria needed to cause illness is called the **infectious dose**.

Now click on the image below to be taken to an interactive activity.

Interactive content is not available in this format.

There is a risk of resistance developing every time an antibiotic is used because only resistant bacteria can survive and reproduce in the presence of antibiotics. This process is called **selection**. The resistant bacteria can then pass their resistant genes to other bacteria.

If the dose of antibiotic is too low, selection ensures that a few resistant bacteria will survive. Although the patient may start to feel better, the surviving bacteria will soon multiply, symptoms will return and the antibiotic will no longer be effective at the original dose used.

- The concentration of antibiotic within the body decreases with time. Why might failing to take an antibiotic regularly as prescribed make it less effective?
- Failure to maintain the antibiotic at a high enough level to kill all the bacteria allows an opportunity for resistant bacteria to be selected and resistance to develop

So far this week you have focused on human behaviours that promote antibiotic resistance. You should by now appreciate the importance of using antibiotics correctly. In the next two sections, you will look at other facets of the problem. First, you will learn why we are running out of options to treat antibiotic-resistant infections.

6 The antibiotic discovery void

The last class of antibiotic approved for clinical treatment was the lipopeptides, such as daptomycin, in 1987 (Figure 9).

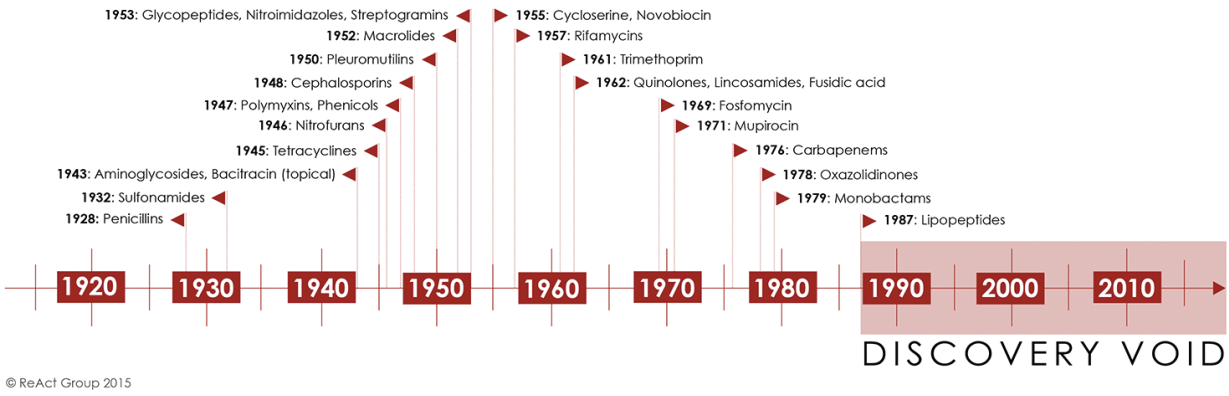


Figure 9 Timeline of antibiotic discovery.

A combination of factors is responsible for the 'discovery void'. It can take between 12 and 15 years to develop a new drug and to clear regulatory hurdles, at a cost of around £1.5 billion (GSK, 2018). The number of novel antibiotics discovered through screening large numbers of soil bacteria has fallen considerably and synthetic approaches have been disappointing. Due to these practical and financial difficulties, many pharmaceutical companies closed their antibiotic development programmes after the 1980s. You will learn more about the barriers to developing new antibiotics in Week 6.

Of the 51 potential new antibiotics currently in development, only ten are expected to be licensed for clinical use within ten years (WHO, 2017a).

A lack of new drugs is not the only problem though, as you will discover next.

7 Inadequate diagnostics and global surveillance

Antibiotic resistance is a global problem which requires a global collaborative approach to combat it. Well-equipped laboratories working in tandem with good surveillance systems can identify resistant isolates and reveal trends and outbreaks of infection. The information can then be used to inform treatment guidelines and clinical decision making, and so rationalise the use of antibiotics.

Unfortunately, the laboratory capacity and surveillance systems of many countries, particularly low-income countries (LICs), are inadequate or non-existent (Figures 10 and 11).

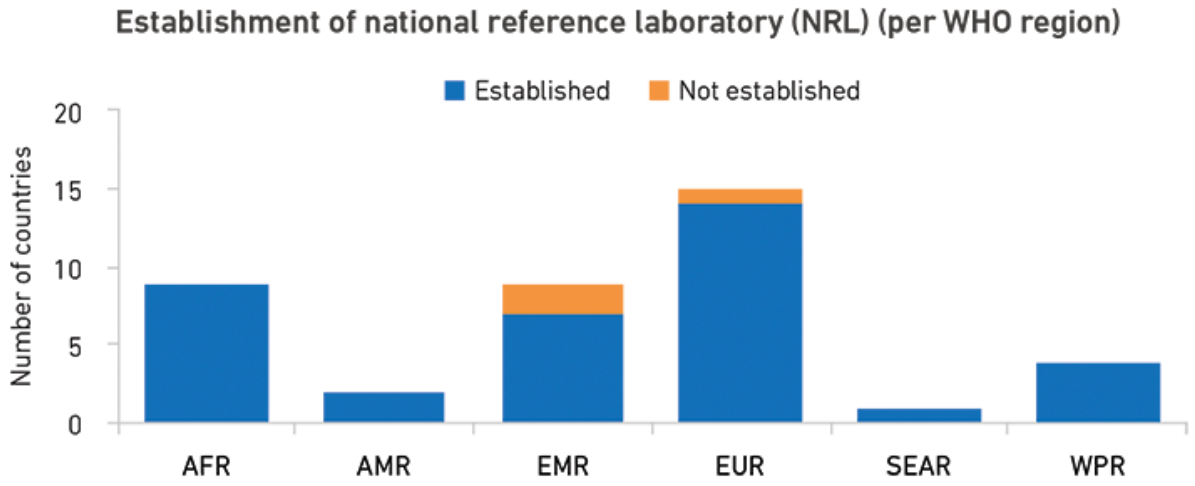


Figure 10 Number of countries in different WHO regions with an established national reference laboratory for AMR (WHO, 2017b): AFR, WHO African region; AMR, WHO region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region.

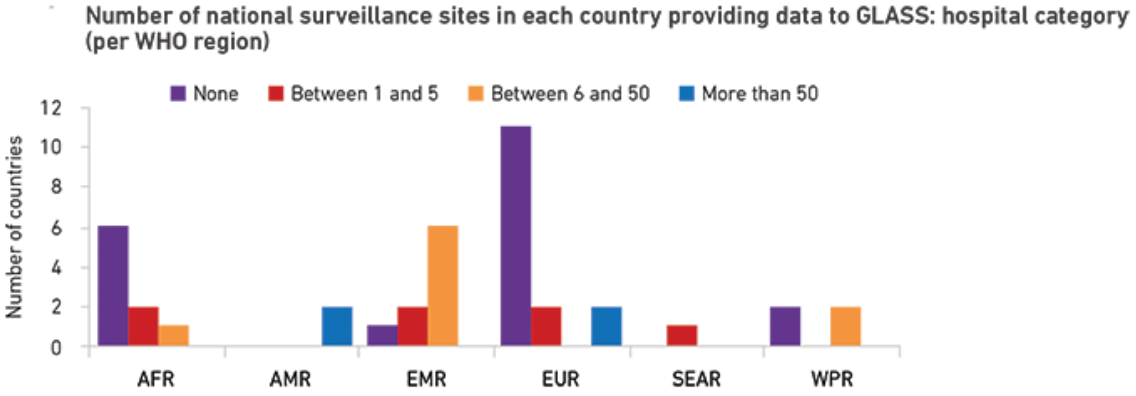


Figure 11 Number of hospital surveillance sites in each country of given WHO regions providing data to the WHO global AMR surveillance system (GLASS) (WHO, 2017b): AFR, WHO African region; AMR, WHO region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region.

Many of the themes discussed this week are brought together in the final section.

8 Case study: *Neisseria gonorrhoeae*

In this week's case study, you will look at how *Neisseria gonorrhoeae*, which causes gonorrhoea, is evolving into a superbug. Third-generation cephalosporins, also known as **extended spectrum cephalosporins (ESCs)**, are the lynchpin of current therapy for gonorrhoea. But resistance to ESCs is emerging.

The next activity will give you an overview of this topic.

Activity 7 Antibiotic-resistant *N. gonorrhoeae* in the USA

Allow about 10 minutes

First, watch the following video about the emergence of antibiotic-resistant gonorrhoea in the USA. The video was produced by the USA's foremost health protection agency – the Centers for Disease Control and Prevention (CDC).

Video content is not available in this format.
Video 5 Drug-resistant gonorrhoea: an urgent public health issue.

Now answer the following questions, based on the video.

1 Which two cephalosporins were introduced in the 2000s to treat gonorrhoea?

Provide your answer...

2 When were cephalosporin-resistant *N. gonorrhoeae* first detected?

Provide your answer...

3 In 2018, only one therapy was recommended for gonorrhoea. What was it?

Provide your answer...

4 Why does the narrator predict that the last treatment option ‘won’t last forever’?

Provide your answer...

Answer

1 Cefixime and ceftriaxone.
2 In 2012.
3 Dual treatment with ceftriaxone and azithromycin – a macrolide antibiotic.
4 *N. gonorrhoeae* has developed resistance to every antibiotic used to treat gonorrhoea. Reports of isolates resistant to ceftriaxone or azithromycin are expected to become more frequent.

ESC-resistant gonorrhoea has been reported in many other countries, as you will see in the next activity.

Activity 8 ESC-resistant gonorrhoea

Allow about 5 minutes

WHO recommends not using an antibiotic in cases where resistance levels are 5% or higher and the bacterial pathogen is unknown. Would this apply to any countries in Figure 12?

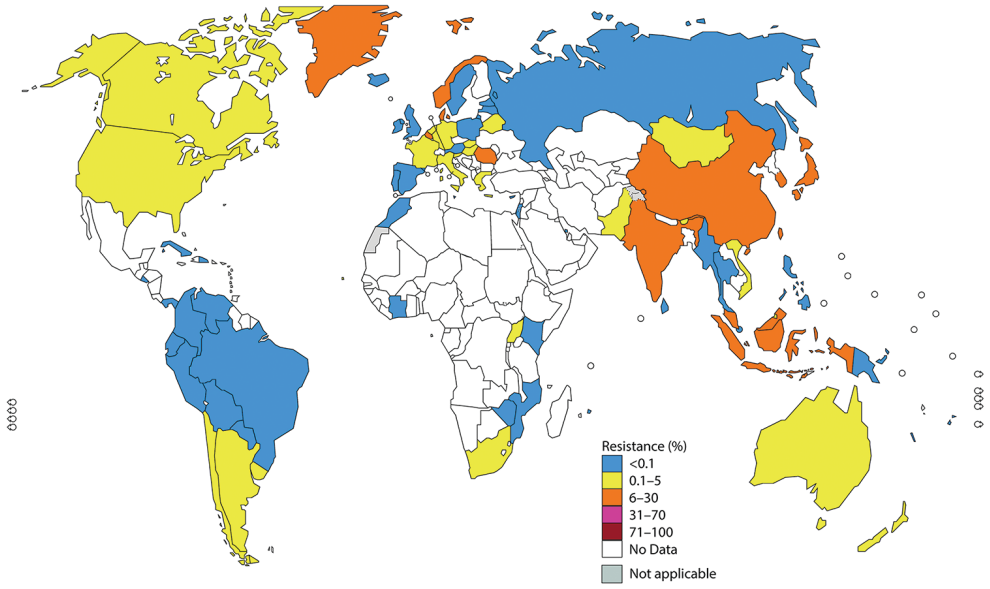


Figure 12 Percentage of isolates with resistance to cefixime and/or ceftriaxone. Data from WHO-GASP (2014 for most countries but 2011–2013 for a few countries) (Wi et al., 2017).

Answer

Yes. ESC-resistance is at least 5% in over 20 countries. Using ESCs in these circumstances increases the likelihood of resistance developing and spreading.

> Although resistance to ESCs is low level and emerging, resistance to azithromycin is widespread. Gonorrhoea superbugs, which are resistant to ESCs *and* azithromycin, have already been isolated from Japan, France and Spain.
>
> (WHO, 2017c).

In the final activity this week, you will look at the scale of the problem and the challenges faced in trying to bring the situation under control.

Activity 9 The rise of antibiotic-resistant gonorrhoea

Allow about 15 minutes

First, read the article below about the global challenge of treating gonorrhoea effectively because of antibiotic resistance.

Article 1: The world is running out of antibiotics, WHO report confirms (WHO, 2017c).

Now answer the following questions, based on the article.

1 How many people become infected with gonorrhoea each year?

Provide your answer...

2 Why is this probably an underestimate?

Provide your answer...

3 What percentage of *N. gonorrhoeae* isolates are ESC-resistant?

Provide your answer...

4 How many countries have reported resistance to cefixime or ceftriaxone?

Provide your answer...

5 Why might antibiotic resistance increase in the absence of suitable diagnostics?

Provide your answer...

6 How many new drugs are currently being developed to treat gonorrhoea?

Provide your answer...

Answer

1 About 78 million people worldwide.
2 LICs, where gonorrhoea is thought to be more common, do not have reliable diagnostic and reporting systems.
3 66%
4 Over 50 countries have reported ESC resistance.
5 Asymptomatic cases are undiagnosed and untreated, and the infection spreads. Conversely, patients presenting with gonorrhoea-like symptoms may be presumed to have the disease and be prescribed unnecessary or incorrect antibiotics.
6 Only three drugs are in clinical development.

Globally, gonorrhoea is becoming increasingly difficult to treat as a result of antibiotic resistance. High infection rates result in high rates of antibiotic use. Inadequate diagnostics and poor monitoring and surveillance of AMR encourage the misuse and overuse of antibiotics. New antibiotics are urgently needed. The threat that gonorrhoea may again become impossible to treat is very real.

9 This week's quiz

Well done – you have reached the end of Week 5 and can now do the quiz to test your learning.

Week 5 practice quiz

Open the quiz in a new tab or window (by holding down Ctrl [or Cmd on a Mac] when you click the link). Return here when you have finished it.

10 Summary

This week you learned how human behaviour has encouraged the spread of infections and antibiotic resistance. You should now be able to explain why the misuse and overuse of antibiotics leads to the selection of resistant bacteria and why resistant infections are becoming an increasingly serious global health problem.

You should now be able to:

- describe the scale and nature of antibiotic resistance worldwide
- summarise how antibiotic resistance spreads
- explain how the overuse and misuse of antibiotics contribute to bacterial resistance
- list the factors which have prevented new antibiotics coming onto the market
- recognise how a lack of laboratory capacity and inadequate surveillance contribute to the development and spread of antibiotic resistance.

Next week, you will look at how the problem of antibiotic resistance can be tackled by developing novel antibiotics or by making existing antibiotics more effective.

You can now go to Week 6.

Week 6: Restocking the antibiotic armoury

Introduction

In Week 5, you found out how and why antibiotic resistance has become a serious global, public health problem. You also learned about the types of behaviour that encourage the development and spread of antibiotic resistance.

This week, you will look at one approach to tackling the crisis – replenishing the depleted stock of drugs used to treat antibiotic-resistant infections. There are two options: to make new types of antibiotic or to make existing antibiotics more effective.

As you will discover this week, scientists and pharmaceutical companies must overcome many challenges in order to bring new drugs to the market. It is also worth bearing in mind the part that serendipity can play in this process.

Start this week by watching the video below about the accidental discovery of penicillin.

Video content is not available in this format.
Video 1 Alexander Fleming's discovery of penicillin.

By the end of this week, you should be able to:

- recall key events in the history of antibiotics
- explain how antibiotics are discovered and produced
- describe the current antibiotic armoury
- give reasons for the decline in the production of antibiotics
- outline approaches to make existing antibiotics more effective
- identify potential sources of novel antibiotics.

1 Origins of antibiotics

You might recall from Week 1 that some antibiotics are produced naturally by bacteria or fungi (moulds) while others are semi-synthetic or fully synthetic. You will explore these terms further in the following sections.

1.1 Natural antibiotics

Most natural antibiotics were discovered before the 1970s, using systematic **non-target-based screening** of soil samples. Relatively few antibiotics in use today are completely natural. Of these, about 20% are produced by fungi and 80% by a group of Gram-positive, filamentous soil bacteria called *Streptomyces* (Lo Grasso et al., 2016).

Two types of fungi – the *Penicilliums* and the *Cephalosporiums* – have proved good sources of antibiotics. For example, *Penicillium notatum* (Figure 1) was the source of the original penicillin discovered by Alexander Fleming in 1928. *Cephalosporium acremonium* gave rise to the first-generation cephalosporins (Clegg, 2015) .

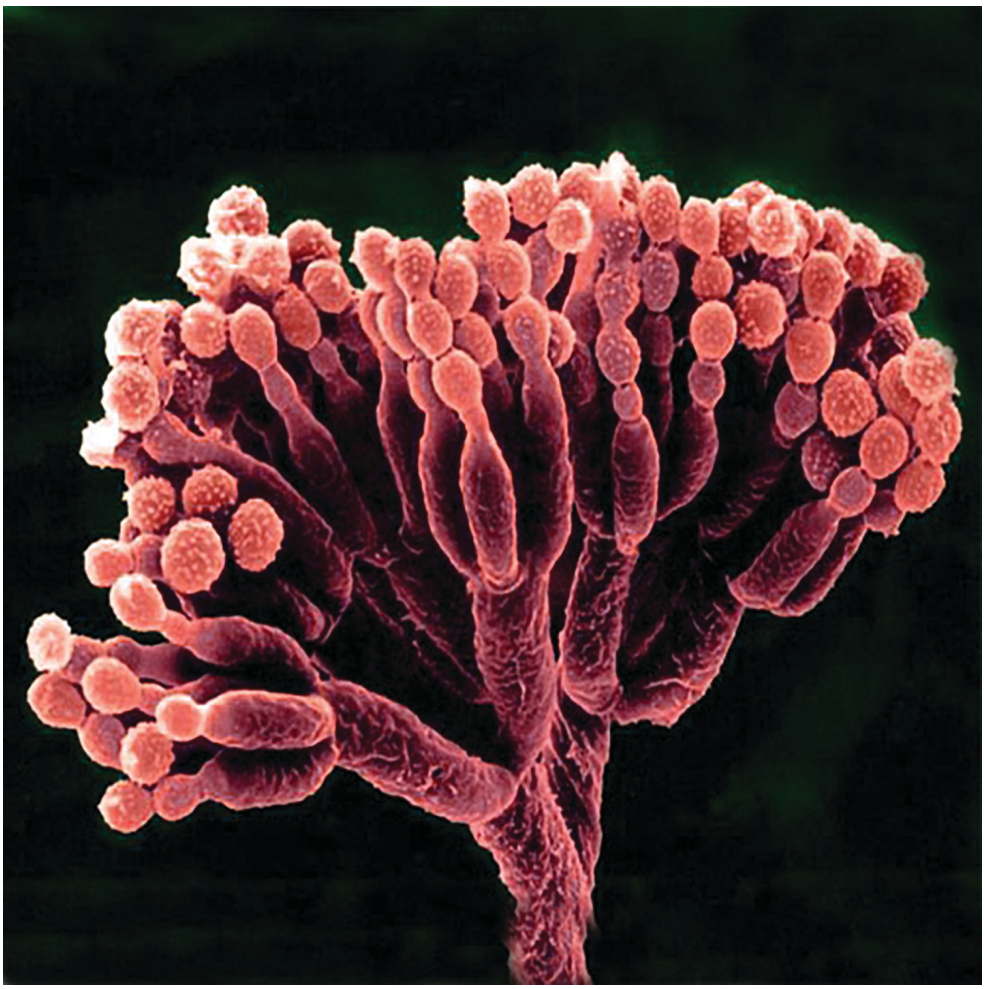


Figure 1 *Penicillium notatum* – the source of penicillin

Natural antibiotics isolated from *Streptomyces* bacteria (Figure 2) include streptomycin, tetracycline, vancomycin, erythromycin and chloramphenicol (de Lima Procopio et al., 2012).

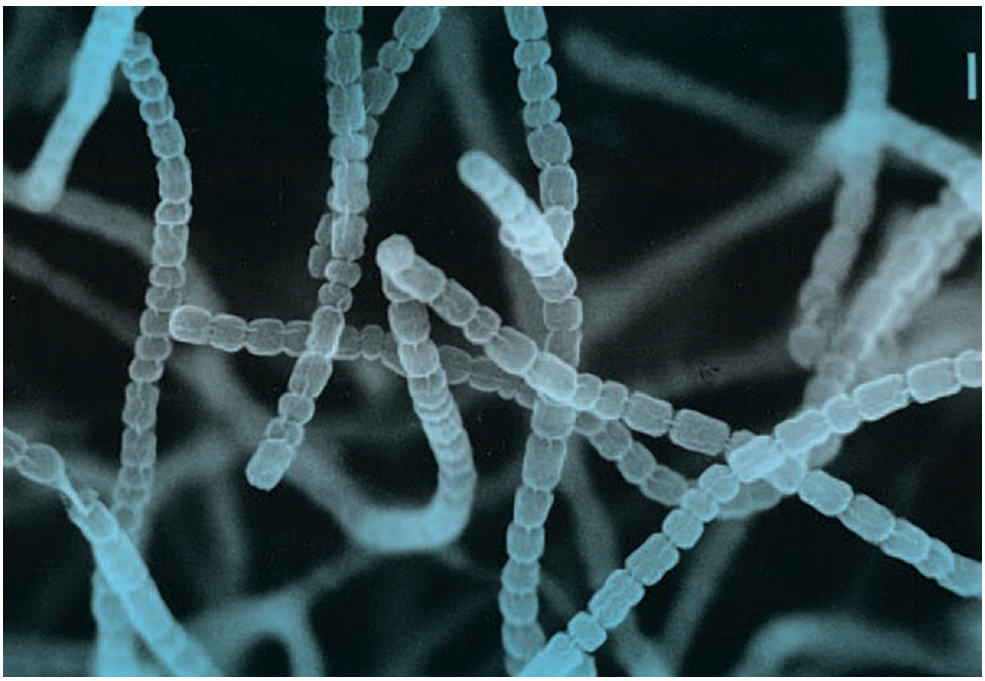


Figure 2 *Streptomyces griseus* – the source of streptomycin (Scale bar, 1 micrometre).

