Antimicrobial Resistance and One Health

Miss: I saw on the news that there is an antibiotic resistance crisis – what is this?

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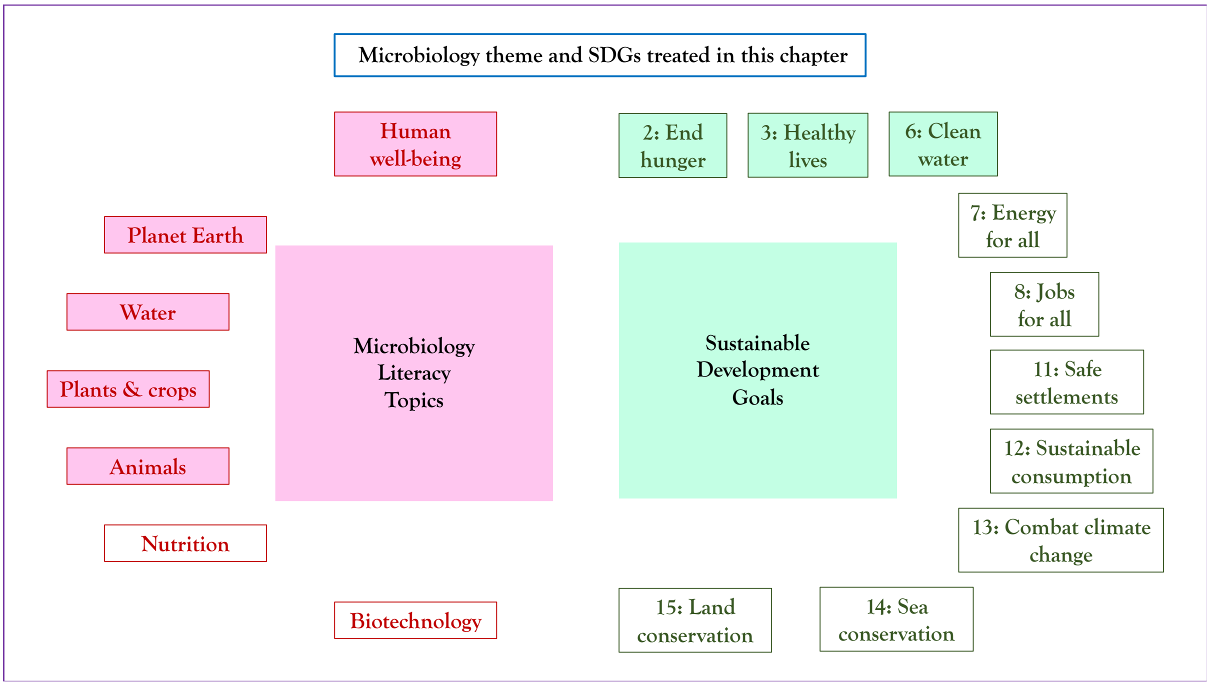
Antimicrobial Resistance (AMR) and One Health

Storyline

Antimicrobial resistance (AMR) is a multifaceted problem. Historical approaches to tackle the problem have siloed human, animal, and environmental aspects independently. The One Health approach to AMR combines the clinical, agricultural, environmental, and societal factors together to consider a holistic picture of AMR, which reveals multisectoral dependencies and potential solutions. This teaching aid will explain the basic microbiology of AMR and some of the problems we need to overcome to manage AMR in the future. We detail numerous AMR case studies, which are explained using a One Health perspective and suggest student exercises and activities to reinforce learning about AMR

The Microbiology and Societal Context

The microbiology: pathogens; infections; antibiotics; antibiotic resistance; One Health. *And, peripherally for completeness of the storyline*: Misuse of antibiotics; empty pipelines of new antibiotics; low commercial interest in antibiotic discovery research; animal husbandry; aquaculture; fruit crops. *Sustainability issues:* health; food production.



AMR: the Microbiology

1. ***Bacteria and disease – why we use antibiotics.*** Microbes are almost everywhere, and the vast majority of them are harmless to humans, animals, and plants. Many are beneficial as they play positive, and often essential, roles in human, animal and plant health. For example, they provide us with essential vitamins including vitamin K and those of the B group, they recycle our waste, help us digest our food and protect our bodies from infections.