1.2 Synthetic and semi-synthetic antibiotics

The very first antibiotics were discovered by screening large numbers of existing compounds from collections of chemical compounds known as **chemical libraries**. These were arsenic derivatives in the case of Salvarsan in 1909, and azo-dyes for sulfonamides in the 1930s.

More targeted screening of chemical libraries later became the norm, such as looking for inhibitors of bacteria-specific metabolic pathways. This is how synthetic carbapenems were discovered (Silver, 2011).

Semi-synthetic antibiotics are derivatives of natural antibiotics with slightly different but advantageous characteristics. For example, they can act against bacteria which are resistant to the original compound, have a greater spectrum of activity or cause fewer side effects.

Semi-synthetic derivatives of penicillins and cephalosporins are known as **generations**. You will find out more about cephalosporin generations in this week's case study.

In the next section, you will find out how antibiotics are produced on an industrial scale.

2 The manufacturing process

For antibiotics to help the masses of people who need them, production needs to be on an industrial scale. Different manufacturing processes are used for natural, synthetic and semi-synthetic antibiotics.

2.1 Producing natural antibiotics

Natural antibiotics are complex chemicals which are synthesised stepwise by the bacteria or fungi that produce them in a series of enzyme-catalysed reactions. The starting compounds are usually products of the cell's mtabolism – chemical reactions that allow a cell to obtain the energy and nutrients it needs to grow and survive. These essential compounds, or **primary metabolites,** are made in the exponential phase of growth. Antibiotics, however, are **secondary metabolites**, that is they are products of metabolism that are not essential for growth.

You might recall from Week 1 that bacteria and fungi produce antibiotics to prevent competing organisms using nutrients and other resources.

- Why aren't antibiotics produced during the exponential stage of growth?
- The exponential stage is when abundant resources allow rapid growth, so only primary metabolites are made. During the stationary phase, competition for nutrients increases and resources are diverted away from growth to make antibiotics.

In manufacturing, pure cultures of antibiotic-producing bacteria and fungi are grown in huge bioreactors (containing thousands of litres) in a process known as **batch fermentation**. Batch fermentation favours antibiotic production by limiting the time that cells spend in the exponential growth phase. The antibiotic products are then harvested and purified.

As you will discover in Activity 1, this process was not always so streamlined.

Activity 1 Commercial production of penicillin – Part 1

Allow about 10 minutes

When Alexander Fleming accidentally discovered penicillin in 1928, he had no idea what to do with it or how to reproduce it. This was left for other researchers to do.

First, watch the video below about how penicillin was 'rediscovered' ten years later by Howard Florey and his Oxford-based research team.

Video content is not available in this format.
Video 2 Penicillin rediscovered.

Now answer the following questions, based on the video.

1 What was the first key thing that Florey's team achieved with penicillin?

Provide your answer...

2 Why were British pharmaceutical companies reluctant to help develop penicillin?

Provide your answer...

3 What did the American pharmaceutical companies achieve with penicillin?

Provide your answer...

Answer

1 The penicillin was purified to a level that was safe for use in humans.
2 In the late 1930s, British companies were prioritising the war effort.
3 They increased production and isolated a more powerful *Penicillium* mould.

In the UK, Florey's team had managed to purify penicillin and treat a bacterial infection. This was a major achievement, but the team was hampered by a lack of funding and equipment, and yields of the drug remained poor. After the move to the USA, the research picked up pace. By 1943, the production of penicillin was under way with the new, more powerful strain growing in a different medium – corn syrup. However, the production process was still inefficient and yields of penicillin remained low.

The second part of Activity 1 looks at the changes made to the manufacturing process that led to much higher yields of penicillin.

Activity 1 Commercial production of penicillin – Part 2

Allow about 10 minutes

The video below explains how the key to increased productivity was growing the *Penicillium* mould in a liquid, rather than as a layer at the bottom of a large flat-bottomed flask.

As you watch the video, consider the following questions.

1 What was the advantage of a liquid medium?

2 Why was it critical to control the level of oxygenation?

Video content is not available in this format.
Video 3 Mass production of penicillin.

Discussion

1 The liquid culture allowed more *Penicillium* to be grown and more penicillin to be produced.

2 If the oxygen level is too low, *Penicillium* will die because it needs oxygen to grow. Too much oxygen can be toxic to fungi and bacteria – as it can be to humans.

2.2 Producing synthetic and semi-synthetic antibiotics

Antibiotics are very complex molecules. Synthetic compounds that resemble or mimic a natural antibiotic are rarely made for this reason. An exception is chloramphenicol (Figure 3). Novel synthetic antibiotics can be made in laboratories from scratch using a multi-step process that starts with the requisite chemical building blocks and ends with the pure compound. However, this process involves considerable development time and production costs.

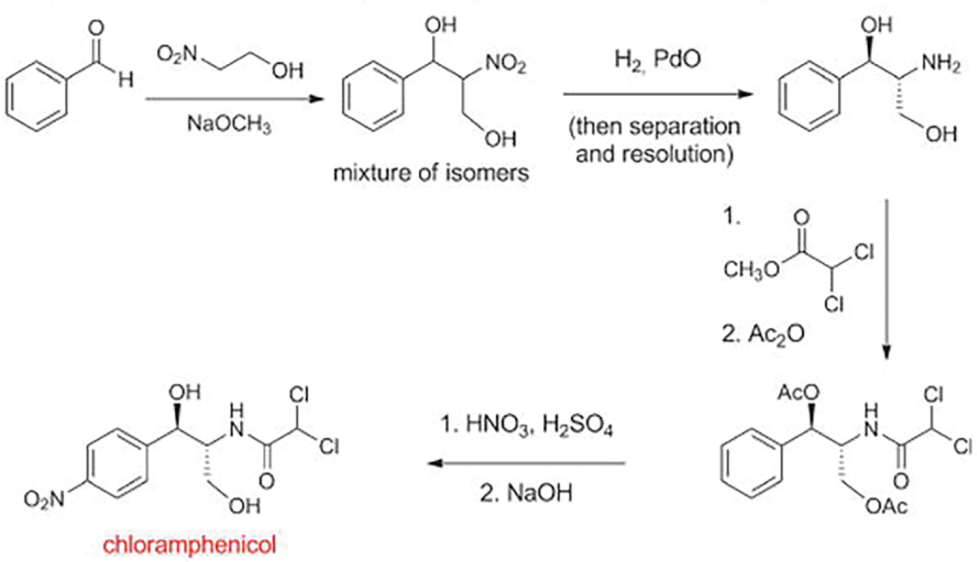


Figure 3 First synthesis of chloramphenicol in 1949. Originally isolated from *Streptomyces venezuelae* in 1947, it is cheaper to synthesise this relatively simple antibiotic than to produce the natural compound. You do not need to study this figure in detail.

Semi-synthetic antibiotics represent a half-way house. They are made by chemically modifying the active part of a natural antibiotic to create a single new molecule. A large amount of natural antibiotic is produced by batch fermentation. Then it is purified and chemically modified to create new antibiotics with enhanced therapeutic activity. Promising compounds identified by screening chemical libraries can similarly be modified to enhance activity and safety.

Next, you will find out how many existing antibiotics are still effective against bacterial infection.

3 Current status of antibiotics

The heyday of antibiotics was from the 1940s to the 1960s and 1970s. This was a time when new antibiotic classes were identified and approved for clinical use, and antibiotic resistance was under control.

Since then, the stock of antibiotics able to cure bacterial infections has been seriously depleted. Antibiotic resistance has soared and the development of new drugs has not kept pace with the need to replace those which no longer work (Figure 4).

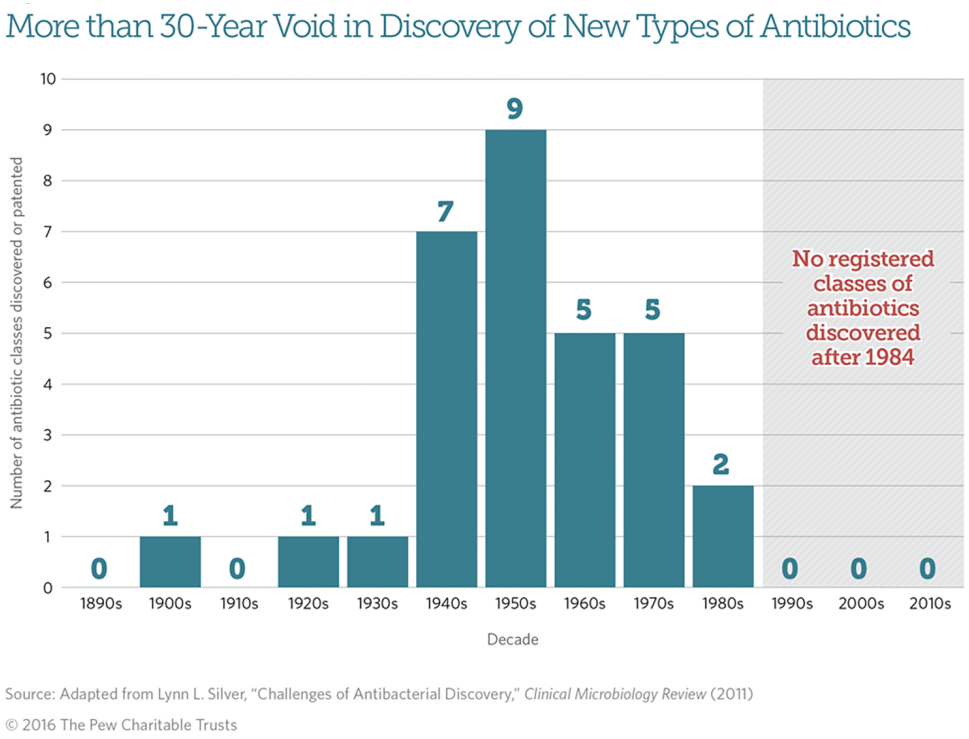


Figure 4 Number of antibiotic classes discovered since the 1900s (Pew Charitable Trust, 2016).

In recent years, two *potential* new classes of antibiotic have been discovered from soil bacteria: teixobactin in 2015 (Ling at al., 2015) and the malacidins in 2018 (Hover, 2018).

In the next activity, you will explore how quickly bacteria develop resistance to newly introduced antibiotics.

Activity 2 Antibiotic activity and resistance timeline

Allow about 10 minutes

Review Figure 5 and then answer the questions below.

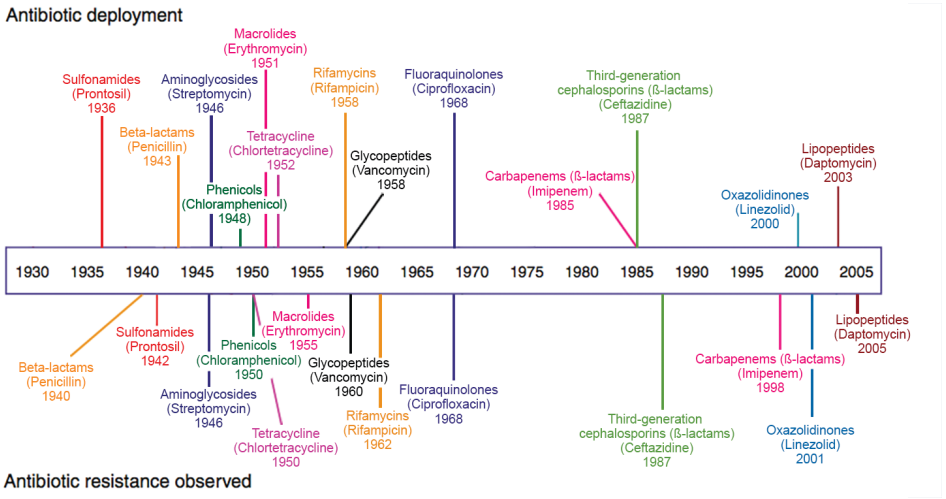


Figure 5 Timeline of introduction and resistance, showing the main antibiotic classes. Introduction (or deployment) of each antibiotic class is shown above the timeline. The date when resistance was first observed for each class is shown below the timeline.

1 Which antibiotic class had the longest interval between its introduction and resistance appearing?

Provide your answer...

2 What can you say in general about how long it takes resistance to develop once an antibiotic is brought into clinical use?

Provide your answer...

3 In some cases, such as penicilin, resistance to the antibiotic is observed before use of the drug becomes widespread. Why is this?

Provide your answer...

Answer

1 It took 13 years before resistance to imipenem, the first carbapenem, to be observed.

2 Resistance can develop quickly once an antibiotic becomes widely used. In most cases, resistance develops within two years of the antibiotic being introduced.

3 As you learned in Week 3, bacteria may have an intrinsic resistance to an antibiotic. It is not too surprising then that resistant bacteria are observed during the period between the initial discovery of an antibiotic and the point at which it is approved for clinical use.

Research and development into new drugs is an essential component of strategies to tackle the antibiotic resistance crisis. Unfortunately, as you will see in Section 4, this is not straightforward.

4 Barriers to new antibiotics – and possible solutions

In Week 5, you were introduced to some of the challenges involved in creating new antibiotics. Complete Activity 3 to see how many you can remember.

Activity 3 Factors which account for the antibiotic discovery void

Allow about 5 minutes

In Week 5, you briefly considered the factors which account for the antibiotic discovery void. Which factors can you remember?

Provide your answer...

Answer

You might have recalled that new drugs are rarely now discovered by screening soil samples or chemical libraries. Pharmaceutical companies are deterred by the financial costs and regulatory hurdles involved and many no longer have the research capacity to develop new antibiotics.

There is belated recognition by governments, public health agencies, medical communities and others that the barriers to antibiotic development must be removed and the **antibiotic pipeline** rebuilt. New regulatory policies and financial incentives to address this problem are being proposed (O'Neill, 2016), but barriers still remain.

4.1 Discovery barriers

After initial successes, non-target-based screening of soil samples soon became unviable. Known natural antibiotics were continually being 'rediscovered', making it difficult to identify promising new compounds. Meanwhile, the screening of chemical libraries faltered because their random contents did not lead to compounds with desirable characteristics.

However, new technologies may revive interest in both types of screening. **Transcription profiling** is a technique that identifies which genes are being expressed by bacteria. Profiling samples from soil or other microbe-rich environments is a quick way of distinguishing between rediscovered and novel antibiotics. Chemical libraries could also be created which are predisposed to generate compounds with antibiotic-like attributes.

4.2 Scientific barriers

The biggest barrier to new antibiotics may be a lack of investment in the basic, multidisciplinary research that underpins drug discovery and development (Figure 6).

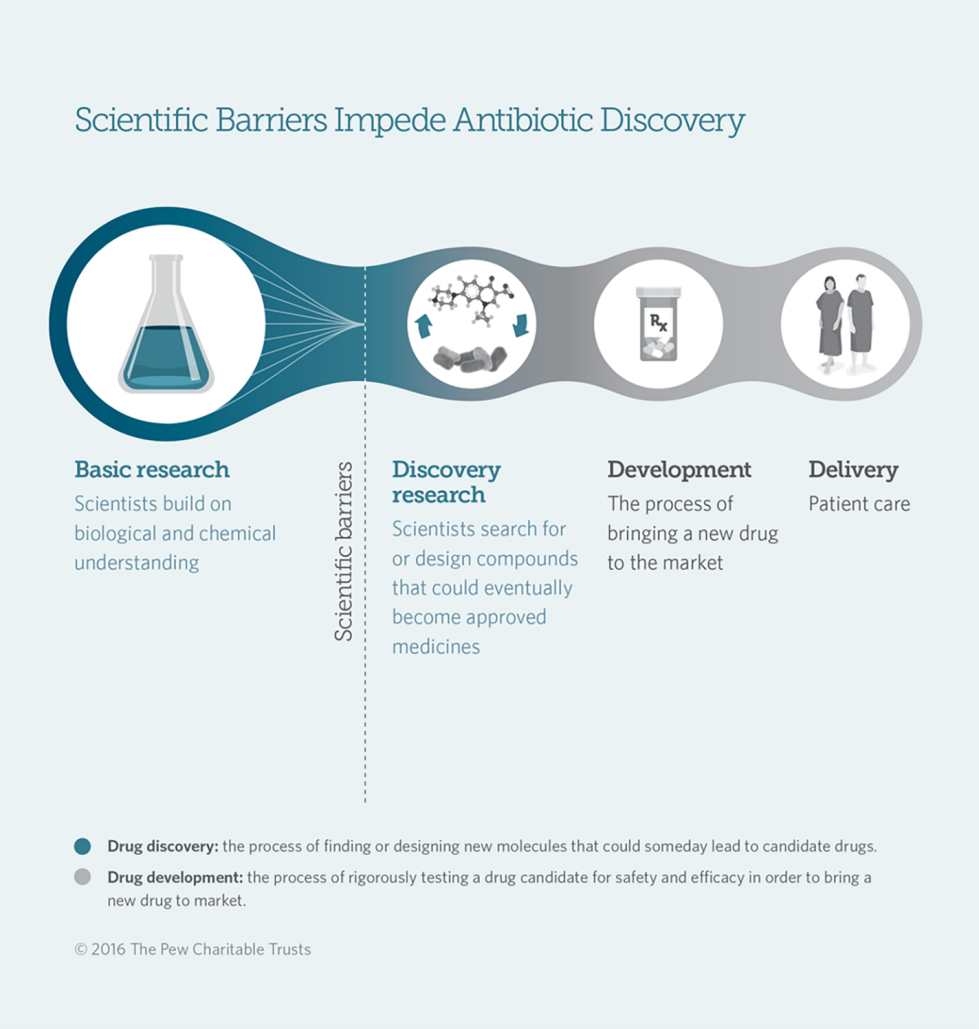


Figure 6 How scientific barriers can impede antibiotic discovery (Pew Charitable Trust, 2016).

Research has focused on identifying compounds that inhibit essential bacterial processes, for example cell wall synthesis. However, other key attributes of antibiotics are poorly understood, hampering efforts to discover new types of drug. The lack of new antibiotics to target infections caused by Gram-negative bacteria is particularly troubling because these are very difficult to treat.

- Can you recall from Weeks 2 and 3 the features of Gram-negative bacteria that make them intrinsically resistant to antibiotics?
- The outer membrane of Gram-negative bacteria is impermeable to many antibiotics. Inside the cell, efflux pumps transport toxic substances, including antibiotics, out of the cell.

Understanding the unique characteristics of antibiotics that allow them to penetrate cells, and to accumulate within in high concentrations, will enable focused chemical libraries to be created. It will also facilitate targeted screening programmes.

An alternative to discovering new antibiotics is to make existing drugs more effective. You will find out more about this in the next section.

5 Making existing antibiotics more effective

Given the challenges in bringing new antibiotics to the market, it makes sense to make existing antibiotics work again. It may also be cheaper and quicker. For example, simply using a combination of three antibiotics can overcome resistance, even if each drug is no longer effective when used on its own (Graham, 2016).

In this section, you will look at other ways in which antibiotics can be made more effective.

5.1 Resistance breakers

Existing antibiotics can be made more effective by co-administering antibiotics with **resistance breakers** – drugs that do not kill bacteria themselves but instead help an antibiotic to overcome resistance. One advantage of using failing antibiotics is that they have already been safety-tested, so development time and costs will be lower. However, this may only be a short-term fix because resistance is likely to develop to these drug combinations too (Garner, 2016).

5.2 Nano-encapsulation

A new but promising area of research is to encapsulate an antibiotic in a polyester polymer to create a nanoparticle, between 1 and 100 **nanometres** in size. (A **nanometre (nm)** is a unit of length equal to one billionth of a metre.)

Nano-sized antibiotic carriers can kill bacteria more effectively than unencapsulated antibiotics. This may be because the transportation of nanoparticles to the site of infection is more efficient, allowing higher concentrations of antibiotic to build up. Another possibility is that the nanoparticles somehow protect the antibiotic from bacterial resistance mechanisms (Friedrich-Schiller-Universitaet Jena, 2017).

5.3 Chemical modification

For many years, scientists have chemically modified antibiotics incrementally, broadening the spectrum of activity and increasing effectiveness and usability. This usually reverses antibiotic resistance at the same time. This happens with the cephalosporins, which are discussed in Section 6.

In the next activity, you will learn about a single, specific modification that could potentially reverse resistance by making the antibiotic more powerful.

Activity 4 Making antibiotics more powerful

Allow about 15 minutes

First, read the short article below about a promising new way of overcoming antibiotic resistance. Then complete the table comparing the characteristics of the two antibiotics vancomycin and oritavancin.

Article 1: 'Brute force' can overcome antibiotic resistance (UCL, 2017).