Some microbes do however cause disease and these are called pathogens or pathogenic microbes. Pathogenic microbes include bacteria, fungi, and viruses. In this framework we will only discuss pathogenic bacteria, which are single-celled, prokaryotic organisms. When bacterial pathogens cause disease there are three possible outcomes; 1) either the human, animal or plant succumb to the disease, 2) the human, animal or plant lives with the pathogenic bacteria or 3) the bacterial infection is cleared by the host immune system, or by using antibiotics.

Antibiotics are chemical compounds that we use to kill, or stop the growth of, pathogenic bacteria in or on humans, animals, and plants. In general, they are incredibly powerful and stop infections within minutes or hours. When an antibiotic is used to treat an infection, the procedure is known as therapy and the antibiotic is known as the therapeutic agent. When antibiotics are used pre-emptively to prevent infection, for example after an operation during which a wound is created that provides pathogens with more easy entry into our body, this is known as prophylaxis. They can also be given to an entire herd of animals if a single animal shows signs of illness; this is known as metaphylaxis.

Antibiotics are just one class of compounds that are collectively referred to as antimicrobials. Antiseptics and disinfectants are also antimicrobials. For the purposes of this lesson, we will focus on antibiotics.

The antibiotics we use are either naturally produced by other bacteria and fungi, or synthetically designed by scientists in a laboratory. These antibiotics have been revolutionary in our ability to treat infectious diseases; they underpin a modern functioning healthcare system, international food production systems and arguably societal development. But not all bacteria are sensitive to all antibiotics, so there has been a determined search over many years for new antibiotics. As a result, until fairly recently, doctors have been able to determine which antibiotics inhibit the pathogen causing an infection and then select just the one that works best.

2. ***Resistance to antibiotics.*** However, scientists understood more than 70 years ago that if antibiotics are used inappropriately, resistance to them can quickly emerge. These warnings have been largely ignored for decades.

Bacteria are masters of adaptation. Given enough time, they will very likely find a way to overcome the effects of any antimicrobial we use. Because of this adaptability and our long-term inappropriate use of antibiotics, which has provided a suitable evolutionary pressure for the selection of resistance, bacteria have collectively evolved resistance to every single antibiotic we have ever used. When we say that bacteria are resistant to an antibiotic it means that that antibiotic is no longer able to kill it or stop it growing. As a consequence, we must treat the disease with a different antibiotic. It is concerning that increasing numbers of bacteria have developed resistance to multiple antibiotics and, as a result, the number of effective antibiotics that are available for treatment progressively diminishes. Clinicians talk about antibiotics of last resort, which means that only one or perhaps two antibiotics are still effective (for the moment) for treatment of some pathogens. In the future, if this resistance trend continues, we may find that successfully treating bacterial diseases with antibiotics becomes impossible.

3. ***The dwindling supply of new antibiotics.*** An obvious solution for this growing problem would be to simply develop more antibiotics. However, this is difficult for several reasons. Discovering new antibiotic compounds (either natural or synthetic) with novel bacterial targets, which do not affect human, animal or plant hosts is time consuming and expensive. Once a new discovery is made, there is a long process (10-15 years) of research and development, clinical trials, regulatory hurdles to navigate and post-regulatory marketing and distribution issues to tackle before a new antibiotic comes to market. The entire process to develop and launch a new antibiotic is estimated to cost more than $1billion US dollars. At the end of this process companies may not be able to sell enough of the antibiotic to make a profit on the initial

investment. For these reasons, pharmaceutical companies are abandoning the antibiotic discovery market for something with greater profitability. Commercial research and development on antibiotics is drying up and the number of new antibiotics on the horizon is very small.

4. ***The need to restrict the use of new antibiotics.*** Another disincentive for commercial involvement in antibiotic discovery results from the issue of antibiotic resistance. The last thing we want to do with a new antibiotic is use it widely, as this would provide the right selective conditions for the rapid emergence of resistance. New antibiotics should preferably be kept in reserve for highly resistant bacterial infections we are unable to treat with other antibiotics. This restricted use would obviously negatively impact sales. This poor economic outcome for new antibiotics means there are very few companies large enough to do this job which are still actively participating in antibiotic discovery and why, consequently, our antibiotic pipeline is running dry. Once no effective antibiotics are available, certain procedures such as surgical and dental operations may be too risky to undertake and food production will be in jeopardy, as well as the livelihoods of those involved in food production.