Characteristic	Vancomycin	Oritavancin
Therapeutic use	*Provide your answer...*	*Provide your answer...*
Killing mechanism	*Provide your answer...*	*Provide your answer...*
Time taken to kill a bacterial cell	*Provide your answer...*	*Provide your answer...*

Answer

Characteristic	Vancomycin	Oritavancin
Therapeutic use	Last resort treatment for MRSA	Complex skin infections
Killing mechanism	Disrupts vital cellular processes	Clusters latch onto bacterial surface and then push apart, generating a strong force that ruptures the cell.
Time taken to kill a bacterial cell	6–24 hours	15 minutes

Now answer the following questions, based on the article.

1 Which is the more powerful antibiotic and why?

Provide your answer...

2 How do the scientists plan to use their findings in future research?

Provide your answer...

Answer

1 Oritavancin is more powerful. The force used by oritavancin to push into a bacterial cell is 11 000 times more powerful than that of vancomycin.

2 To help inform the design of new antibiotics, and to make similar modifications to existing antibiotics, in order to make them more powerful

Next, you will look at the modifications that have been made to different generations of cephalosporins.

6 Case study: cephalosporin antibiotics

In this week's case study you will learn about the history and development of cephalosporin antibiotics. You might recall from previous weeks that these are broad-spectrum, bactericidal, ß-lactam antibiotics.

The story starts in Italy where the first cephalosporin, cephalosporin C, was discovered in cultures of *C. acremonium* found growing in a sewer near the Sardinian coast. You can find out more in Activity 5.

Activity 5 The history of cephalosporins

Allow about 15 minutes

First, listen to the following audio recording about the discovery and development of cephalosporins.

Audio content is not available in this format.
Audio 1 Discovery and development of cephalosporins.

Now answer the following questions, based on the audio recording.

1 Who discovered the first cephalosporin?

Provide your answer...

2 What antibacterial activity did a crude extract derived from *C. acremonium* demonstrate?

Provide your answer...

3 Which chemical structure is described as the 'nucleus' of cephalosporins and why is it significant?

Provide your answer...

4 What is the difference between the first and later generations of cephalosporins in terms of their spectrum of activity?

Provide your answer...

Answer

1 The Italian scientist Giuseppe Brotzu (1895–1976).

2 The extract could suppress the growth of *Salmonella typhi* and *Staphylococcus aureus*.

3 The starting point for all cephalosporin derivatives (generations) is 7-aminocephalosporic acid, or 7-ACA.

4 First-generation cephalosporins are only effective against Gram-positive bacteria. The later generations have increasing activity against Gram-negative bacteria.

Guy Newton and Edward Abraham were interested in cephalosporin C because, although it was a weak antibiotic, it was resistant to ß-lactamase.This is the bacterial enzyme and resistance factor that can inactivate ß-lactam antibiotics.

The drive behind the experiments that resulted in 7-aminocephalosporic acid (7-ACA) was to create a chemically modified derivative of cephalosporin C with enhanced antibacterial activity and intact ß-lactamase resistance. Newton and Abraham found that modifying cephalosporin C could effect the desired change, as long as the 7-ACA 'nucleus' containing the ß-lactam ring remained intact (Figure 7).

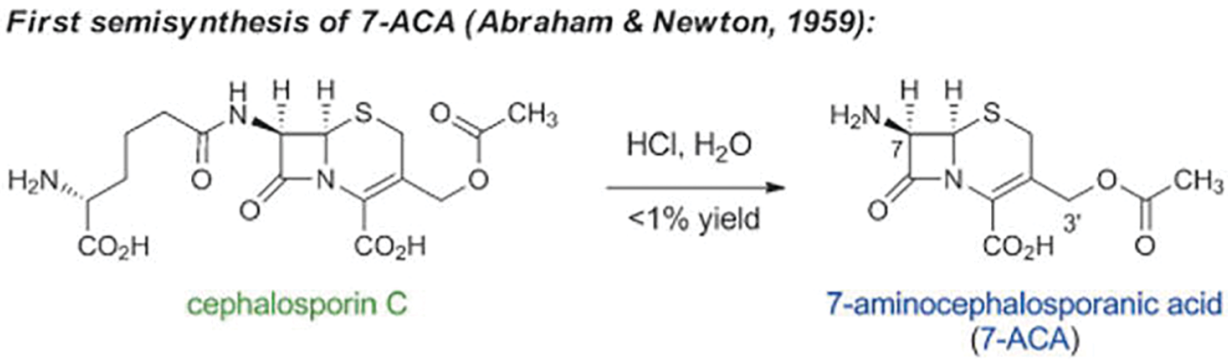


Figure 7 Synthesis of 7-ACA by Newton and Abraham (Wright et al., 2014). You do not need to know the chemical structures in this figure.

To this day, all cephalosporins are semi-synthetic and are derived from cephalosporin C via 7-ACA. Batch fermentation of the natural antibiotic produces vast quantities of the drug which is converted to the 7-ACA intermediate before being further modified to produce the range of cephalosporins on the market (Wright et al., 2014).

6.1 Different generations of cephalosporins

There are five generations of cephalosporins. Figure 8 shows how two chemical groups of 7-ACA, the acetyl group and the acylamino side chain can be modified, leaving the 'nucleus' intact. Do not worry if you are not familiar with these chemical structures. For this course you should just be aware that these modifications give rise to different generations of cephalosporins with a different spectrum of activity. If you would like to know more about chemical reactions you might like to try our free OpenLearn course *Discovering chemistry*. For examples of each generation, see Figure 9.

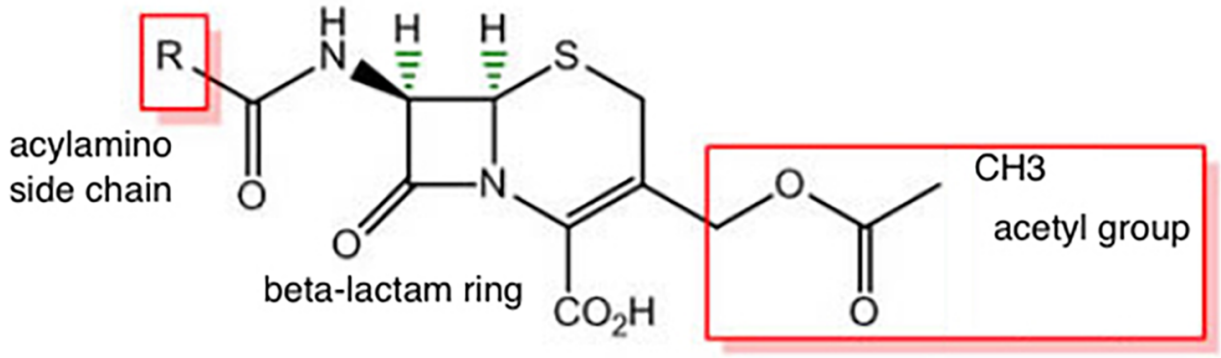


Figure 8 The chemical structure of 7-ACA highlighting the side groups which can be modified.

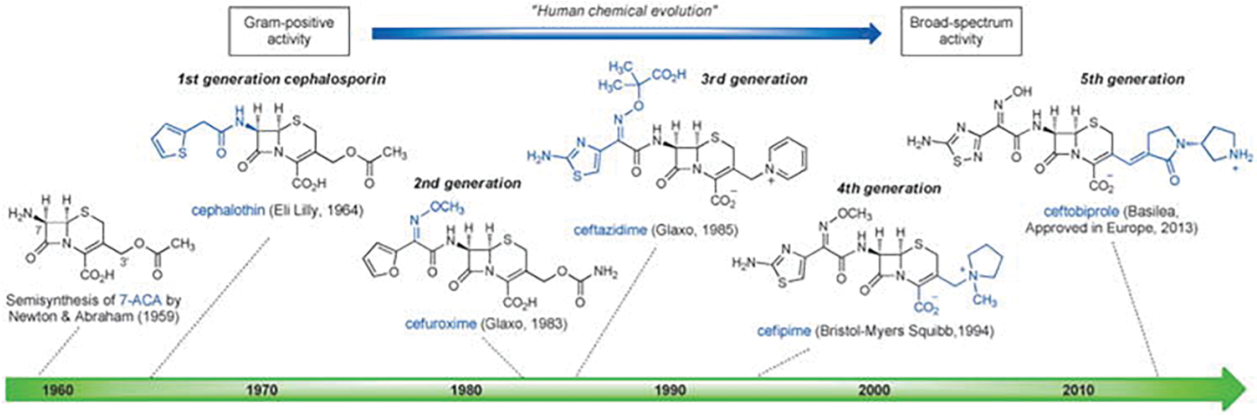


Figure 9 The evolution of semi-synthetic cephalosporins (Wright et al., 2014)

Each successive cephalosporin generation has improvements in the spectrum of activity and in some **pharmacological properties**. This greatly expands the clinical uses of these drugs. The later generations are sometimes called 'extended spectrum cephalosporins' (ESCs).

In Activity 6, you can compare the characteristics of different generations of cephalosporins.

Activity 6 Characteristics of cephalosporin generations

Allow about 10 minutes

Table 1 below summarises the characteristics of different cephalosporin generations.

Table 1 Spectrum of activity of different cephalosporin generations

Cephalosporin generation	Activity against:			Resistance to:		Examples
	Gram-positive	Gram-negative	MRSA	ß-lactamase	ESBLs	
1	++++	+	no	+	no	cephalothin cefazolin
2	+++	++	no	++	no	cefamandole cefaclor

3	++	+++	no	++	no	cefixime ceftriaxone
4	++++	++++	no	+++	no	cefepime cefclidine
5	++++	++++	yes	+++	no	ceftobiprole

(Based on Reygaert, 2011; Wright et al., 2014)

Key: + = trace amount; ++ = small amount; +++ = moderate amount; ++++ = large amount.

Review the table and then answer the following questions.

1 Which generation has the lowest activity against Gram-negative bacteria and which has the highest?

Provide your answer...

2 With each successive generation, what do you notice about the activity against Gram-positive and Gram-negative bacteria?

Provide your answer...

3 Which generation(s) have the greatest resistance to ß-lactamases?

Provide your answer...

4 Are any cephalosporins resistant to ESBLs?

Provide your answer...

5 Which cephalosporin has activity against MRSA?

Provide your answer...

Answer

1 The first-generation drugs have the lowest activity against Gram-negative bacteria; the fourth and fifth generations have the greatest.

2 The first-generation cephalosporins had good activity against Gram-positive bacteria but poor activity against Gram-negative bacteria. Activity against Gram-negative bacteria improved with second and third generation drugs, but at the expense of activity against Gram-positive bacteria. The last two generations of cephalosporins have good activity against both Gram-positive and Gram-negative bacteria.

3 The fourth and fifth generations

4 No. Resistance to ESBLs, particularly those produced by Gram-negative bacteria, is becoming a serious problem.

5 Fifth generation cephalosporins, like ceftobiprole, are active against MRSA.

The chemical evolution of cephalosporin C via 7-ACA into over 30 new broad-spectrum antibiotics was a breakthrough in the fight against antibiotic resistance. Unfortunately, the widespread practice of using cephalosporins for **empiric treatment**, that is treatment without a definitive diagnosis, may have selected for multi-drug-resistant bacteria and encouraged the spread of resistance (Clegg, 2015).

The need for new antibiotics is urgent and, as you will see in the final section this week, scientists are looking in some unlikely places for them.

7 ‘Bioprospecting’ for new antibiotics

Our planet is a rich, largely untapped source of antibiotics and other drugs. Most antibiotics in use today can be traced back to bacteria. But only a tiny proportion of bacteria have been screened for antibiotics and nearly all of them were isolated from soil.

There is now renewed interest in a systematic search for natural antibiotics in every conceivable location worldwide. This is known as **bioprospecting**.

7.1 Back to the soil

Recent technological advances and innovations have allowed a much wider range of microbes to be cultured and novel species and new metabolites to be identified. For example, Activity 7 reveals how teixobactin was discovered in 2015 by a team of scientists in the USA who managed to isolate and culture a previously unidentified soil bacterium. Teixobactin is a new class of antibiotic which is active against Gram-negative but not Gram-positive bacteria (Ling et al., 2015).

Activity 7 Discovering teixobactin

Allow about 15 minutes

First, listen to the interview with Dr Kim Lewis, leader of the research team who discovered teixobactin.

Audio content is not available in this format.
Audio 2 Discovery of teixobactin.

Now put the steps below in the correct order to match the culturing technique described by Dr Lewis.

Collect soil sample

First

Mix diluted soil sample with agar

Second

Sandwich sample between **semi-permeable membranes**

Third

Place diffusion chamber in soil

Fourth

Remove diffusion chamber from soil

Fifth

Select colonies and grow in a Petri dish

Sixth

Screen for ability to make antibiotics

Seventh

Assess compounds for **efficacy** and usefulness

Eighth

What are the advantages of this new technique?

Answer

It re-creates the normal growing conditions of the bacteria, allowing them to be successfully cultivated. The recovery rate by this method is 50% compared with only 1% of cells from soil samples cultured on a Petri dish (Ling et al., 2015).

7.2 Antibiotics from leafcutter ants

The close relationship between South American leafcutter ants and the fungus *Leucoagaricus gonglophorus*, which the ants farm for food, has also opened up potential avenues of research. Watch the video below to find out more.

Video content is not available in this format.

Video 4 South American leafcutter ants.

7.3 Antibiotics from extreme environments

Scientists are looking further and further afield to discover new bacterial types and antibiotics, including some extreme locations like the Atacama Desert and under the sea.

The Atacama Desert (Figure 10) is one of the driest places on Earth. Some areas have just 1 mm of rain per year. This inhospitable place is home to a recently discovered bacterium – *Streptomyces leeuwenhoekii*. It produces metabolites called chaxamycins which have antimicrobial activity (UEA, 2016).

Figure 10 The Atacama Desert in Chile.

Bacteria living in a symbiotic relationship with marine sponges (Figure 11) produce various metabolites which are thought to protect their sponge host from predators and pathogens. Marine *Streptomyces* and the *Salinispora*, which were only discovered in 1989, are two groups of bacteria currently attracting the attention of scientists (UEA, 2016).

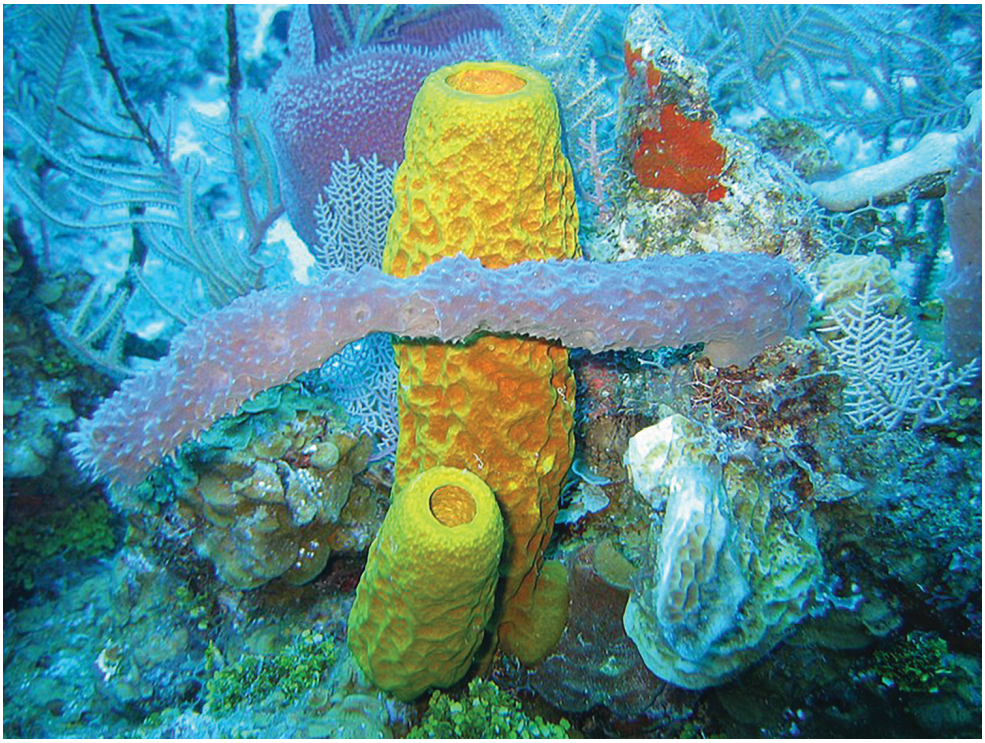


Figure 11 Marine sponges in the Caribbean Sea (Twilight Zone Expedition Team 2007, NOAA-OE).

7.4 Looking closer to home

Scientists are also bioprospecting closer to home and looking at samples taken from everyday objects and places. A bioprospecting project which recruited thousands of people to help is described in Activity 8.

Activity 8 Citizen Science 'Swab and Send' project

Allow about 10 minutes

First, listen to the following interview with Dr Adam Roberts about the 'Swab and Send' project. Listen from 13:35 to 21:00.

Now answer the following questions.

1 What is 'Swab and Send'?

2 What sort of samples have the swabs come from?

3 Have any new antibiotics been identified through this initiative?

Answer

1 It is a crowd-funded Citizen Science project to get members of the public involved in the discovery of new antibiotics.

2 Anything and everything, including dead bald eagles, workplace objects, faeces and train tickets.

3 Yes. Twenty candidates have been discovered that can kill multidrug resistant *E. coli* and the yeast *Candida albicans* or MRSA.

8 This week's quiz

Well done – you have reached the end of Week 6 and can now do the quiz to test your learning.

Week 6 practice quiz

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link. Return here when you have finished it.

9 Summary

This week, you learned that we have few working antibiotics left to treat bacterial infections. More and better treatment options are urgently needed, either in the form of new antibiotics or by modifying existing drugs. Unfortunately, as you should now realise,

scientific, financial and regulatory barriers to the discovery and development of new antibiotics means that this is not an easy option.

You should now be able to:

- recall key events in the history of antibiotics
- explain how antibiotics are discovered and produced
- describe the current antibiotic armoury
- give reasons for the decline in the production of antibiotics
- outline approaches to make existing antibiotics more effective
- identify potential sources of novel antibiotics.

Next week, you will learn about another approach to tackling the antibiotic resistance crisis – reducing the use of antibiotics.

You can now go to Week 7.

Week 8: Alternatives to antibiotics

Introduction

As you should now appreciate, if we are to preserve antibiotics for the future, we need to make sure that they are used carefully and not wasted. In Week 7, you looked at two ways of reducing antibiotic use. This week, you will look at some alternatives to antibiotics.

Begin this week by watching the following video, which describes how vaccines can help to tackle antibiotic resistance.

Watch the Video at YouTube.com

Video 1 How vaccines help to beat superbugs

The wider use of vaccines can help to combat antibiotic resistance because they prevent infections in humans and animals, reducing the need for antibiotics (Figure 1).

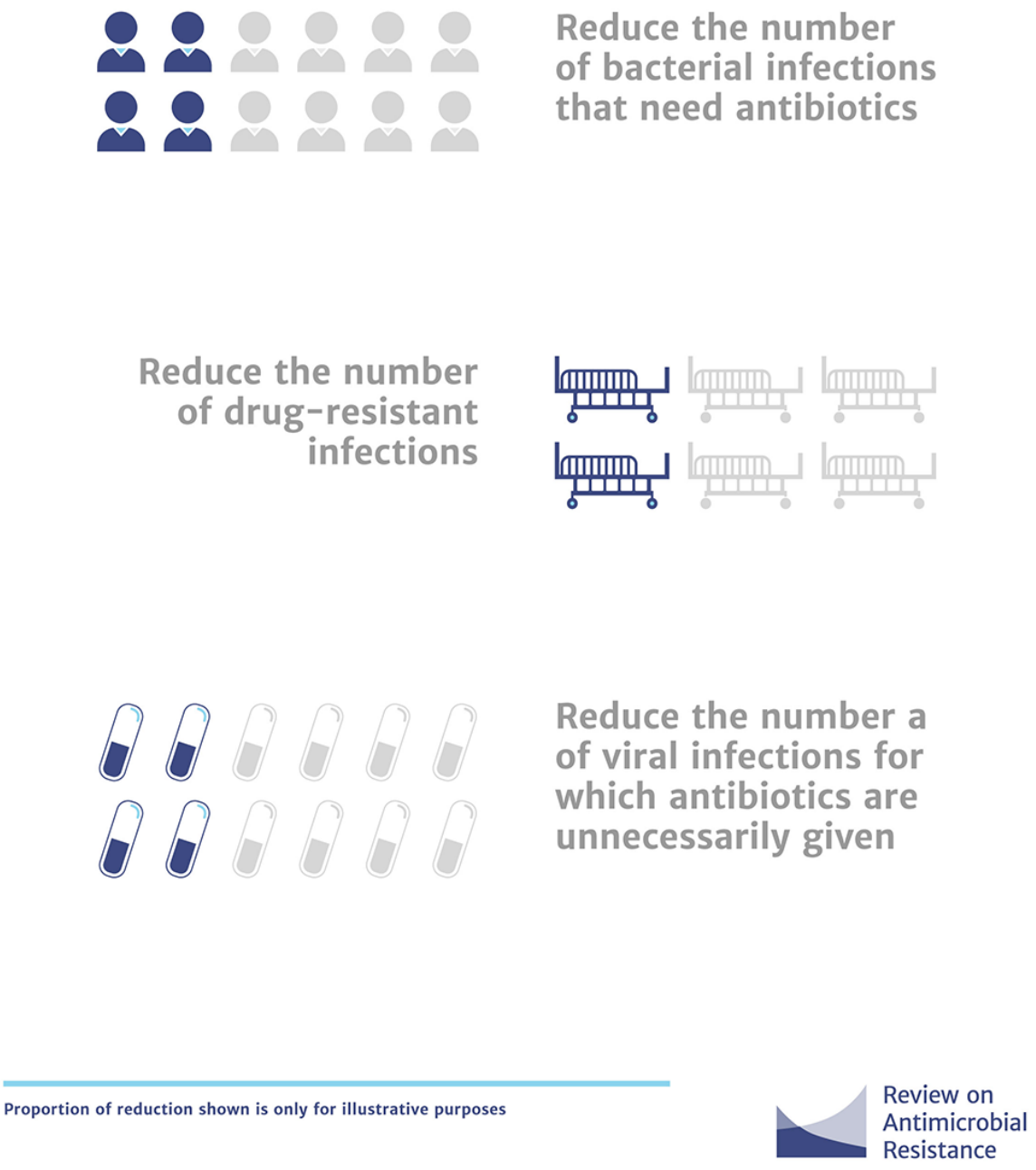


Figure 1 Vaccination can reduce antibiotic use in humans.