5. ***How microbes resist antibiotics.*** Bacteria can develop resistance to antibiotics using multiple mechanisms. These include

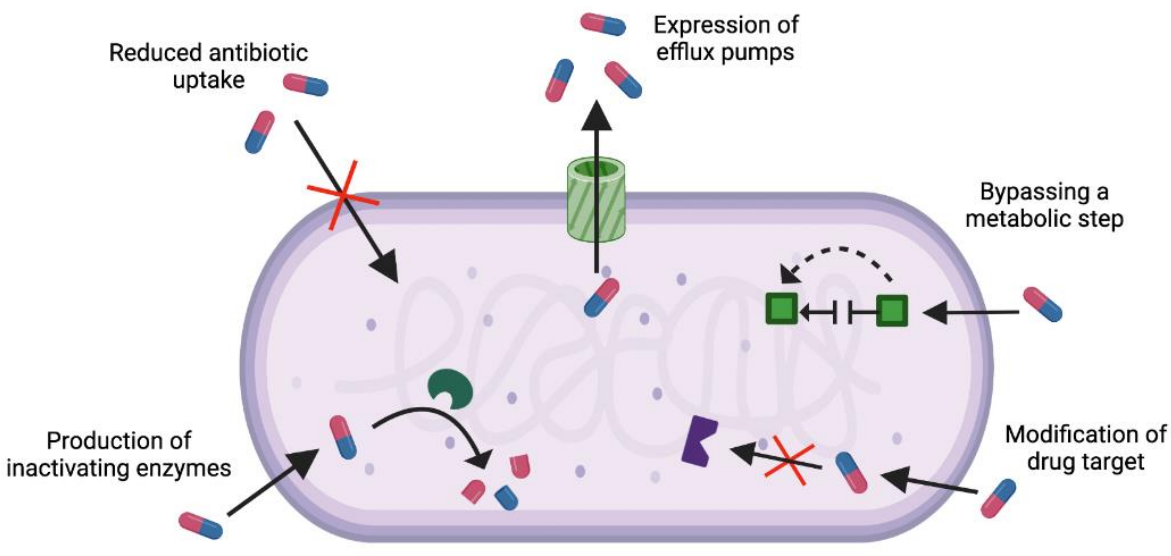
a. producing an enzyme that destroys the antibiotic (e.g. the case for penicillin),

b. preventing entry of the antibiotic into the pathogen cell, thereby stopping the antibiotic finding its target, by changing the cell wall (e.g. daptomycin),

c. pumping out the antibiotic so the concentration inside the cell is tolerable (e.g. efflux pumps exporting erythromycin),

d. protecting or altering the target site of the antibiotic inside the cell (e.g. tetracycline resistance), and

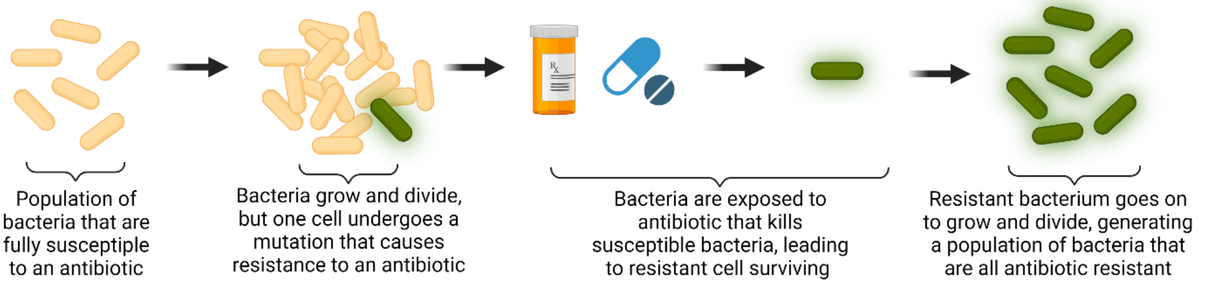
e. bypassing the metabolic step which had been the target for an antibiotic (e.g. trimethoprim resistance).



There are multiple different mechanisms of antibiotic resistance.

Bacteria can often use more than one mechanism of resistance for the same antibiotic. When a bacterium acquires resistance to three or more antibiotics of different classes it is called multidrug resistant (MDR). These MDR bacteria are often called "superbugs" in the media.

6. ***How antibiotic resistance arises.*** Antibiotic resistance can either arise naturally by mutations in the DNA of the genome of the bacterium, or be acquired from another bacterium through the process known as horizontal gene transfer; a process where bacteria can transfer sections of their DNA containing antibiotic resistance genes to other bacteria. These processes can occur individually or together to give rise to antibiotic resistance. When a bacterium becomes antibiotic resistant, it gains an advantage over its millions of neighbours if the antibiotic to which it has developed resistance is present to "select" for this resistance. The presence of an antibiotic is called a selection pressure. When resistance develops AND the correct selection pressure is present, antibiotic resistant bacteria will thrive by outcompeting sensitive bacteria. In fact, what we often observe is that only the resistant ones survive.



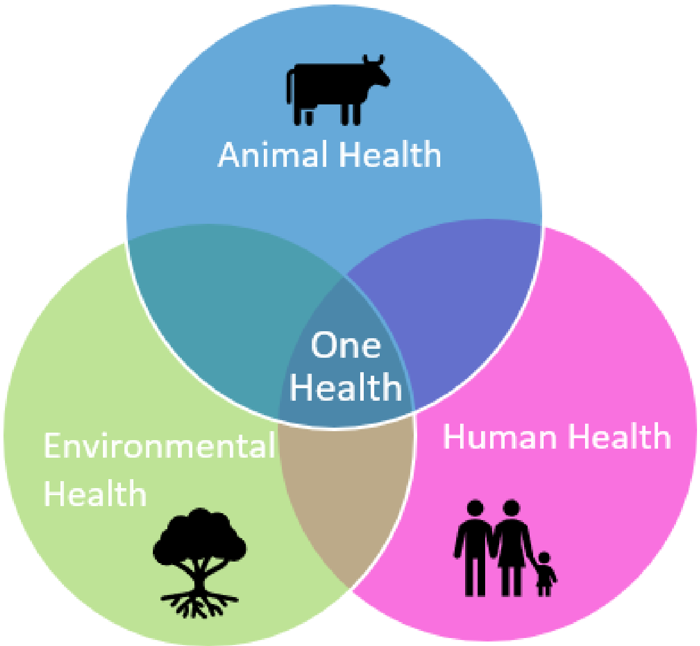
Mutation to resistance and competitive success under the selective pressure of antibiotics.

We can see this on an antibiotic-infused agar plate easily in the laboratory, but it also happens in our hospitals, on our farms and in aquatic and terrestrial environments. The more often we use antibiotics, the greater chance there is for bacteria to develop antibiotic resistance in the presence of the correct selective pressure.

7. ***The selection of resistance is greatly increased by the misuse of antibiotics.*** Misuse of antibiotics can happen anywhere and includes the prescribing of and taking antibiotics when they are not needed, for example, if you take antibiotics for a cold that is caused by a virus. The inappropriate use of antibiotics also happens in farming. In several countries of the world antibiotics are given to entire herds or flocks of livestock to make them grow a little bit faster. Antibiotics are also used in aquaculture. When antibiotics are used this way the are called antibiotic growth promoters. For plants, antibiotics are also routinely sprayed on agricultural crops like fruit trees. Excess antibiotics, which are not metabolised, end up in the environment with the antibiotic waste from hospitals, farms, and the factories that produce them, and also from humans being treated with antibiotics. This increases selective pressure for antibiotic resistance in the environment. When we consider human, animal, and environmental health together, this is called One Health.

8. ***One Health: an overview.*** One Health is a framework that considers three contributing sectors affecting, in this case, antibiotic resistance. These sectors include antibiotic use for the health of humans, animals and the environment. As we have described, antibiotics are used across many different sectors including human, animal and plant health and therefore in global food production. For many years, each of these sectors were considered separately. However,

scientists are becoming increasingly aware that each sector is intimately linked, and that antibiotic use in the animal and environmental health sectors can select for resistant bacteria which can affect human health and *vice versa*. Scientists are now investigating AMR using a One Health approach where the drivers of antibiotic resistance are being explored in a more holistic manner. In this section we will outline examples of AMR in different areas of One Health.



An overview of the One Health framework

Sometimes, specific antibiotics are used exclusively by one sector. For example, several therapeutic agents used in veterinary medicine are toxic to humans or, in human health, some infections are treated differently from equivalent ones in veterinary medicine. For example, tuberculosis (TB) in humans is treated with antibiotics but cattle infected with bovine TB are destroyed. However, in most cases, the antibiotics used for humans, animals and the environment are the same, so it is important to consider all health sectors together within a One Health framework.