In addition to vaccines, there are many new areas of scientific research that could lead to the development of future alternatives to antibiotics. In this week, you will look at some of this research.

You will focus on alternative treatments rather than alternative strategies that could be used to prevent infection. Consequently, you will not look at approaches such as the use of probiotics. Currently, none of these alternatives could replace antibiotics as a treatment

for infections. However, using these alternatives in combination with antibiotics to treat minor infections could preserve antibiotics for treating life-threatening cases in the future.

By the end of this week, you should be able to:

- identify some alternatives to antibiotics
- explain how inhibiting quorum sensing decreases bacterial virulence
- describe the advantages and disadvantages of using phage therapy to kill bacteria
- understand how predatory bacteria can be used to tackle infections
- give examples of how traditional remedies can be used to treat infections.

1 Disrupting bacterial communication

Bacteria are single-cell organisms. For many years, they were thought to act as individuals and not be influenced by the bacteria around them. However, bacteria can communicate with each other in a process called **quorum sensing**.

Activity 1 What is quorum sensing?

Allow about 10 minutes

Watch part of the video at the following link in which Bonnie Bassler from Princeton University describes the discovery of quorum sensing.

The discovery of quorum sensing. Watch from 51:24 until 53:57.

Now answer the following questions, based on the video.

1 When do the fluorescent bacteria *Vibrio fischeri* fluoresce (emit light)?

- ☐ a) When they detect other bacteria
- ☐ b) When they are on their own
- ☐ c) Always
- ☐ d) Never

Answer

The correct answer is (a) when they detect other bacteria. *Vibrio fischeri* use quorum sensing to detect the presence of other bacteria and alter their behaviour so that they fluoresce.

2 How do the bacteria detect the presence of other bacteria?

- ☐ a) Using chemical messengers
- ☐ b) By touching each other
- ☐ c) Both of the above

Answer

The correct answer is (a) chemical messengers. Bacteria release chemical messengers that build up as the number of bacteria increases. Above a critical level, receptors on the surface of bacteria detect the chemical messenger and change their behaviour.

3 Which of the following statements about quorum sensing are true?

- ☐ (a) Quorum sensing is the mechanism that bacteria use to communicate.
- ☐ (b) Quorum sensing allows bacteria to synchronise changes in their behaviour.
- ☐ (c) Quorum sensing allows bacteria to detect the presence of other bacteria.
- ☐ (d) All of the above

Answer

The correct answer is (d) all of the above. Quorum sensing is the process by which bacteria use chemical messengers to detect and communicate with other bacteria, in order to synchronise changes in their behaviour.

As you saw in Activity 1, bacteria release **chemical messengers** which can be used to detect the presence of other bacteria. When the number of bacteria reaches a critical level, these chemical messengers cause bacteria to alter their behaviour (Figure 2).

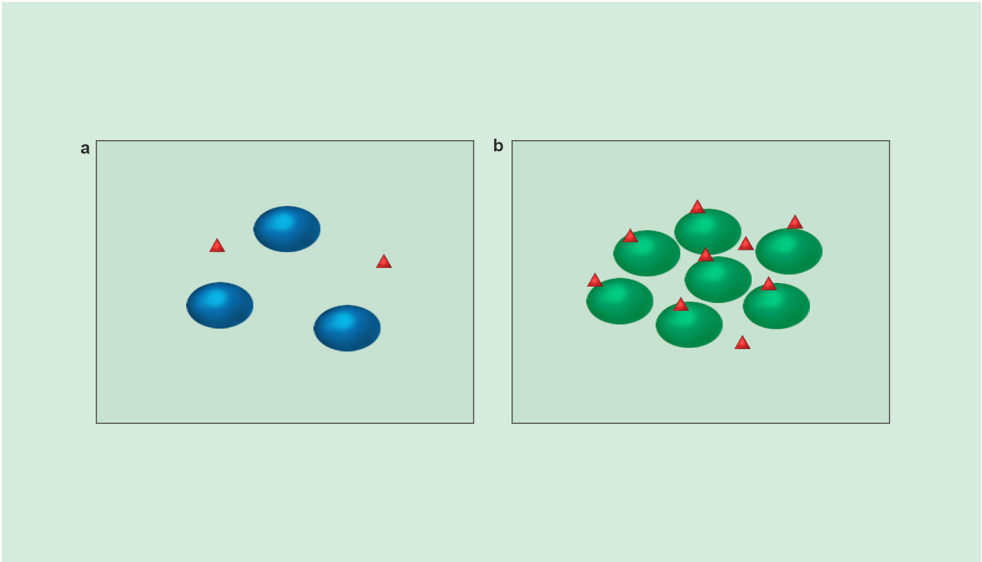


Figure 2 During quorum sensing, chemical messengers are produced and detected by bacteria. (a) When the number of bacteria (in blue) is low, levels of chemical messenger (red triangles) are low. (b) When the number of bacteria (in green) reaches a critical level, the high levels of chemical messenger (red triangles) are detected by other bacteria, causing them to alter their behaviour.

1.1 Using quorum sensing to treat infections

On its own, a single bacterium cannot cause an infection but, just like the bacteria in Activity 1, pathogenic bacteria use quorum sensing to coordinate their behaviour and attack together. Disrupting this coordinated response by blocking quorum sensing could help to treat infections, as you will see next.

Activity 2 Preventing infections by disrupting quorum sensing

Allow about 15 minutes

Watch part of the video in the following link in which Bonnie Bassler explains how quorum sensing **antagonists** (drugs that disrupt quorum sensing) can prevent infections by *Vibrio cholerae*.

Preventing infections by disrupting quorum sensing. Watch from 54:50 until 57:05.

Now answer the following questions, based on the video.

1 What effect would a quorum-sensing antagonist have on bacteria?

- ☐ a) It kills them
- ☐ b) It blocks their ability to communicate with each other
- ☐ c) It helps them to communicate with each other
- ☐ d) It makes them grow faster

Answer

The correct answer is (b) it blocks their ability to communicate with each other.

2 What effect does the quorum-sensing antagonist have on the fluorescence of *Vibrio fischeri* bacteria?

- ☐ a) It stops them fluorescing
- ☐ b) It makes them fluoresce more
- ☐ c) It does not have any effect

Answer

The correct answer is (a) it stops them fluorescing.

3 How many people die from *Vibrio cholerae* infections?

- ☐ a) Less than 100 000 per year
- ☐ b) 100 000 per week
- ☐ c) Over 100 000 per year

Answer

The correct answer is (c) over 100 000 people per year.

4 What is the first step in a *Vibrio cholerae* infection?

- ☐ a) Expression of a protein that causes the bacteria to fluoresce
- ☐ b) Expression of a virulence protein that allows the bacteria to stick to the gut
- ☐ c) Expression of a protein that makes the bacteria move faster

Answer

The correct answer is (b) expression of a virulence protein that allows the bacteria to stick to the gut.

5 How does blocking quorum sensing affect the expression of this protein and the *Vibrio cholerae* infection?

- ☐ a) It increases protein expression and prevents the infection

- ☐ b) It decreases protein expression and prevents the infection
- ☐ c) It increases protein expression and increases the likelihood of infection
- ☐ d) It decreases protein expression and increases the likelihood of infection
- ☐ e) It has no effect on protein expression or infection

Answer

The correct answer is (b) it decreases protein expression and prevents the infection.

1.2 Using quorum sensing to reduce antibiotic resistance

Vibrio cholerae are not the only pathogenic bacteria that use quorum sensing to control the expression of virulence genes. Quorum sensing in MRSA promotes the formation of biofilms which are aggregates of bacteria attached to a surface or tissue.

Biofilm formation on medical devices such as catheters or respiration tubes can be a major source of infection in intensive care units (ICUs) (Figure 3). Preventing biofilm formation by blocking quorum sensing could reduce the rate of antibiotic-resistant healthcare-associated infections (HCAIs).

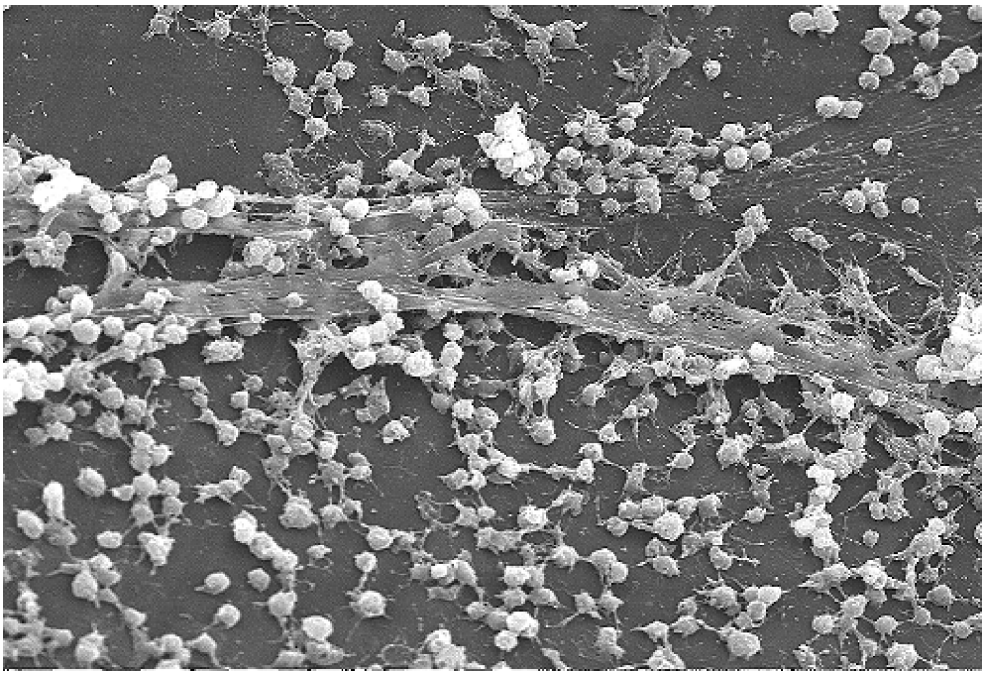


Figure 3 Biofilm formation by *Staphylococcus aureus* on a catheter.

2 Other ways to kill bacteria

Unlike quorum sensing, some antibiotic alternatives are bactericidal. Just like the bactericidal antibiotics you looked at in Week 2, these treatments work by killing the bacteria that cause infections.

In Week 4, you learned about the horizontal gene transfer mechanism of transduction. In this process, DNA is transferred between bacteria via infection with viruses known as bacteriophages.

Bacteriophages can also be exploited to treat infections. When bacteriophages infect bacteria, they replicate and assemble new virus particles, before lysing (bursting) and killing the bacteria, releasing the new bacteriophage particles (Figure 4).

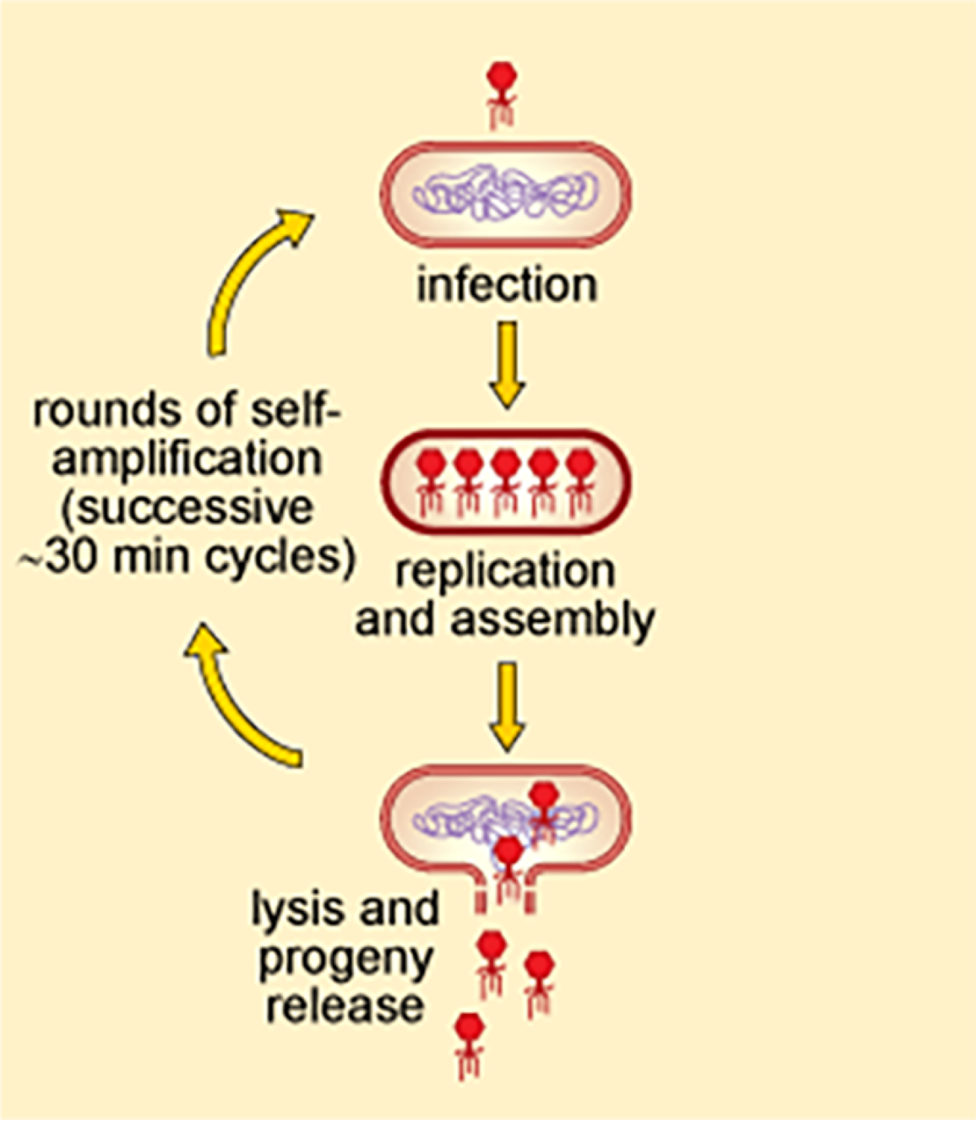


Figure 4 The lytic cycle of a bacteriophage.

2.1 Phage therapy

Phage therapy to treat bacterial infections exploits the bactericidal lysis step of bacteriophage infection to kill bacteria. It was first developed more than 90 years ago by researchers in the former Soviet Union and is routinely used to treat chronic infections in former Soviet states such as Georgia. In the next activity, you will look at some of the advantages and disadvantages of this treatment.

Activity 3 The advantages and disadvantages of phage therapy

Allow about 10 minutes

Listen to the following interview with Martha Clokie, a phage researcher, who discusses the advantages and disadvantages of phage therapy. While you are listening, note down any advantages and disadvantages of phage therapy in Table 1 below. You may also like to think about any ways in which phage therapy is similar to and different from antibiotic treatment.

Audio content is not available in this format.
Audio 1 Interview with Martha Clokie on phage therapy.

Advantages	**Disadvantages**
Provide your answer...	*Provide your answer...*
Similarities to antibiotic treatment	**Differences from antibiotic treatment**
Provide your answer...	*Provide your answer...*

Discussion

Advantages	**Disadvantages**
Resistance is less likely to develop (bacteria that are resistant to phage therapy are also often less virulent).	• Require more information about the bacteria causing the infection because they are often very specific for a particular bacterial types • More difficult to make than antibiotics • No regulatory pathway and very few clinical trials in the UK or the west
Similarities to antibiotic treatment	**Differences from antibiotic treatment**
• Bactericidal	• Phage therapy is specific for each bacterial strain • Broad-spectrum antibiotic treatments can target many different pathogens

Historically, phage therapy has relied on identifying bacteriophages that target the infection-causing bacteria and then administering these bacteriophages to infect and lyse the bacterial cells. However, more recently, the isolation of phage-derived enzymes known as lysins has opened the possibility of developing new phage-based pharmaceuticals.

2.2 Lysin treatment

Lysin treatment is similar to phage therapy because it uses the ability of phages, and enzymes derived from them, to kill bacteria by cell lysis. Phage lysins (also known as endolysins) are bacteriophage enzymes that destroy the peptidoglycan cell wall of target bacteria. This causes them to burst and release new bacteriophage particles. Like the bacteriophage they are derived from, lysins are specific for certain bacteria and can target different peptidoglycan types.

- Would you expect Gram-negative or Gram-positive bacteria to be more susceptible to phage lysins? You may need to revisit Week 2 Section 4.1 to remind yourself of the differences between Gram-negative and Gram-positive bacteria.
- In Gram-negative bacteria, the peptidoglycan layer is protected by an outer membrane. In contrast, Gram-positive bacteria do not have an outer membrane, so disrupting the peptidoglycan layer is more likely to cause these bacteria to burst.

In the next activity, you will look at data from an experiment measuring the effect of phage lysin treatment on bacteria.

Activity 4 Measuring the effect of phage lysins on bacteria

Allow about 15 minutes

In this experiment, the presence of intact bacteria is measured using light.

Turbidity is a measure of how well light passes through a liquid. If a sample contains lots of suspended particles, it will appear turbid or cloudy and light will not easily pass through it. In contrast, light will pass straight through pure water which does not contain any particles. As a result, the water will appear clear, not turbid.

Turbidity can be used as a measure of the density of bacterial cells in a sample (Figure 5).

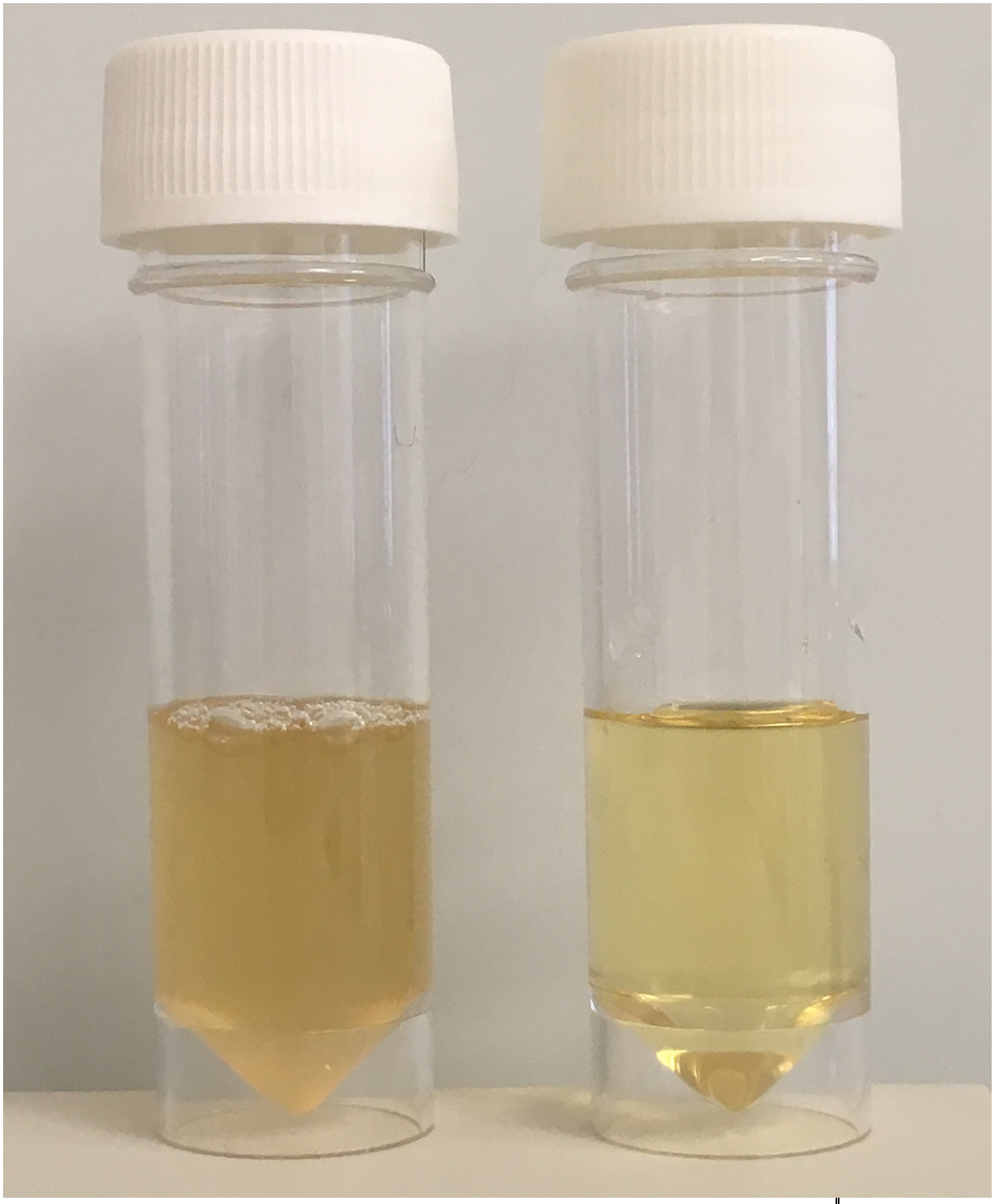


Figure 5 The turbidity of bacterial samples. The sample on the left contains a high density of bacterial cells and appears turbid or cloudy. The sample on the right does not contain any bacteria and appears clear.

Microbiologists use spectrophotometers to shine light through bacterial samples to determine their turbidities. Samples with a high bacterial cell density will appear more turbid than samples with a low bacterial cell density.

In this experiment, the turbidity of two bacterial samples was measured over 5 minutes (300 seconds) using a spectrophotometer. Sample 1 (orange line in Figure 6) was treated with a phage lysin while sample 2 (blue line in Figure 6) was not. Figure 6 shows the results of the experiment (Schmelcher et al., 2012). The turbidity of the sample is plotted on the vertical *y*-axis (labelled 'normalised OD (optical density)'), while the time in seconds is plotted on the horizontal *x*-axis.

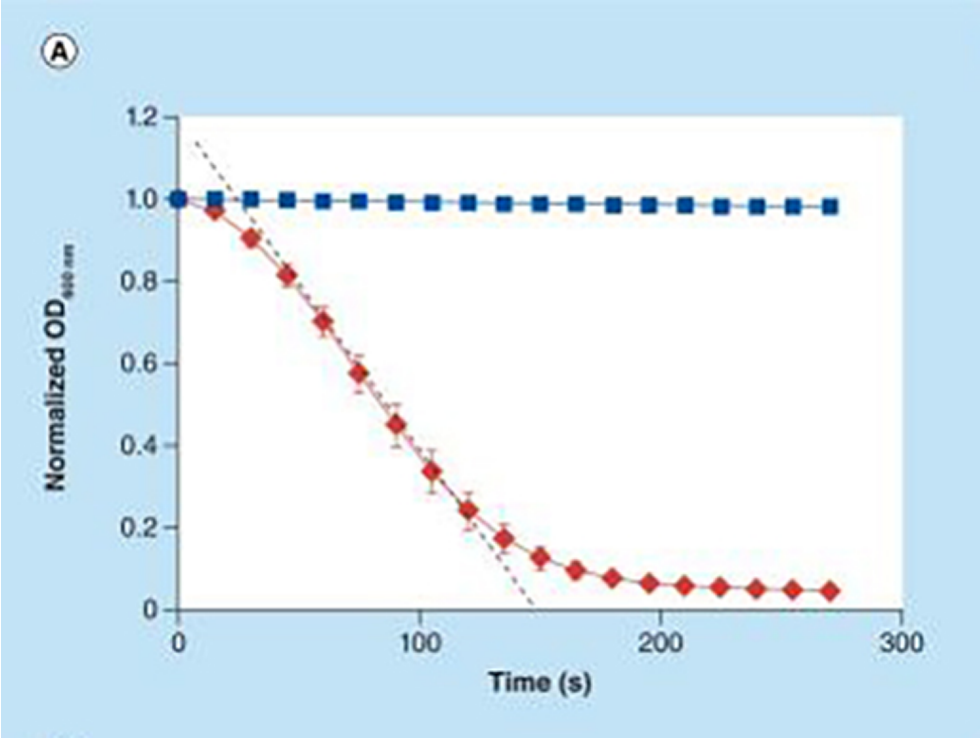


Figure 6 The effect of phage lysin treatment on bacterial cell density (Schmelcher et al., 2012).

Study the graph carefully and then answer the following questions.

1 What happens to the turbidity of the lysin-treated sample over time?

Provide your answer...

Answer

At the start of the experiment, the sample has a turbidity of 1.0. As the time progresses, the turbidity of the sample decreases until it reaches almost 0 at around 200 seconds.

2 What happens to the density of the bacterial cells in this sample during the experiment?

Provide your answer...

Answer

At the start of the experiment, the bacterial cell density is high but, as the experiment continues, the cell density decreases

3 Why?

Provide your answer...

Answer

The phage lysin lyses the bacteria, killing them so that the sample no longer appears turbid.

4 Does the turbidity of the sample without lysin change during the experiment?

Provide your answer...

Answer

No. The turbidity of the untreated sample does not change.

5 Why do you think this sample has been included in the experiment?

Provide your answer...

Answer

This sample shows that the decrease in turbidity in the sample during the experiment is caused by the presence of lysin in the sample and not by another factor.

In this section, you looked at one alternative to antibiotics that works by killing bacteria. Next you will look at research into the natural defences of a bacterium called *Bdellovibrio bacteriovorus* which has the potential to be exploited as another bactericidal alternative to antibiotics.

3 Exploiting the natural defences of bacteria

In Weeks 3 and 4, you saw how antibiotic resistance naturally evolved to protect bacteria as they compete for limited resources in the wild. But antibiotics are just one weapon in bacteria's defence arsenal. Some bacteria prey on other microbes, attacking and killing them. These predatory bacteria could be exploited to kill infectious pathogens as another alternative to antibiotics.

The best known type of predatory bacteria is ***Bdellovibrio bacteriovorus*** (Figure 7).

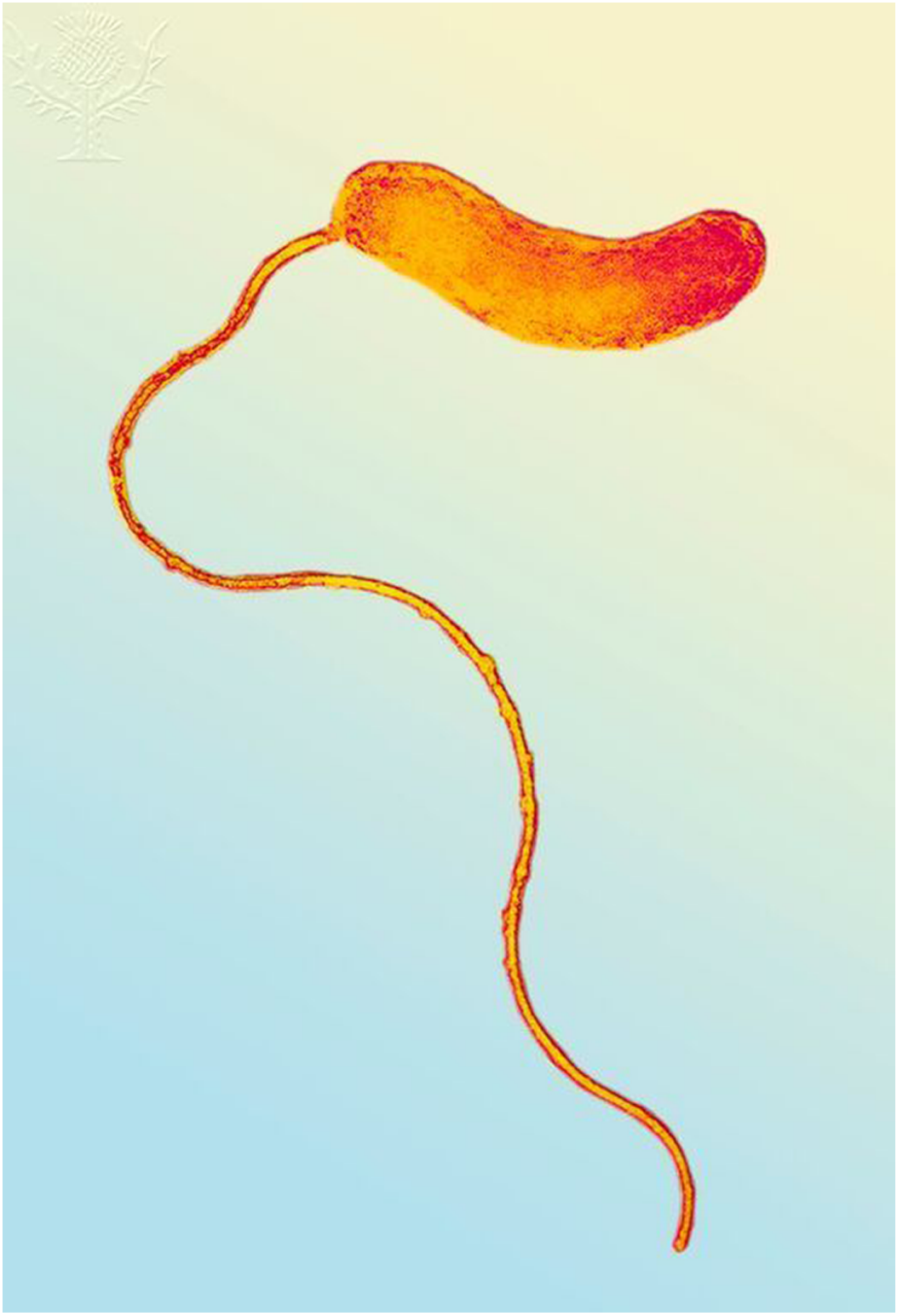


Figure 7 The predatory bacterium *Bdellovibrio bacteriovorus*.

Bdellovibrio bacteriovorous attaches to the surface of its prey. Once attached, it penetrates the bacterial cell membrane and replicates. Finally, the prey bacterium is lysed, releasing new *B. bacteriovorous* particles into the environment (Figure 8).

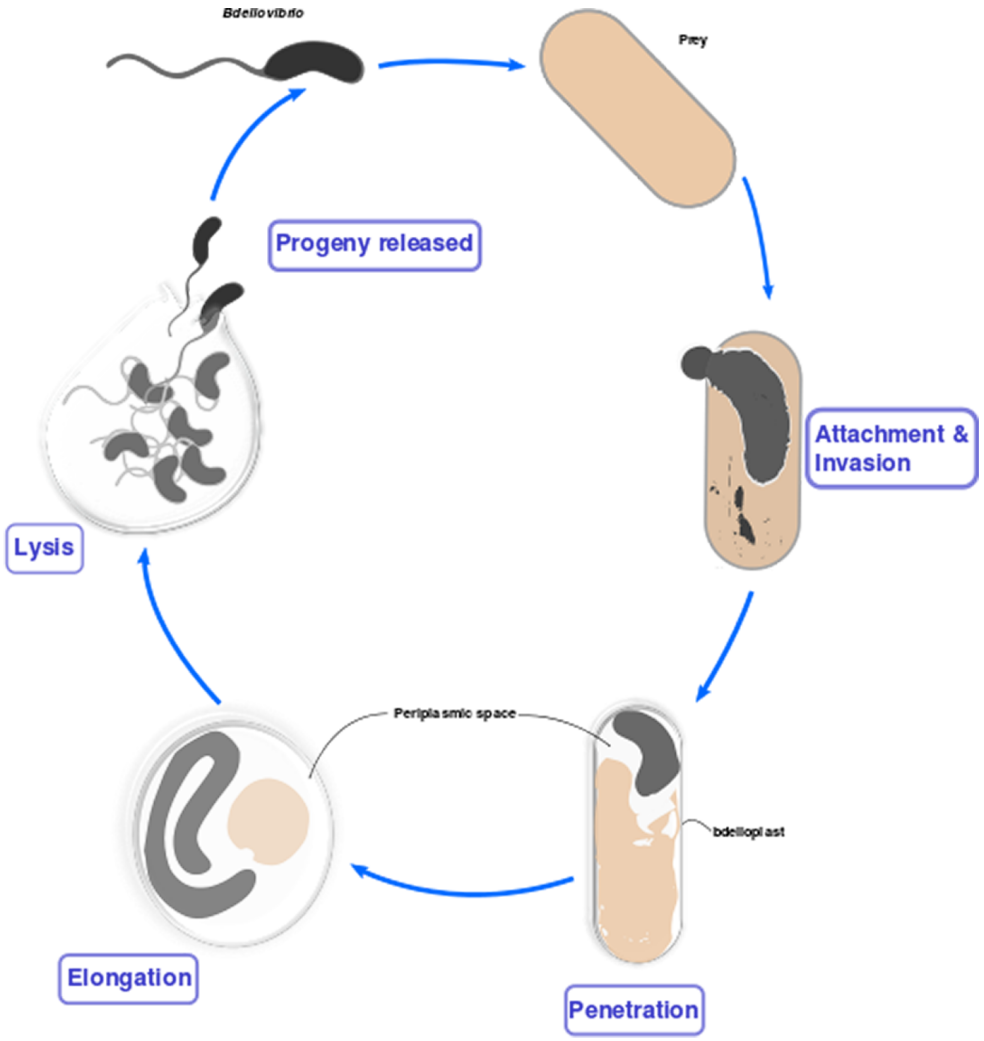


Figure 8 The life cycle of *Bdellovibrio bacteriovorus*.

3.1 Treating infections with *Bdellovibrio bacteriovorus*

In the next activity you will look at some recent research that uses *Bdellovibrio bacteriovorus* to treat infections in an experimental model.

Activity 5 Treating infections with *Bdellovibrio bacteriovorus*

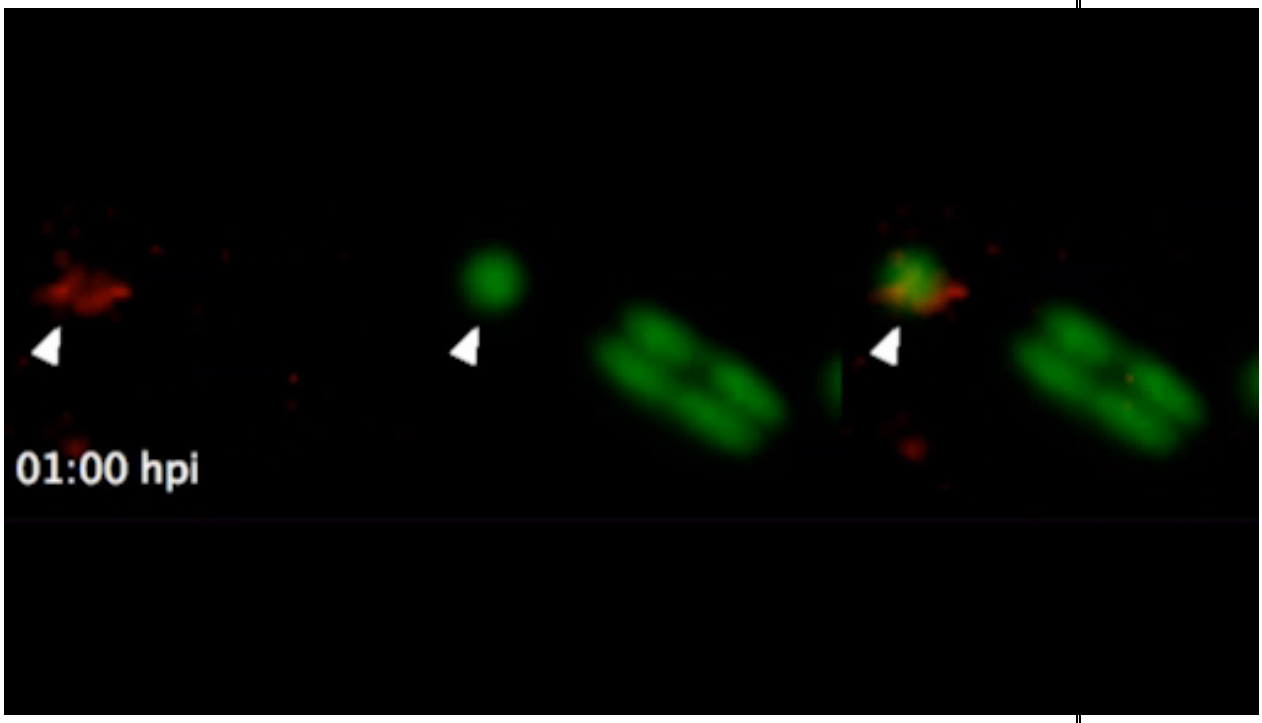
Allow about 15 minutes

Listen to the following audio clip from the BBC's *Inside Science* programme. Liz Sockett from the University of Nottingham talks about research using *Bdellovibrio bacteriovorus* to treat *Shigella* infections in zebrafish. You may also like to watch Video 2 which shows a *Bdellovibrio bacteriovorus* bacterium (labelled in red) preying on a *Shigella* bacterium (labelled in green) inside a zebrafish larva.

Audio content is not available in this format.
Audio 2 Interview with Liz Sockett about research with *Bdellovibrio bacteriovorus*.

Video content is not available in this format.

Video 2 Predation of *Shigella* by *Bdellovibrio bacteriovorus* inside a zebrafish larva (Willis et al., 2016).



Using the information in the interview, complete the following statements about the experiment described by Professor Sockett. The missing words are given below to help you.

Bdellovibrio bacteriovorus

Shigella

Zebrafish

(a) _____ were used as the host for the infection. (b) _____ infections are normally lethal for zebrafish. (c) _____ preys on _____ killing them and stopping the infection.(d) As well as killing the _____ bacteria directly, _____ stimulate the host immune system to help clear the infection.

Answer

a) Zebrafish were used as the host for the infection.

(b) *Shigella* infections are normally lethal for zebrafish.

(c) *Bdellovibrio bacteriovorus* preys on *Shigella*, killing them and stopping the infection.

(d) As well as killing the *Shigella* bacteria directly, *Bdellovibrio bacteriovorus* stimulate the host immune system to help clear the infection.

Now listen to another clip from the same interview in which Professor Sockett discusses how *Bdellovibrio bacteriovorus* could be used as a treatment and the advantages that this treatment might have.

Audio content is not available in this format.
Audio 3 Interview with Liz Sockett about *Bdellovibrio bacteriovorus*.

Note down in the table below any differences between a potential *Bdellovibrio bacteriovorus* treatment and antibiotics that Professor Sockett mentions in the audio clip.

	Bdellovibrio bacteriovorus	**Antibiotics**
Type of treatment	*Provide your answer...*	*Provide your answer...*
Likelihood of resistance arising	*Provide your answer...*	*Provide your answer...*
Tackles antibiotic-resistant bacteria	*Provide your answer...*	*Provide your answer...*

Answer

	Bdellovibrio bacteriovorus	**Antibiotics**
Type of treatment	Local injection at site of infection, e.g. a wound	Systemic – taken orally and spreads throughout the body to treat infections at many sites
Likelihood of resistance arising	Low – living treatment so can adapt as the infectious pathogen changes Uses many enzymes to kill the bacteria, rather than one specific target, so resistance would require many changes in the infectious bacteria	High – one mechanism of action so may require a single change in the bacteria for resistance arise
Tackles antibiotic-resistant bacteria	Yes	No (depending on whether the bacteria are resistant to the prescribed bacteria)

4 A lesson from history

Before antibiotics were discovered, people developed their own approaches to treating infections. These traditional remedies were often developed through trial and error and were passed on by word of mouth. Their effectiveness was very unlikely to have been rigorously tested by a clinical trial.

In the light of the antibiotic era, old remedies can seem bizarre. However, some of them were effective at treating infections and scientists have uncovered some interesting potential antibiotic alternatives among them. You can read about one historical example in the next activity.

Activity 6 An Anglo-Saxon remedy for MRSA

Allow about 10 minutes

> Eat leeks in March and wild garlic in May, and all the year after the physicians may play.
>
> (Traditional Welsh rhyme)

Is there any truth in this rhyme? Read the following short article from *New Scientist* magazine to help you decide!

Article 1: 'Anglo-Saxon remedy kills hospital superbug MRSA'

As the article in Activity 6 mentions, the challenge in developing traditional remedies as antibiotic alternatives is to understand *how* they work. In the following sections, you will look at the scientific mechanisms underlying the antibacterial activity of two traditional remedies that have attracted interest as antibiotic alternatives – natural honey and metals.

4.1 Natural honey

Honey is a natural product that has been widely used in traditional medicine for centuries and is still used in modern medicine.

The antibacterial properties of honey were first reported by the Dutch scientist van Ketel in 1892 (Dustmann, 1979) and it is active against up to 60 types of bacteria. Table 1 summarises some of the clinically important bacteria mentioned in this course that honey has antibacterial activity against.

Table 1 Antibacterial activity of honey against clinically important infections.

Bacterial type	Clinical importance
Staphylococcus aureus	Hospital and community acquired infections
Vibrio cholerae	Cholera
Escherichia coli	Urinary tract infections, septicaemia, wound infections
Pseudomonas aeruginosa	Wound and urinary infections

Honey can be both bacteriostatic and bactericidal, depending on the concentration used. Its antibacterial activity is related to the following four properties.

- High **hydroscopicity**Honey has a high sugar content and is **hydroscopic**; that is, it absorbs moisture from its environment. This causes bacteria to dehydrate in the presence of honey.
- AcidityHoney is acidic, with a pH between 3.2 and 4.5. At this acidic pH, many bacteria cannot grow.

- Hydrogen peroxide contentWhen it is diluted, honey produces the chemical hydrogen peroxide (H_2O_2) from glucose. This chemical reaction requires the enzyme glucose oxidase (Figure 10). H_2O_2 can kill bacterial cells.