Here we provide ten examples of One Health situations where the interface between animal, plant and environmental health is important for understanding the routes of transmission of AMR bacteria or where selective pressure in one of these areas can select for resistance, which will impact another.

9. The Human dimension of One Health

a. *Example 1. Methicillin resistant* Staphylococcus aureus *(MRSA): a modern superbug.* Hospital and healthcare environments are a melting pot of people who are colonised with bacteria. Some of these bacteria originated from their pets or livestock, or by coming into contact with service or therapy animals. Staff, patients, and visitors all interact either directly or indirectly via their environment (such as touching door handles), which can and does lead to transmission of bacteria amongst groups of humans within a particular space such as a hospital ward.

Staphylococcus aureus is a normal member of the skin and upper respiratory tract microbiome but is able to cause opportunistic infections. Methicillin resistant *S. aureus* (MRSA) rose to prominence in the news and media as one of the first so called “superbugs”. MRSA is responsible for a range of hard-to-treat infections including wound infections, osteomyelitis, and endocarditis. While MRSA is most commonly associated with hospitals, it can also be found in livestock, and in this context animal to human transmission has been observed. Currently in the UK, patients are screened for MRSA before planned hospital admissions as 1 in 30 people will carry it on their skin or in their nose. If found, patients will be given a decolonisation treatment to prevent MRSA carriers from entering the hospital environment and contributing to the spread of this pathogen. When people develop MRSA infections, there are antibiotics to treat these infections, but increasing resistance in MRSA means the efficacy of these antibiotics are being compromised. (*https://aricjournal.biomedcentral.com/articles/10.1186/s13756-020-00737-2*)

b. *Example 2. The spread of methicillin resistant* Staphylococcus epidermis *(MRSE) between healthcare workers, hospitals, the environment, and the community.* A large study conducted within a Swedish hospital highlighted that methicillin resistant *Staphylococcus epidermis* (MRSE) was transferable between patients referred to the hospital and healthcare workers. MRSE was isolated from doctors and nurses in the hospital, patients referred from other hospitals, patients who entered the hospital from the local community, and from the environment within the hospital, including keyboards and computer screens. Initial colonisation in patients was low, but this increased with antibiotic usage and time spent in the hospital. This study illustrates that patients and healthcare workers can act as a reservoir for antibiotic resistant bacteria and highlights the need for robust infection prevention and control measures within healthcare environments. (*https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5148920/*)

c. *Example 3. The transmission of MRSA from a Healthcare Worker to patients and subsequently into the wider community in Denmark.* Antibiotic resistant infections can spread from hospitals into the wider community. One study demonstrated that 37 cases of MRSA were clearly linked to hospital transmission. A healthcare worker (HCW) travelled to south-east Asia and acquired MRSA. The HCW then had contact with 26 patients who subsequently developed MRSA, including 9 members of these patients' households who had no contact with the HCW. This demonstrates the importance of international travel in terms of spreading bacteria geographically and shows that contacts between HCWs, patients and their relatives can spread a bacterial infection both into and out of healthcare environments. (*https://pubmed.ncbi.nlm.nih.gov/31640842/*)

10. The Animal dimension of One Health

a. *Example 4. Antibiotic use in Chilean salmon farms.* Antibiotic use in Chilean salmon farms more than doubled over 6 years from 143.2 in 2010 to 382.5 tons in 2016. Antibiotics were prophylactically used to treat *Piscirickettsia salmonis,* a pathogenic bacterium which infects salmon. *P. salmonis* infects fish blood cells, which enables it to infect multiple organs and cause ulcers, anaemia and eventually death.