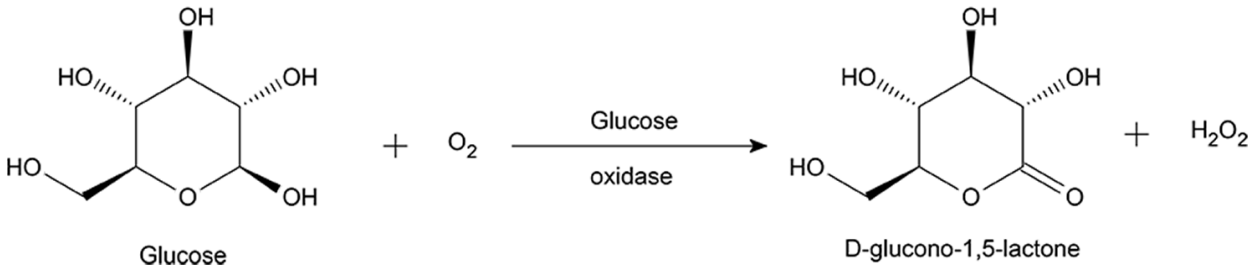


Figure 9 Conversion of glucose to hydrogen peroxide (H_2O_2) and D-glucono-1,5-lactone, catalysed by glucose oxidase. You do not need to study the chemical structures in this figure in detail.

- Phytochemical factors Honey contains a large number of phytochemicals which are chemicals produced by plants. Many phytochemicals have antibacterial properties. For example, allicin (Figure 10), produced by crushing garlic, has antibacterial activity against several bacterial pathogens, including MRSA and *P. aeruginosa*.

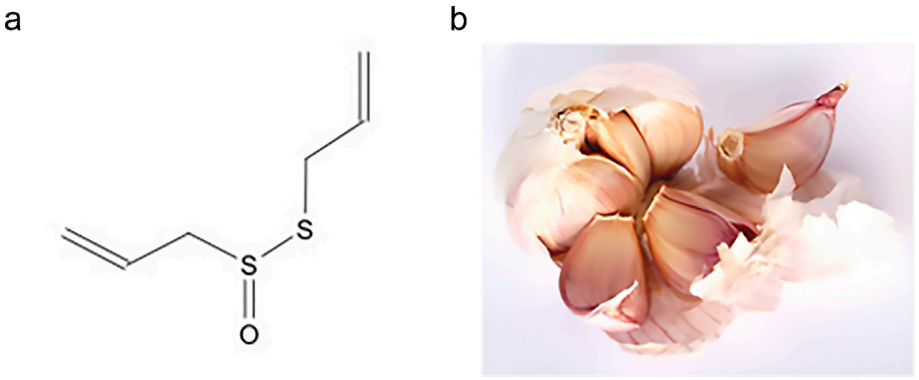


Figure 10 (a) Allicin is produced from (b) crushed garlic and has antibacterial activity against several pathogens. You do not need to study the chemical structure in this figure in detail.

4.2 Metals

In the fourth century BCE, the Greek physician Hippocrates used metals such as copper and silver to treat wounds (Alexander, 2009). Thus metals could be the oldest antimicrobial agents. More recently, dressings impregnated with silver have been used to improve wound healing. However, we are only just starting to understand how these metals exert these effects.

Metals can:

- disrupt biofilms
- act togther with other antibacterial agents
- inhibit bacterial metabolism
- kill bacteria.

The mechanisms that metals use to kill bacteria depend on the chemistry of the metal but they can include:

- producing chemicals that damage DNA
- damaging bacterial proteins
- disrupting the bacterial cell membrane
- preventing bacteria from acquiring the nutrients they need to grow.

It is important to remember that metals can also be toxic to humans, which may limit their effectiveness as antibiotic alternatives.

4.2.1 Modern antibacterial applications of metals

Many modern applications of metals have focused on the use of **nanoparticles** (particles between 1 and 100 nanometres in size) (Figure 11).

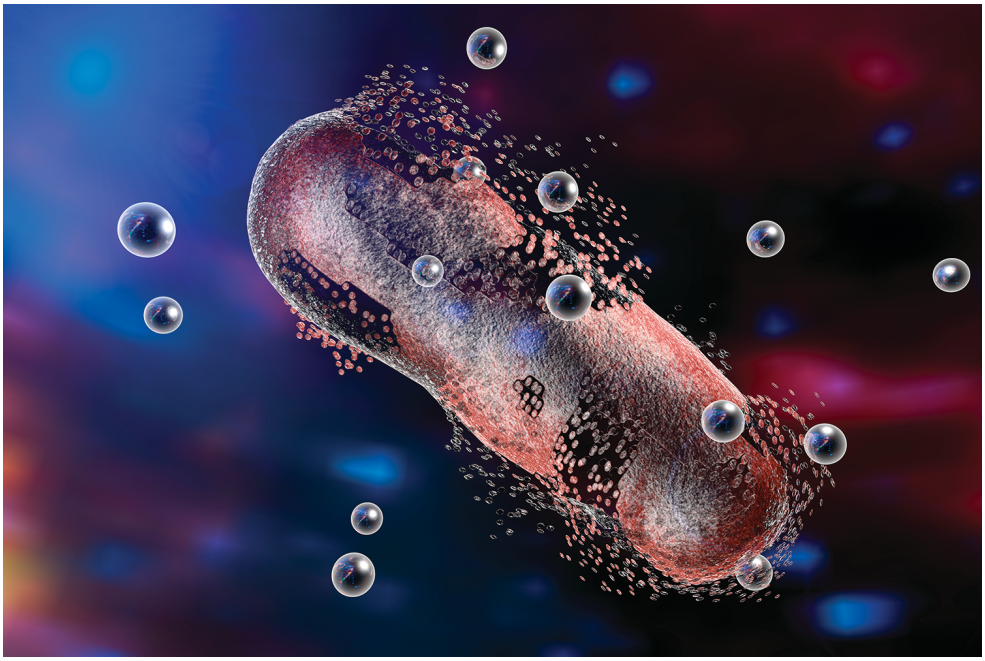


Figure 11 Illustration of silver nanoparticles destroying a bacterium.

Activity 7 Using silver nanoparticles to improve the effectiveness of antibiotics

Allow about 10 minutes

Silver nanoparticles can be used to improve the effectiveness of antibiotics. Read the following short excerpt from an article in the *Guardian* newspaper and then answer the questions below.

> At Boston University, a team of biomedical engineers found that conventional antibiotics could kill between 10 and 1,000 times as many bacteria, including many previously resistant strains, when boosted with silver ions. This ancient remedy for infection – described by the Greeks in 400 BC – works in two ways: first by disrupting bacterial metabolism, causing bacteria to self-destruct; and second by making their cell membranes more permeable to the antibiotic. However, while the research is promising, these drugs still have to pass safety testing, as ingesting too much silver can be toxic for humans.
>
> (Cox, 2017)

1 The researchers showed that silver nanoparticles enhanced the ability of antibiotics to treat Gram-negative bacterial infections. Why do you think this might be? (Hint: you may want to revisit some material in Weeks 2 and 3 to help you answer this question.)

Provide your answer...

Answer

Gram-negative bacteria are resistant to many antibiotics because the antibiotics cannot cross their impermeable membrane. By disrupting the cell membrane of Gram-negative bacteria, silver nanoparticles make it easier for the antibiotic to enter the cell and reach its target.

2 How would improving the effectiveness of antibiotics in treating Gram-negative infections help to tackle antibiotic resistance?

Provide your answer...

Answer

Improving the effectiveness of an antibiotic could reduce either the dose of antibiotic required or the amount of time needed to treat the infection. Both of these will help to reduce antibiotic demand. The ability to treat infections caused by Gram-negative bacteria with new antibiotics may provide alternatives that could be used when the infection is resistant to routinely used antibiotic treatments.

Metals can also be used as antibacterial surfaces. Copper surfaces can kill microbes, including HCAIs such as MRSA, within minutes to hours. The use of antibacterial copper surfaces in hospitals has been suggested to reduce the spread of HCAIs.

Activity 8 Reducing the spread of HCAIs by using copper surfaces

Allow about 10 minutes

Read the following article which describes a trial using copper surfaces to reduce infection transmission in a Birmingham hospital.

Article 2 Copper fittings ‘all but eliminate superbugs’

Where else do you think copper surfaces could be used to reduce infection transmission?

Provide your answer...

Answer

Copper could be used to make medical devices. It could also be used in care homes, schools and other public places; in fact, anywhere that stainless steel is currently used. For example, one of South America's largest theme parks – Fantasilandia in Chile – has recently replaced many of its most frequently touched surfaces with copper to try to reduce infection transmission (Keevil, 2017).

You have now looked at several different alternatives to antibiotics. Many of these alternatives are still a long way from being used routinely to treat infections. It is likely that a combination of these alternatives, together with new and existing antibiotics, will be required to treat infections in the future.

You should now complete this week's quiz which covers material from the last four weeks of this course.

5 This week's quiz

It's now time to complete the Week 8 badged quiz. It is similar to the previous quizzes but this time, instead of answering 5 questions, there will be 15, covering Weeks 5 to 8.

Week 8 compulsory badge quiz

Remember that the quiz counts towards your badge. If you're not successful the first time, you can attempt the quiz again in 24 hours.

Open the quiz in a new tab or window by holding down Ctrl (or Cmd on a Mac) when you click on the link.

6 Summary

This week you learned about some alternatives to antibiotics. You should now be able to identify some antibiotic alternatives and understand some of the science underlying how they work.

You have now reached the end of this course. You should have a better understanding of:

- how antibiotics treat infections
- how bacteria become resistant to antibiotics
- how our use of antibiotics has influenced resistance to them
- the approaches that are being used to tackle resistance.

Finally, you might like to reflect on what you have learned by completing the antibiotic quiz which you first did in Week 1.

Activity 9 Has your opinion changed?

Allow about 5 minutes

In Activity 9 in Week 1, you used the four questions below to help you form your own opinion on antibiotic resistance. Now answer these questions again and compare your answers with those in Week 1. Has what you have learned in this course changed your opinion?

(a) On a scale of 1 (low) to 10 (high), how serious a problem is antibiotic resistance?

Provide your answer...

(b) What, if anything, can be done about antibiotic resistance?

Provide your answer...

(c) Whose responsibility is it to address this problem? You might like to think about:

- whether individuals should take some responsibility or whether it is up to the medical profession, governments, etc.
- the extent to which different countries and regions should work together to address this problem.

Provide your answer...

(d) How urgent a problem is it? How soon should action(s) be taken?

Provide your answer...

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Week 7: Reducing antibiotic use

Introduction

At this point in the course, you should appreciate that our use of antibiotics is contributing to the growing problem of antibiotic resistance. The Review on Antimicrobial Resistance led by Jim O'Neill (2016) proposed a ten-point plan to tackle the problem (Figure 1).

Figure 1 The ten-point plan to tackle antimicrobial resistance (O'Neill, 2016).

Begin this week by watching the following video which introduces the ten-point plan from the O'Neill report.

Video content is not available in this format.
Video 1 Ten steps to reducing antimicrobial resistance.

In Weeks 5 and 6, you looked at two of these ten points – surveillance and drugs. You saw how antibiotic-resistant infections can be tracked and how new antibiotics are being developed. This week, you will look at two other points mentioned in the O'Neill report – sanitation and hygiene, and rapid diagnostics.

By the end of this week, you should be able to:

- reflect on how antibiotic use can be reduced
- understand how infections are transmitted
- describe the role of good hygiene in reducing the spread of infectious diseases
- give examples of how the diagnosis of antibiotic-resistant infections can be improved to reduce antibiotic use.

1 Why do we need to reduce antibiotic use?

Antibiotics have revolutionised modern medicine and demand for them is high. However, as you saw in Week 5, there is a high correlation between the use of antibiotics and antibiotic resistance.

Antibiotic use is often unnecessary, so strategies to lower the demand for antibiotics or reduce their unnecessary use are crucial to tackling resistance. Several points in O'Neill's ten-point plan contribute to lowering demand and reducing antibiotic use (Figure 2).

Figure 2 Strategies to reduce unnecessary use and lower the demand for antibiotics (O'Neill, 2016).

- Public awareness – increasing public awareness of when and how to take antibiotics correctly will reduce unnecessary use and lower demand.
- Sanitation and hygiene – reducing the spread of infectious diseases (including antibiotic-resistant ones) by improving sanitation and hygiene lowers the demand for antibiotics.
- Antibiotics in agriculture and the environment – reducing the unnecessary use of antibiotics in healthy animals to prevent infections in large-scale farming.
- Vaccines and alternatives – vaccines and alternatives to antibiotics that prevent and treat infections will lower the demand for antibiotics. You will learn more about this in Week 8.
- Rapid diagnostics – broad-spectrum antibiotics are often given before the infection is identified, just in case. Tools to rapidly diagnose infections will reduce the unnecessary prescribing of broad-spectrum antibiotics.
- Human capital – increasing the number of trained microbiologists and infection control specialists, while increasing awareness of antibiotic resistance among healthcare professionals, will reduce the unnecessary use of antibiotics by reducing infection rates and altering prescribing habits.

For the rest of this week you are going to look at two of these strategies – sanitation and hygiene, and rapid diagnostics.

2 A simple way to reduce the spread of

infections

You might recall from Week 1 that, before the discovery of antibiotics, the best way to treat infections was to prevent them.

Activity 1 Preventing infections: a lesson from history

Allow about 10 minutes

Watch the video below in which you will see how, even before we knew bacteria existed, the Hungarian physician Ignaz Semmelweis (Figure 3) demonstrated the importance of hygiene in controlling the spread of infections.

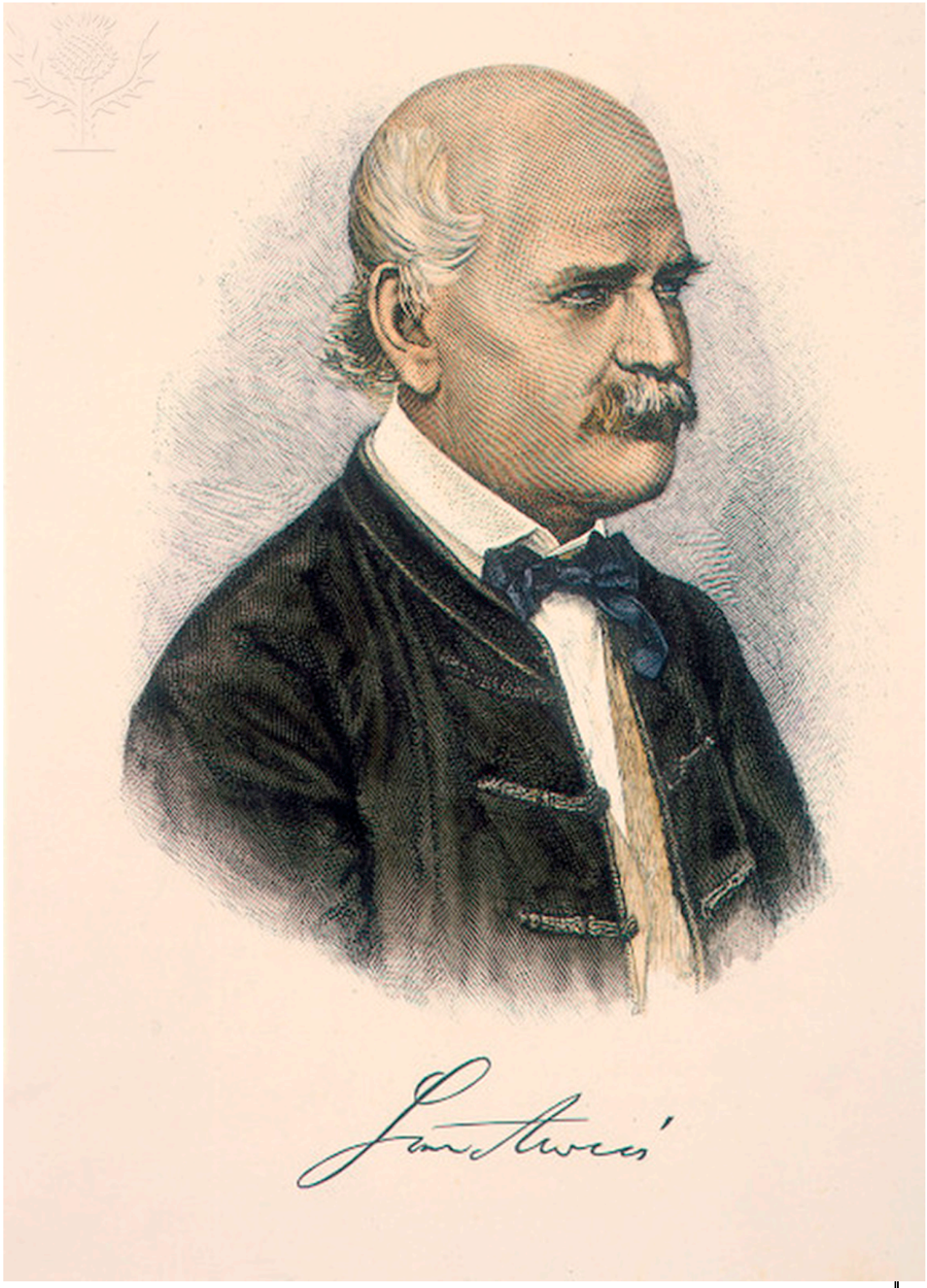

Figure 3 Ignaz Semmelweis (1818–1865).

Video: Ignaz Semmelweis and the birth of infection control

We all now know how important it is to wash our hands but Semmelweis's colleagues refused to accept his findings. Thinking back to Week 1 of this course, what scientific discoveries might have led to a wider acceptance of Semmelweis's hypothesis that hand washing could prevent the spread of infection?

Provide your answer...

Discussion

When Semmelweis proposed his theory that hand washing could control the spread of infections, many people believed that miasmas – bad components of the air – were the cause of disease. Once Louis Pasteur and Robert Koch provided the scientific proof for germ theory, the value of hand washing was appreciated and Semmelweis was given credit for his work.

Sanitation and hygiene have improved since the 19th century but 2.3 billion people in low-middle-income countries (LMICs) do not have basic sanitation facilities (WHO and UNICEF, 2017). Even in high-income countries (HICs), with access to good sanitation, hygienic behaviours are often poorly carried out. Improving sanitation and hygiene can prevent infection, reducing the need for treatment and limiting the opportunities for antibiotic resistance to develop.

To understand how improving sanitation and hygiene can reduce the spread of infectious diseases, you first need to look at how infections are transmitted.

2.1 How infections are transmitted

Bacteria can be transmitted (passed from one individual to another) either directly between people, or indirectly through air, water, food or other objects in the environment. In addition, bacteria can be transmitted from animals to humans via infected meat or water contaminated with animal faeces.

- How might **transmission** from animals to humans lead to antibiotic-resistant infections in humans?
- As you saw in Week 5, healthy farm animals are sometimes fed antibiotics to prevent infections. This increases the chance of resistance to these antibiotics developing. Transmission from animals to humans will increase the risk of resistant bacteria being transmitted to humans.

2.1.1 Direct person-to-person transmission

Bacteria can be transmitted directly between people. This can occur by touching, during unprotected sex, or from a mother to her child during birth or breastfeeding.

2.1.2 Indirect transmission of pathogens

Indirect transmission occurs when an infected person sheds bacteria into the air, water, food or onto other objects in the environment (known collectively as **fomites**), which can then infect someone else. Figure 4 summarises these indirect transmission routes.

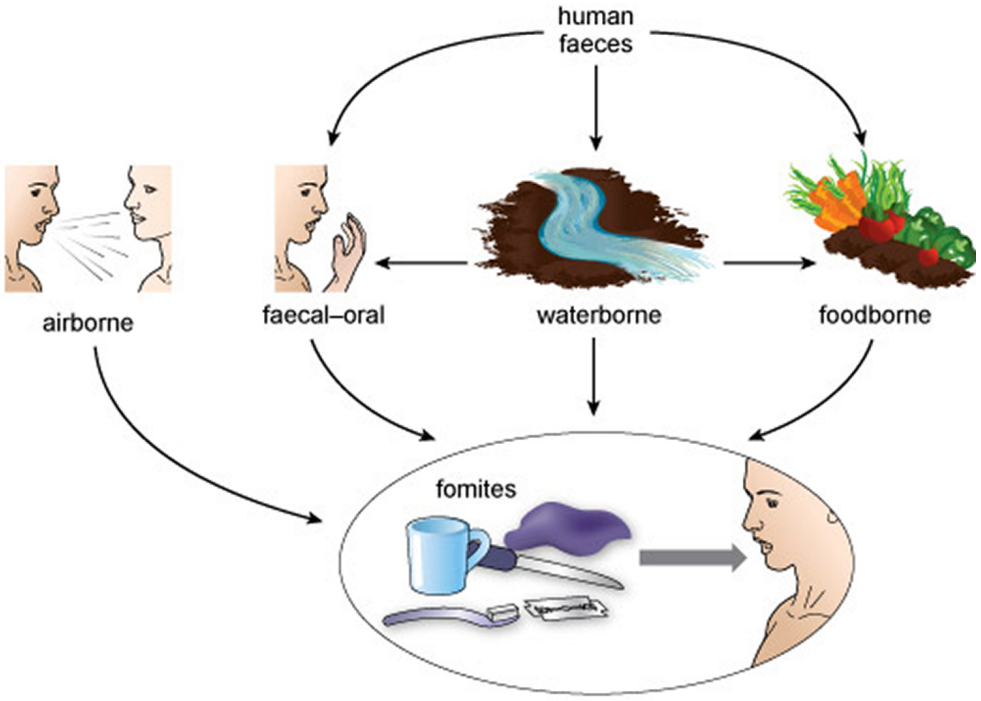

Figure 4 Routes of indirect person-to-person transmission of infection.

Fomites are objects in the environment, such as door handles, cups and pens, that are routinely touched and can transmit infections. Healthcare-associated infections (HCAIs) can easily be indirectly transmitted to susceptible patients via fomites. A quarter of HCAIs are caused by antibiotic-resistant bacteria such as MRSA.

In the next activity, you will look at fomites that might transmit HCAIs.

Activity 2 Fomites and healthcare-associated infections

Allow about 5 minutes

Identify the fomites in this picture of hospital staff in 2001 that might transmit HCAIs.

Figure 5 Hospital staff photographed in 2001.

Provide your answer...

Answer

Neck ties, stethoscopes, long-sleeved clothing, hospital badges worn at waist height and wrist watches could all brush against patients with infections and act as fomites, transmitting the infection to a susceptible individual. Consequently, in UK hospitals today, all staff must have their arms bare below the elbows and wrist watches and neck ties are banned.

Sanitation and hygiene both play an important role in preventing indirect transmission via the routes summarised in Figure 5. Next, you will look at how sanitation and hygiene prevent **faecal–oral transmission** and the effect that this could have on antibiotic use.

2.2 The role of sanitation and hygiene

As you saw in the previous section, pathogens can be transmitted indirectly by the faecal–oral route. Faecal–oral transmission occurs when unclean hands, food or other objects contaminated by faeces enter the mouth. These different faecal–oral transmission routes are illustrated by the ‘F-diagram’ (Figure 6).

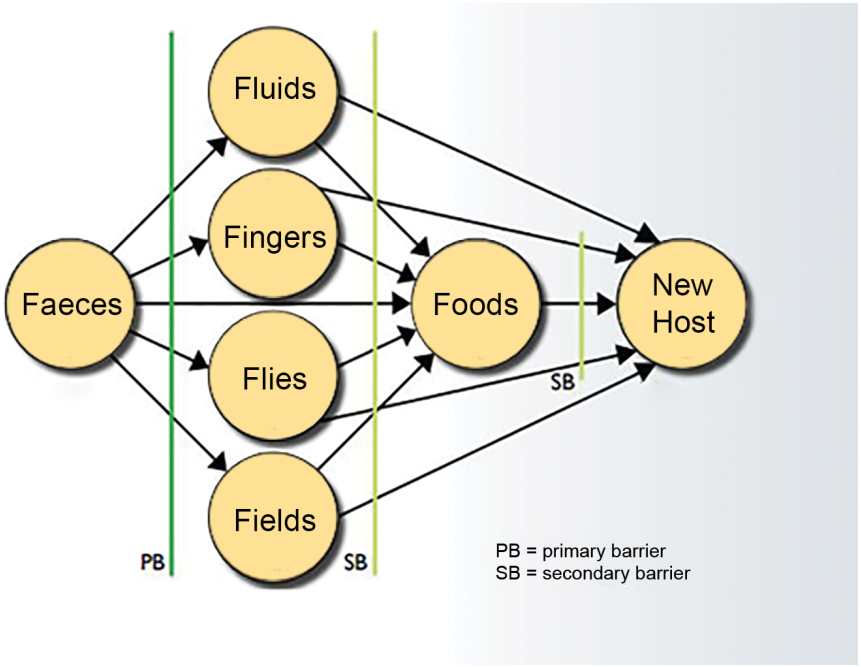

Figure 6 The 'F-diagram': faecal–oral transmission routes and barriers to transmission.

Transmission by these routes can be stopped (or reduced) by sanitation and hygiene barriers (Figure 6).

- A **primary barrier** prevents the initial contact with faeces. This includes improving access to toilets to separate faeces from the environment and washing hands after going to the toilet.
- A **secondary barrier** prevents infectious pathogens being eaten by the new host. This includes using a clean water source, washing hands before preparing or consuming food, and covering food.

Next, you will look at how these hygiene barriers can be used to lower antibiotic demand and reduce unnecessary use.

2.3 The role of hand washing in reducing the spread of bacteria

Unwashed hands transmit bacteria from hand to mouth and by the faecal–oral route (see Video 2).

Video content is not available in this format.
Video 2 Bacteria on our hands.

Hygienic behaviours such as hand washing are an important **public health** measure that can prevent transmission by the faecal–oral route. Hand washing with soap may be 'the single most cost-effective way of reducing the global burden of infectious disease' (Curtis et al., 2011).

- Is hand washing with soap an example of a primary or a secondary hygiene barrier?
- Washing hands after going to the toilet is a primary barrier; washing hands before preparing or consuming food is a secondary barrier.

In the next activity, you will look at the effectiveness of hand washing to remove bacteria.

Activity 3 Investigating the effectiveness of hand washing with soap

Allow about 30 minutes

In this activity you carry out a very simple experiment to look at the effectiveness of hand washing to remove bacteria. Since bacteria are too small to see, you will use glitter to represent the infectious pathogens.

Materials

- Glitter (environmentally friendly glitter can be found online)
- Hand lotion
- Soap and hand-washing facilities
- Paper kitchen towel

Method

(a) Put a small amount of hand lotion on your hands and rub it in so that it is spread out evenly.

(b) Place a pea sized pile of glitter in the palm of one hand and rub your hands together to spread the glitter over both palms.

(c) Note down where the glitter is spread over your hands. You may like to take a photograph or draw a sketch of the areas of your hands with glitter on them. Record your observations in Table 1.

(d) Wipe your hands with a dry piece of kitchen towel.

Now consider the following questions:

- How much of the glitter is still on your hands?
- Has the paper towel effectively removed all of the 'glitter bacteria'?

(e) Record your observations in Table 1.

(f) Now repeat the experiment but at the end of Step c wash your hands in cold water.

(g) Record your observations in Table 1.

(h) Finally repeat the experiment once more, washing your hands in warm water with soap at the end of Step c.

(i) Record your observations in Table 1 and then answer the questions below.

Table 1 Experimental results

Hand washing intervention	Observations
No hand washing	*Provide your answer...*
Dry kitchen towel	*Provide your answer...*
Cold water	*Provide your answer...*
Warm water with soap	*Provide your answer...*

1. Which hand-washing method was the most effective at removing the 'glitter bacteria'?

Provide your answer...

Discussion

Hand washing with soap and warm water is more effective than a paper towel or cold water at removing bacteria.

2. Were there any areas where the 'glitter bacteria' remained on your hands after using all of the hand-washing techniques?

Provide your answer...

Discussion

You may have found ‘glitter bacteria’ between your fingers or on the backs of your hands even after hand washing with soap. These places are frequently missed when washing hands, allowing bacteria to be transmitted.

3. What hand-washing advice would you give to healthcare workers hoping to reduce the spread of antibiotic-resistant bacteria?

Provide your answer...

Discussion

Many hospitals and other healthcare settings now provide training and guidance on effective hand washing as part of their infection control procedures (see Video 3). Posters with this guidance are often displayed near handwashing stations.

Video content is not available in this format.
Video 3 Effective hand washing.

In LMICs, the lack of access to clean water and soap can make sustaining effective hand washing difficult. However, even when clean water and soap are freely available, many people, including healthcare professionals, still do not wash their hands thoroughly (Judah et al., 2010) (Figure 7).

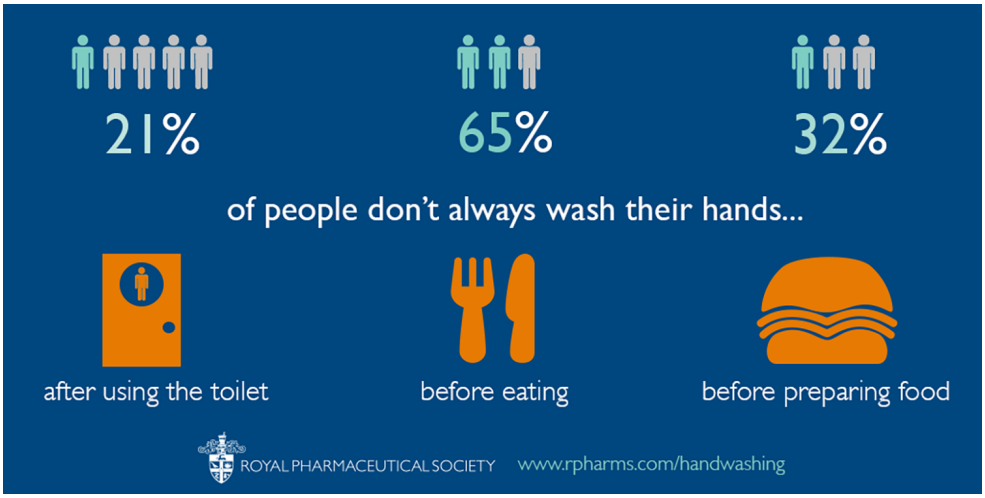

Figure 7 Results of Royal Pharmaceutical Society (2016) hand washing survey.

On average, healthcare workers adhere to recommended hand hygiene procedure only 40% of the time (WHO, 2009) but, as you will see in the next section, improving hand washing in hospitals and other healthcare settings can be an effective way to reduce the spread of antibiotic resistance.

3 Case study: reducing antibiotic resistance by improving hand washing

There have been many campaigns to improve hand washing, particularly in healthcare settings. In the next activity, you will look at how effective these campaigns have been in reducing the transmission of antibiotic-resistant bacteria and, in particular, bacteria that are resistant to cephalosporins.

Activity 4 Improving hygiene to reduce antibiotic-resistance – Part 1

Allow about 15 minutes

Reducing HCAIs

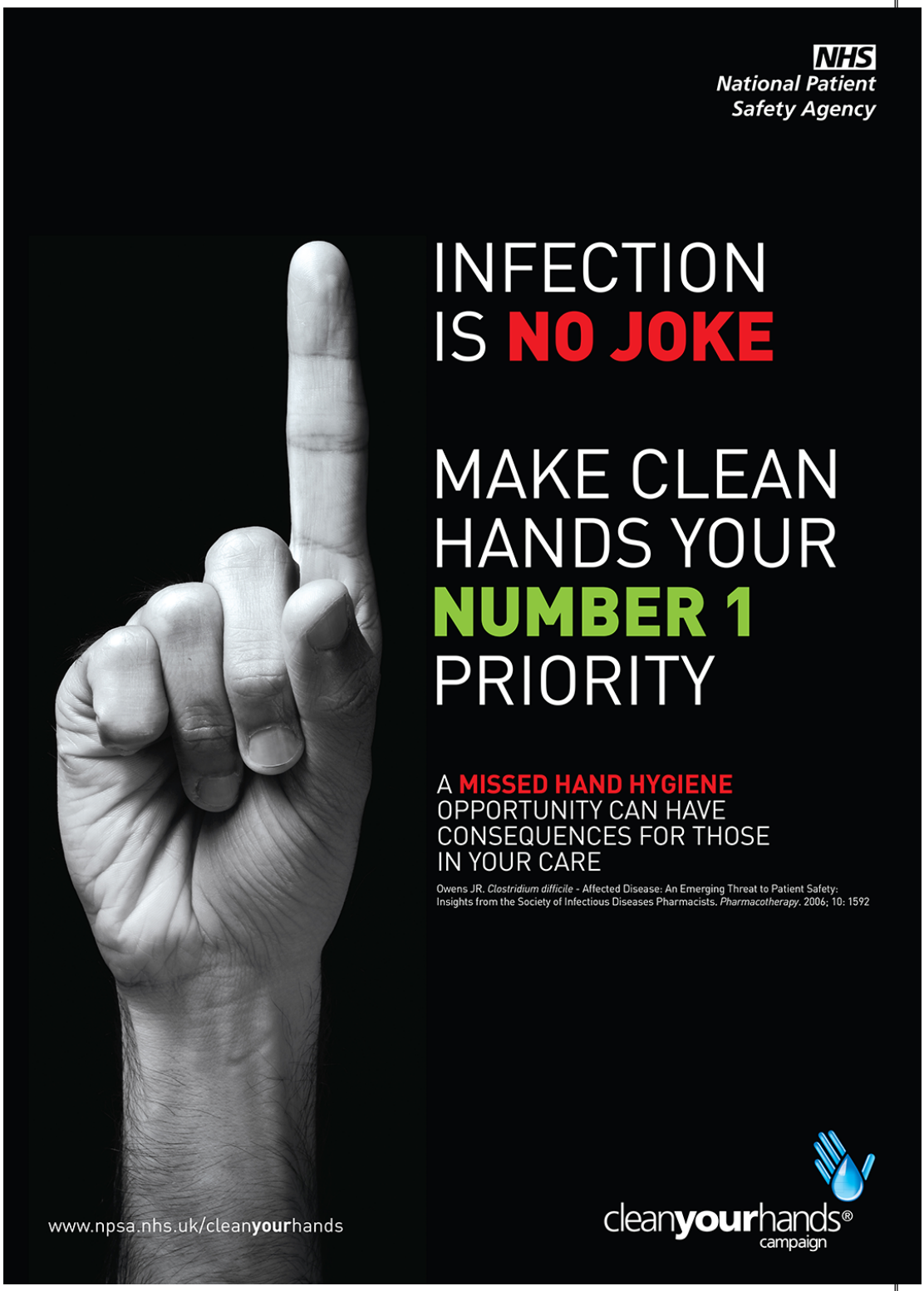

Figure 8 A poster from the 'Clean Your Hands' campaign.

Read the following short article about the 'Clean Your Hands' campaign (Figure 8) and then answer the questions below.

Article 1: Hand Hygiene campaign 'cut superbug infections'.

1 How was hand washing measured in the campaign?

Provide your answer...

Answer

Hand washing was measured by looking at the amount of soap and alcohol-based hand gel being purchased by hospitals.

2 Was hand washing altered during the campaign?

Provide your answer...

Answer

Yes, the amount of alcohol gel and soap purchased by hospitals during the campaign trebled from 22 ml to 60 ml per patient per day.

3 What happened to infection rates during the campaign?

Provide your answer...

Answer

Rates of MRSA infection more than halved while rates of *C. difficile* infection decreased by more than 40%.

4 Is there a correlation between hand washing and infection rates? A correlation simply means that there is a relationship between the two sets of data. For example, there is a positive correlation between antibiotic use and antibiotic resistance: as antibiotic use increases, antibiotic resistance also increases.

Provide your answer...

Answer

Yes, there is a negative correlation between hand washing and the rate of antibiotic-resistant infections: as hand washing increased, rates of infection decreased.

Activity 4 Improving hygiene to reduce antibiotic-resistance – Part 2

Allow about 15 minutes

Reducing the spread of cephalosporin-resistant infections

You might remember from Weeks 3 and 4 that ESBL-producing bacteria are resistant to cephalosporins. In the second part of this activity, you will look at how hand hygiene in intensive care units (ICUs, also known as intensive therapy units (ITUs)) can affect the rate of cephalosporin-resistant infections.

Hospital ICUs must work to reduce the emergence and spread of antibiotic-resistant infections because patients are frequently treated with broad-spectrum antibiotics. They are also at high risk of infection from the use of invasive medical devices such as respiration tubes and catheters.

In 2006, a study aimed to assess the effect of a hand hygiene **intervention** on the number of ESBL-producing *Klebsiella pneumoniae* infections in ICUs (Prospero et al., 2010). The intervention consisted of a training course and the introduction of alcohol-based hand gels.

Two ICUs took part in the study. ICUb continued its normal hand hygiene practices. ICUa introduced the use of alcohol-based hand gel in addition to its previous hand-washing measures.

The number of cases of ESBL-producing *K. pneumoniae* infection was recorded before and after the intervention was introduced. Table 2 shows the findings of the study. The infection rate is recorded as the number of cases of infection per 1000 days of patient hospitalisation.

Table 2 Cases of infection in two ICUs before and after the introduction of a hand hygiene intervention.

	ICUa (with intervention)	ICUb (no intervention)
Pre-intervention cases (no. per 1000 days hospitalisation)	4.50	4.02
Post-intervention cases (no. per 1000 days hospitalisation)	1.68	8.31

Now use the data in the table to answer the following questions.

1 What happened to the number of infection cases in the ICU where the intervention was introduced (ICUa)?

Provide your answer...

Answer

The number of infection cases decreased during the intervention period from 4.50 cases per 1000 days hospitalisation to 1.68 cases per 1000 days hospitalisation.

2 What happened to the number of infection cases in the ICU without the intervention (ICUb)?

Provide your answer...

Answer

The number of infection cases increased during the intervention period from 4.02 cases per 1000 days hospitalisation to 8.31 cases per 1000 days hospitalisation.

3 Was the hand-washing intervention successful?

Provide your answer...

Answer

Yes, the number of infection cases decreased in the ICU with the intervention but increased in the ICU without the intervention. This suggests that using the alcohol-based hand gel was effective at reducing infections.

4 What effect would you expect the campaigns in this activity to have on the demand for antibiotics?

Provide your answer...

Answer

Improving hand washing and decreasing the transmission of antibiotic-resistant infections should decrease the demand for antibiotics by lowering the number of infections requiring treatment.

In Sections 2 and 3 you saw how improving hygiene can act as a barrier to pathogen transmission, reducing the unnecessary use of, and lowering the demand for, antibiotics. Next, you will look at another way to reduce antibiotic use – using rapid diagnostics to reduce the unnecessary prescribing of broad-spectrum antibiotics.

4 Rapid infection diagnostics

Prescribing unnecessary antibiotics increases the chances of antibiotic resistance developing. This is often because broad-spectrum antibiotics are prescribed before the infection is diagnosed. Reducing the amount of time taken to diagnose an infection will help to reduce the unnecessary prescribing of antibiotics (Figure 9). This is the goal of rapid diagnostics.

Figure 9 Unnecessary prescription of antibiotics to treat respiratory problems in the USA (O'Neill, 2016).

4.1 Traditional approaches to infection diagnosis

Your family doctor often relies on **empirical diagnosis** to decide what kind of infection you have. This means that they use their clinical experience to diagnose the infection based on your symptoms.

- Why might an empirical diagnosis lead to unnecessary antibiotics being prescribed?
- Empirical diagnoses rely on symptoms to diagnose an infection. For example, a persistent cough and fever could be symptoms of a chest infection. However, infections can be bacterial, viral or fungal and an empirical diagnosis cannot determine the cause of the infection. Antibiotics will not treat infections caused by viruses or fungi, therefore a prescription for antibiotics would be unnecessary in these cases.

In many cases a family doctor will send a sample of the infection for laboratory diagnostic testing. In the next activity, you reflect on your personal experience of being treated for an infection.

Activity 5 Being prescribed antibiotics

Allow about 5 minutes

Think about a time when you, or someone you know, was prescribed antibiotics. Then answer the questions below, based on your experience.

1 Did the doctor send a sample for testing?

Provide your answer...

2 How long did you have to wait for the results?

Provide your answer...

Discussion

If your family doctor suspects that you have a bacterial infection, they will often send samples for traditional laboratory diagnostic tests. However, as you will see below, it can take up to a week to get the results of these tests. Meanwhile, you might be prescribed broad-spectrum antibiotics to try to treat the infection and prevent it from becoming worse.

Traditional laboratory diagnostic tests rely on culturing the bacteria for at least 36 hours to determine the type of infection and the drugs that it is susceptible to (see Video 4). This can delay the prescription of narrow-spectrum antibiotics that specifically target the infection.

Video content is not available in this format.
Video 4 Culturing bacteria to test for antibiotic susceptibility.

While the results of a traditional laboratory diagnostic test are being processed, broad-spectrum antibiotics are often prescribed to try to treat the infection before diagnosis. In some cases, the treatment will be effective. However, if the infection is not caused by pathogenic bacteria, or if the infection-causing bacteria are resistant to the prescribed antibiotic, another prescription may be required.

Rapid diagnostic tests do not rely on culturing bacteria so they can reduce the time taken to diagnose the infection (Figure 10). This means that doctors can quickly prescribe a treatment that effectively and specifically targets the infection. This helps to reduce the unnecessary prescribing of broad-spectrum antibiotics.

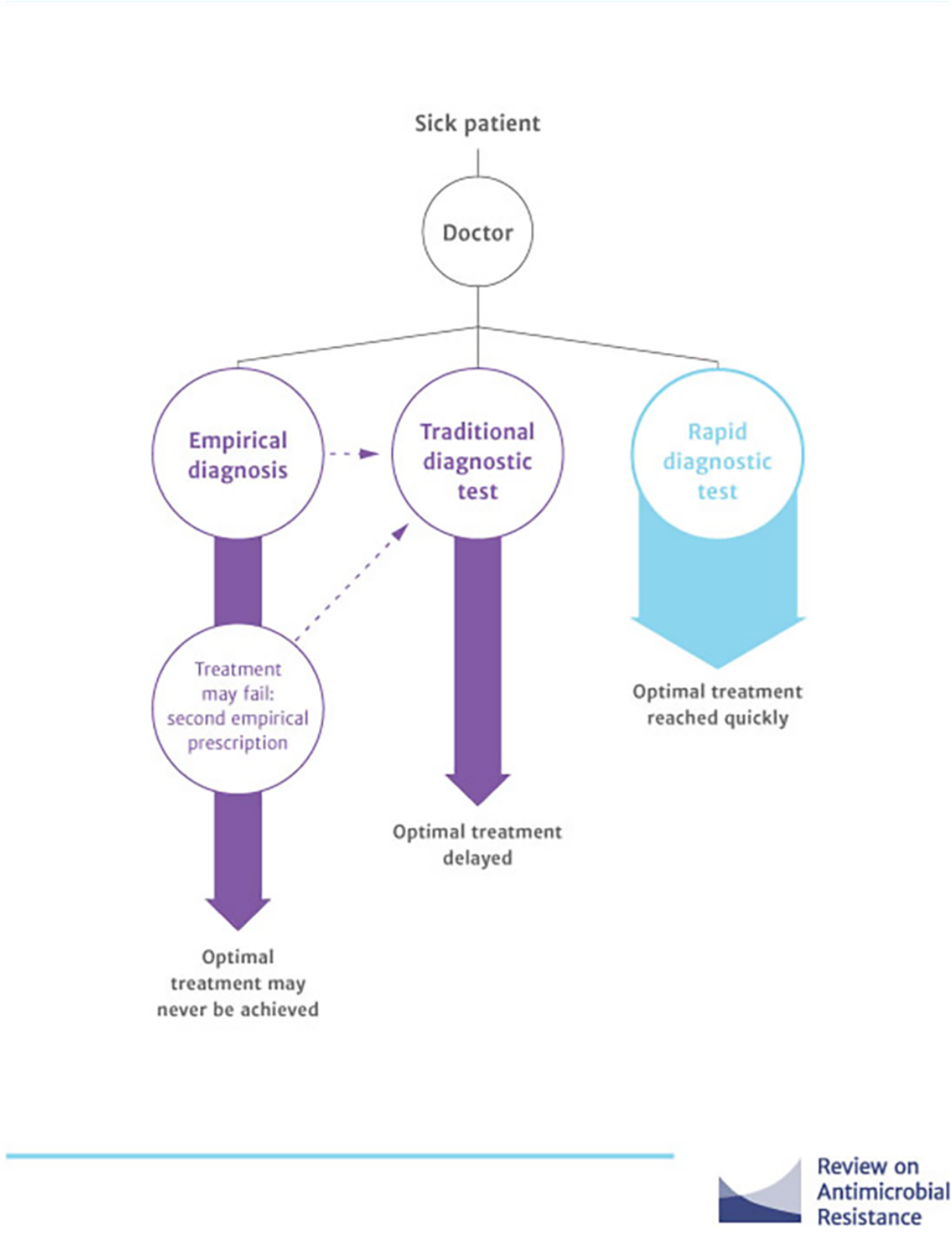

Figure 10 Empirical and traditional diagnoses can delay optimal treatment but rapid diagnostic tests allow optimum treatments to be prescribed more quickly (O'Neill, 2016).