Scientists suggest this is a poor use of antibiotics as between 40-90% of these antibiotics are immediately lost by the fish via urination and defecation. As the bacteria invade and live inside fish blood cells, it is also difficult to deliver antibiotics to the right tissue at effective concentrations. The most used antibiotic is oxytetracycline, and consequently, scientists discovered more oxytetracycline resistant bacteria in these farms and in the surrounding environment. Scientists argue the use of antibiotics in this environment is excessive, selecting for more antibiotic resistant bacteria in the environment, which may affect humans and does not correlate to improved growth of the fish. The agricultural industry in Chile argues that the use of these antibiotics is essential, and it is set to increase. (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)00100-6/fulltext)

b. *Example 5. The use of colistin in pig production in China and the emergence of transferable colistin resistance.* Since the 1980s, many farms in China used an old antibiotic called colistin as a supplement in their pig feed. Colistin has been available since the late 1950s but fell out of clinical use for humans due to toxic side effects. With increasing rates of antibiotic resistance colistin is increasingly becoming a very important antibiotic in human health, and is reserved for treatment of MDR infections. The extensive use of colistin in pig farms created a strong selection for bacteria that developed resistance to colistin. It was discovered in 2015 that resistance to colistin had evolved and importantly was easily transferable between bacteria. The gene responsible (called *mcr-1*) was located on a piece of DNA called a plasmid that could transfer between different species of bacteria. Bacteria containing this plasmid-located resistance gene (mcr-1) quickly spread into hospitals and healthcare environments globally, leading to a ban on the use of colistin in animal feed China. This discovery also prompted other countries such as Brazil to ban colistin use in agriculture.
(*https://www.sciencedirect.com/science/article/pii/S1473309915004247?via%3Dihub#ceab10*)

c. *Example 6. Transmission of bacterial infections between people and pets.* In a hospital in China a strain of the *Escherichia coli* bacterium, with resistance to colistin, was isolated from a male patient who worked at a pet-shop. Upon further exploration, it was found that 6 of the pets in the shop, 4 dogs and 2 cats, had the same strain of *E. coli* in their bodies, suggesting a zoonotic transmission event from the animals to the human. This study highlights that companion animal health and human health is closely interlinked, and that use of antibiotics for either may affect the other. (https://wwwnc.cdc.gov/eid/article/22/9/16-0464_article)

d. *Example 7. Use of antibiotics on Chinese poultry farms.* An interview-based study focussing on 88 Chinese chicken farms revealed over 70% of farmers continued to use antibiotics inappropriately after their use was banned. The improper use of antibiotics in these cases was associated with smaller farms, lower education level and lower income. Furthermore, the study highlighted a large gap existed between policy and enforcement in the community. There are clear socio-economic factors associated with misuse of antibiotics. (https://aricjournal.biomedcentral.com/articles/10.1186/s13756-019-0672-6).

11. The Environmental dimension of One Health

a. *Example 8. The pros and cons of antibiotic use in orange production.* Californian farmers spray their orange orchards with over 440,000 kilograms of streptomycin and oxytetracycline per year to combat Huanglongbing disease, also known as yellow dragon disease and 'citrus greening'. Citrus greening is caused by the bacterium called *Liberibacter*, which lives in the plant's vascular system (phloem). The bacteria are carried by the Asian citrus psyllid insect (a jumping plant louse), *Diaphorina citri*, and are likely injected into the plant when the insects feed. There is a concern that this antibiotic treatment will lead to an increase in antibiotic resistance and antibiotic resistant infections in humans. However, farmers argue that they risk losing 50% of their crops to *Liberibacter* infections. Scientists warn that the limited data on antibiotic spraying suggests it does not effectively stop citrus greening. A long-term solution would be to breed a tree that is immune to citrus greening infection (https://www.nature.com/articles/d41586-019-00878-4).

b. *Example 9. The result of all antibiotic usage; wastewater.* Following production and use of antibiotics in any of the above situations, humans, animals or plants, the antibiotics can end up in wastewater, and from there into groundwater, rivers and seas. The major sources of antibiotics in the environment are from agriculture, from pharmaceutical factory waste waters and hospital effluents that are released into the nearby water bodies without adequate treatment. Scientists have shown that excessive amounts of these antibiotics lead to significant selective pressure and subsequent increases in antibiotic resistant bacteria to many different antibiotics, including multiple resistant strains. These bacteria can pose a danger to human and animals. A study in India revealed that between 17 and 100% of groundwater samples analysed contained bacteria resistant to the clinically important third generation cephalosporin antibiotics (https://pubmed.ncbi.nlm.nih.gov/29757184/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563737/)