In the next section, you will look at rapid diagnostic tests for infection more closely.

4.2 The perfect rapid diagnostic test

The perfect diagnostic test for bacterial infection should answer four questions:

- Is the infection bacterial or viral?
- If the infection is bacterial, what type of bacteria is causing the infection?
- Are the bacteria resistant to a particular drug?
- Which drugs are the bacteria susceptible to?

Traditional diagnostic tests – such as those shown in Video 4 – can answer all four questions but not quickly. The challenge for rapid diagnostics is to answer these questions within minutes so that doctors and other healthcare professionals can decide which antibiotics are needed.

4.3 What rapid diagnostic tests detect

There are many rapid diagnostic tests in development and clinical use. In this course, it is impossible for you to look at all of them. Broadly speaking, they are designed to detect either the pathogen or the patient's response to pathogen infection.

4.3.1 Detecting the patient infection response

Some tests detect chemicals produced by the patient in response to infection – these are known as **biomarkers**. One example is the chemical **procalcitonin (PCT)** which is made in response to bacterial, but not viral, infections. It can easily be detected in a blood sample taken from the patient.

In the following video you will see how PCT tests can be used in clinical practice to reduce the unnecessary use of antibiotics. You can then practise interpreting PCT levels in Activity 6.

Video content is not available in this format.

Video 5 How rapid diagnostic testing for PCT reduces unnecessary antibiotic prescribing.

Activity 6 Interpreting PCT levels

Allow about 10 minutes

Figure 11 shows the levels of PCT – in micrograms (µg) of PCT per litre of serum – in a patient with an infection and receiving treatment over 3 days (72 hours).

Study Figure 11 carefully and then answer the questions below.

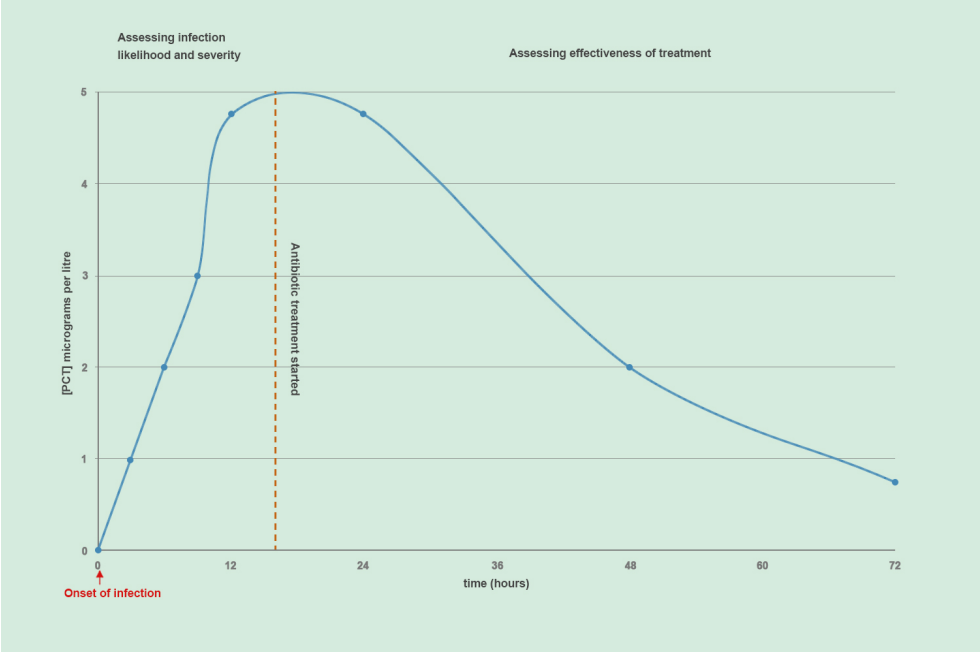

Figure 11 Levels of procalcitonin in a patient with an infection.

1 How do the patient's PCT levels change over the 72-hour period?

Provide your answer...

Answer

The patient's PCT levels rise from 0 at infection onset to 5 micrograms per litre after approximately 16 hours. When antibiotic treatment starts, PCT levels decline from 5 micrograms per litre to less than 1 microgram per litre after 72 hours.

2 Does the patient have a bacterial infection? How can you tell?

Provide your answer...

Answer

Yes, the patient's PCT levels rise from 0 at infection onset to 5 micrograms per litre after approximately 16 hours. Elevated PCT levels indicate that the patient has a bacterial, rather than a viral, infection.

3 Is the antibiotic treatment effective? How can you tell?

Provide your answer...

Answer

Yes. Once, antibiotic treatment has started, the patient's PCT levels decrease from 5 micrograms per litre to less than 1 microgram per litre, indicating that the patient's infection has cleared and the antibiotic treatment is effective.

4 How could measuring the PCT levels in a patient be used to reduce unnecessary antibiotic use?

Provide your answer...

Answer

Decreasing PCT levels show that the infection is being effectively treated by the prescribed antibiotics. If PCT levels remain high after treatment, doctors could quickly prescribe an alternative treatment, reducing the need to take ineffective antibiotics for an extended period.

4.3.2 Detecting the pathogen

Many rapid diagnostic tests detect the presence of infectious bacteria directly. Some tests can detect the presence of bacterial DNA, or antibiotic resistance genes in the sample, by a laboratory technique called **polymerase chain reaction (PCR)**. This is known as **molecular diagnostics** which can be an extremely powerful diagnostic tool. Other tests rely on chemical reactions that cause a detectable colour change when bacteria (or a bacterial enzyme or product) are present in the sample.

The information these tests provide can vary. Some, such as the urinary tract infection (UTI) dipstick test, detect the presence of bacteria in a sample. Others, such as the Nordmann/Doret/Poirel test, can provide information on the bacteria's susceptibility to antibiotics.

4.3.3 The UTI dipstick test

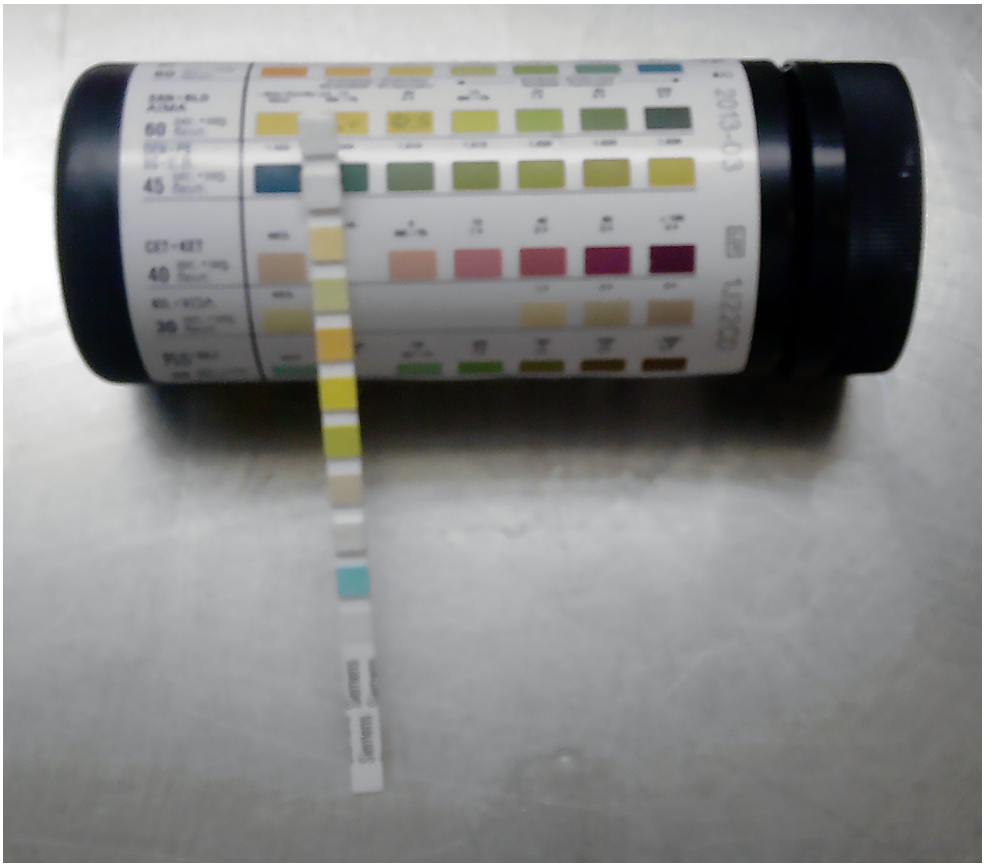

Figure 12 Urine test strips.

Several Gram-negative bacteria cause urinary infections, for example *E. coli* and *Klebsiella*. They produce an enzyme called nitrate reductase and can convert the nitrates in urine to nitrites. You do not need to know the details of this reaction, just that these nitrites can be detected using the Greiss reaction in which nitrites react to produce a pink dye. The presence of pink on the dipstick test can therefore indicate a bacterial urinary infection, although this test is not completely reliable.

4.3.4 The Nordmann/Dortet/Poirel test

The Nordmann/Dortet/Poirel (NDP) test can detect the presence of ESBL-producing bacteria in blood samples in less than two hours (Nordmann et al., 2012). As you might remember from Week 4, ESBLs are a major determinant of resistance to cephalosporin antibiotics. The presence of ESBLs in a bacterial strain can be used to diagnose a cephalosporin-resistant infection. The NDP test detects the enzyme activity of ESBLs in the sample.

- What enzymatic reaction do ESBLs catalyse?
- Recall from Week 3 that β-lactamases destroy β-lactam antibiotics by hydrolysing the β-lactam ring.

When cefotaxime (a third-generation cephalosporin) is hydrolysed by ESBLs, it results in **acidification**; that is, the sample becomes more acidic. In the NDP test, this acidification can be measured as a colour change in the sample using a **pH indicator**. The colour of a sample gives a visible indication of the presence of ESBL-producing bacteria (Figure 13).

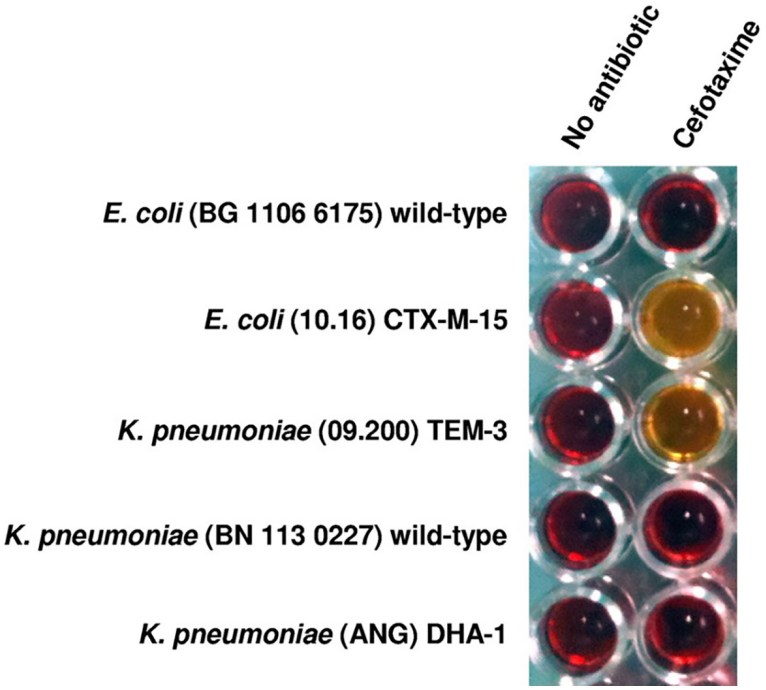

Figure 13 The NDP test to identify ESBL-producing bacteria. Samples containing ESBL-producing bacteria (*E. coli* (10.16) CTX-M-15 and *K. pneumoniae* (09.200) TEM-3) hydrolyse cefotaxime, leading to acidification which is detected as a change from red to orange using a pH indicator (Nordmann et al., 2012). You do not need to study the details of this figure.

4.4 The future for rapid diagnostics

Although rapid diagnostic tests are faster than traditional diagnostic tests at diagnosing an infection, they still often need to be carried out in a laboratory by highly trained staff. Since antibiotics are often given in non-hospital settings, particularly in LMICs, delivering diagnostic information at the **point-of-care (POC)** is key to reducing unnecessary antibiotic use. The POC is where a patient presents with the illness, for example a doctor's surgery, hospital, care home, pharmacy or mobile clinic.

In the next activity you will look at the factors that are important when designing a POC test.

Activity 7 Designing the perfect point-of-care diagnostic test

Allow about 10 minutes

The Longitude prize is a competition to design a POC diagnostic test. Figure 14 is taken from the Longitude prize website and illustrates some of the factors that need to be considered when designing a POC diagnostic test.

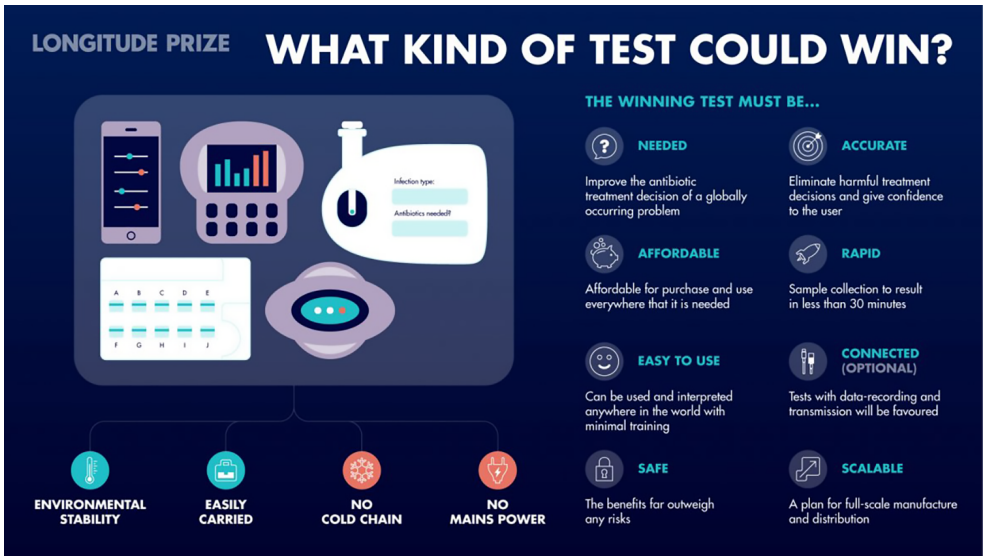

Figure 14 Factors to be considered when designing a POC diagnostic test.

Imagine that you are part of the design team developing a new POC diagnostic test for use in mobile clinics in rural Africa. How would the factors above influence the design of your device?

Discussion

You may have noted down several factors, some that we considered include:

- Mobile clinics in LMICs may not have access to reliable refrigeration or mains power therefore the POC test should be able to be stored at ambient temperature and should operate without the need for external power sources.
- Clinics may not be staffed by highly-trained laboratory technicians so the test should be easy to use and interpret with minimal training.
- Clinics may be in remote locations and patients may have to travel long distances to attend therefore the results should be rapidly obtained so that patients can be diagnosed and prescribed appropriate treatment without needing to return to the clinic.

5 This week's quiz

Well done – you have reached the end of Week 7 and can now do the quiz to test your learning.

Week 7 practice quiz

Open the quiz in a new tab or window (by holding down Ctrl [or Cmd on a Mac] when you click the link). Return here when you have finished it.

6 Summary

This week, you learned more about the relationship between antibiotic use and antibiotic resistance. You should now appreciate the role of hygiene and sanitation and rapid diagnostics in reducing demand and preventing the unnecessary use of antibiotics. You should also understand how pathogens are transmitted and the role of good hygiene in blocking this transmission.

You also learned that traditional diagnostic methods can contribute to unnecessary antibiotic use. You should now be able to give some examples of rapid diagnostic tests and appreciate their role in tackling antibiotic resistance.

You should now be able to:

- reflect on how antibiotic use can be reduced
- understand how infections are transmitted
- describe the role of good hygiene in reducing the spread of infectious diseases
- give examples of how the diagnosis of antibiotic-resistant infections can be improved to reduce antibiotic use.

In the final week of this course, you will look at some possible alternatives to antibiotics that could also be used to prevent unnecessary antibiotic use and reduce demand.

You can now go to Week 8.

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Audio-visual

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Figure 9: taken from: PharmaFactz; Medicinal Chemistry of Beta-Lactam Antibiotics; © PharmaFactz 2018

Audio-visual

Video 2: *Penicillin rediscovered*, clip from Britains Greatest Invention (broadcast on BBC) courtesy Thoroughly Modern Media

Video 3: *Mass production of penicillin*, Pain, Pus and Poison, Episode 2, © BBC.

Video 4: South American leafcutter ants, clip from BBC Britains Greatest Invention (2017) courtesy of Thoroughly Modern Media

Audio 1: Cephalosporins-Chemistry in its element, Chemistry World; https://www.chemistryworld.com.

Audio 2 Inside Science, Radio 4, International Year of Soil, broadcast 15/1/2015. © BBC

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Article 1: Brute force can overcome antibiotic resistance (UCL 2017), courtesy of Joseph Ndieyira; UCL

Week 7

Images

Figures 1 and 2: from 'Review on Antimicrobial Resistance.' https://amr-review.org/sites/default/files/HI%26S%20Infographic_1_v4%20white.jpg https://creatiand 5vecommons.org/licenses/by/4.0/

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Figure 7: Royal Pharmaceutical Society

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Figure 9: '*Tackling drug-resistant infections globally: Final report and recommendations*'; HM Government and Wellcome Trust; https://creativecommons.org/licenses/by/4.0/

Figure10: https://amr-review.org/infographics.html
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Figure 11: Safely Reduce Antiobiotic Exposure; BRAHMS Procalcitonin (PCT): Thermo-Fisher Scientific

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Figure 13: taken from Journal of Clinical Microbiology; Rapid Detection of Extended-Spectrum-ß-Lactamase-Producing Enterobacteriaceae Patrice Nordmann, Laurent Dortet and Laurent Poirel

Figure 14: Nesta; https://creativecommons.org/licenses/by-nc-sa/4.0/

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Video 1: Ten steps to reducing antimicrobial resistance.The Association of the British Pharmaceutical Industry; 10 Steps to Reducing AMR - The Review on Antimicrobial Resistance

Video 5: Bang Goes the Theory, Series 7, broadcast 11 March 2013, © BBC

Week 8

Images

Figure 1: from 'Review on Antimicrobial Resistance.'
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Figure 3: Janice Carr (2005) https://phil.cdc.gov/Details.aspx?pid=7483

Figure 5: Activity 4; courtesy Rachel McMullan

Figure 6: Activity 4; adapted from
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563964/figure/F3/

Figure 7: Science Photo Library/UIG

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https://commons.wikimedia.org/wiki/File:Bellovibrio-cycle.svg

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https://creativecommons.org/publicdomain/zero/1.0/deed.en

Figure 11: Kateryna Kon/Science Photo Library

Audio-visual

Video 1: How vaccines help to beat superbugs; Vaccines Today

Video 2; Predation of Shigella by Bdellovibrio bacteriovorus inside a zebrafish larva (Willis et al., 2016). Predation of GFP - Shigella by mCherry

Audio 1: *Interview with Martha Clokie on phage therapy*, Inside Science, Radio 4, © BBC 2016

Audio 2: *Interview with Liz Sockett about research with Bdellovibrio bacteriovorus*, Inside Science; Radio 4 © BBC 2016

Audio 3: *Interview with Liz Sockett about research with Bdellovibrio bacteriovorus*, Inside Science; Radio 4 © BBC 2016

Text

Article 1: courtesy © New Scientist Ltd (2015) https://www.newscientist.com/article/dn27263-anglo-saxon-remedy-kills-hospital-superbug-mrsa/

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