c. *Example 10. Bacterial resistance to plant chemicals in basil makes them more resistant to antibiotics.* Most of the antibiotics in use are originally derived from chemicals produced by bacteria and fungi. However, other environmental compounds can be antimicrobial in nature, including metals and plant-produced chemicals known as phytochemicals. This creates a selective pressure in the environment for resistance to these chemicals, and the mechanisms of resistance may also offer protection against antibiotics. An example is the compound linalool produced by the basil plant. The bacterium *Salmonella enterica*, which have evolved to thrive on the basil plant by resisting the antibacterial effects of linalool, also demonstrated resistance to antibiotics used for human medicine such as chloramphenicol. It is important to consider that bacteria are exposed to an entire range of conditions and chemicals in the environment, which may select for resistance to antibiotics. (*https://pubmed.ncbi.nlm.nih.gov/28258149/*)

d. *Example 11. Antibiotics in cleaning products.* Many cleaning products often used in households and work environments contains antibiotics, one of the most well-known antibiotics contained in cleaning products is triclosan. There is competing evidence to suggest whether the use of triclosan in these environments causes an increase in antibiotic resistance. However long term use could lead to a persistence of antibiotic resistance in the environment. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3366732/)

Relevance for Sustainable Development Goals and Grand Challenges

The role of AMR and One Health:

- **Goal 2. End hunger.** Antibiotics are used globally in agriculture and aquaculture to increase both food animal and fruit crop yields in order to feed the growing world population. But increasing yields of monocrops through administration of antibiotics comes at a price: the increasing environmental load of AMR microbes and its consequences for the spread of resistance into pathogens and for human health.
- **Goal 3. Ensure healthy lives and promote well-being for all at all ages**. Antimicrobial resistance affects all lives, both health and unhealthy, at all ages. By tackling AMR using a One Health perspective allows for an improvement of global health at multiple levels, by considering the knock-on effects of actions in multiple settings.
- **Goal 4. Ensure availability and sustainable management of water and sanitation for all.** The use of antimicrobials in both agricultural, clinical and social settings leads to increased accumulation of antimicrobial and resistant contaminants within water.

Potential Implications for Decisions

1. ***Individual***
   a. Is it safer, or more economically friendly for the individual to use products that are produced using large amounts of antimicrobials?

2. ***Community policies***
    - **a.** Healthcare costs associated with increased AMR.
    - **b.** Economic costs with reducing use of AMR in different environments.
    - **c.** Increased pressure due to the morbidities associated with AMR infections.
    - **d.** Environmental impact of use of antimicrobials and dissemination in the environment.

3. ***National policies relating to AMR and One Health***
    - **a.** Healthcare economics of AMR and the use of antibiotics in healthcare.
    - b. Environmental concerns associated with the pollution of AMR in the environment.
    - c. Economic concerns of farmers, or fisheries depending on allowed use of antimicrobials.

Pupil Participation

1. ***Class discussion of the issues associated with the use of antimicrobials in different environments.***

2. ***Pupil stakeholder awareness***
    - a. How does the use of antimicrobials affect the SDGs, which of these do you thing is the most important?
    - b. Can you think of anything that might be done to reduce the negative impact of the use of antimicrobials on the SDGs?
    - c. Can you think of anything you might personally do to reduce the environmental contamination of antibiotics?

3. ***Exercises***

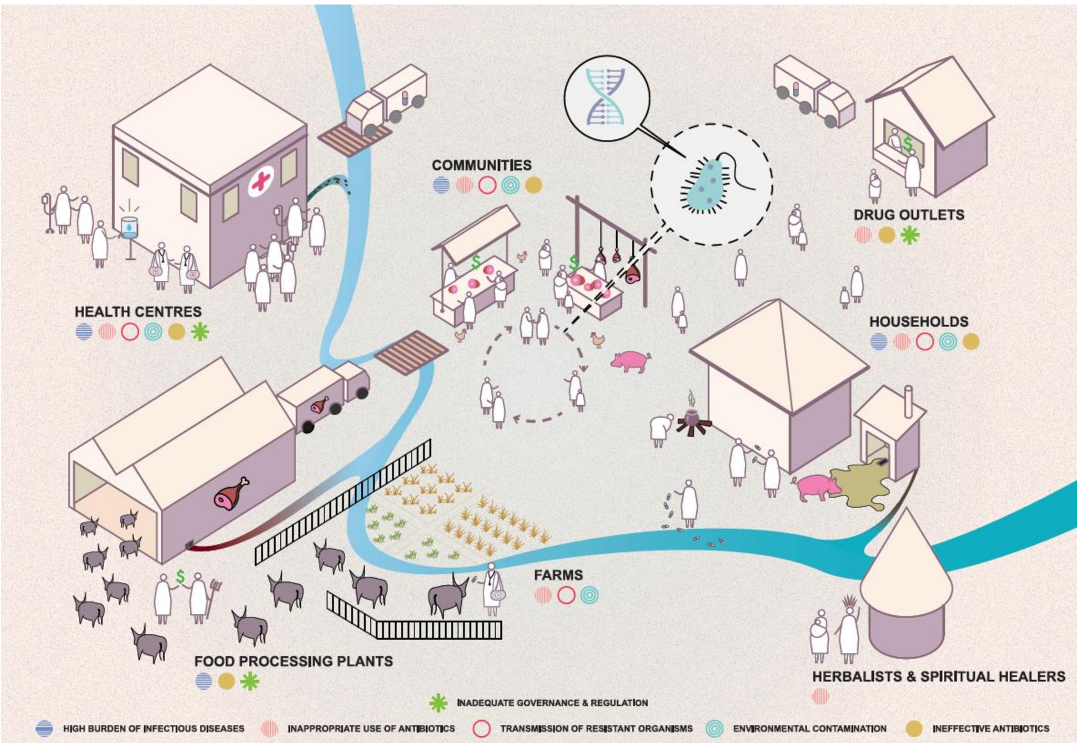
In 2018, the World Health Organisation (WHO) suggested that improving awareness and understanding of antimicrobial resistance is essential in tackling this global issue. Ensuring the general public is well informed about this global health threat may inspire interest in the issue, facilitate discussion and lead to creative ideas to combat and manage AMR. A study on children's attitude and learning of antimicrobial resistance shows that drawing pictures, participating in small interactive activities such as discussions improve their assimilation of this kind of information. Storytelling was shown to be an ineffective method for teaching this subject.

a. Using all the different examples given, discuss as a class the different pros and cons of using antibiotics in all three areas of One Health (human, animal and environmental). Can you think of any ideas not mentioned that stakeholders or scientists could do to limit antibiotic use in the different scenarios? Some example questions around the 10 different examples are given below:

- i. **Example 1**; describe the route of transmission between animals and humans, particularly in the farm environment. How could bacteria from a farm end up in a hospital?
- ii. **Example 2**; what measures could we take to minimise the numbers of pathogenic bacteria entering hospitals?

iii. **Example 3**; think about your interactions from the previous day, how many people did you meet and interact with? Can you draw a map of these interactions?
iv. **Example 4**; how likely is it that the antibiotic resistance selected for in Chilean salmon farms will affect humans? Think of the transmission routes. Who is right; scientists calling for reduction of antibiotic use or the Chilean government calling for an increase?
v. **Example 5**; should colistin have been used in agriculture? Was it right to ban colistin use in animals with a growing population requiring more food?
vi. **Example 6**; should we use the same antibiotics for pets and humans?
vii. **Example 7**; should education about antibiotics be increased? Who would benefit? Would paying more for our food mean farmers don't need to produce so many animals? Who may suffer if prices increased?
viii. **Example 8**; should farmers use antibiotics to prevent fruit trees from getting this disease? Would antibiotics affect insects that pollinate the trees?
ix. **Example 9**; how could we prevent antibiotics from reaching our water? How do they get there? Should industry regulation be tighter?
x. **Example 10**; what additional research should we conduct on the different selective pressures that drive the emergence of AMR?

b. The picture below represents many areas of life which may be a source of AMR bacteria or where transmission may occur. Looking at this picture, can you point out all the various places antimicrobials might be used, thinking back to the examples given, and how transmission between the different parts of the picture may happen. Ask the students to draw a similar picture representing their own day to day experiences.



c. In groups design a short play of one example of antibiotic use and how that may contribute to the spread of antibiotic resistance. Examples include not finishing a course of antibiotic, discarding left over antibiotics to landfill, or flushing them down the toilet.

d. Design a mini game in groups to communicate the role of antibiotics and the spread of resistance. Try and incorporate as many different possible transmission events between the One Health areas as possible. One possible scenario is that you pretend you are a bacterium. What kind of place would you like to live - on a plant, a human or animal or in the environment? Where could you live to avoid antibiotics?

e. Thinking about all the examples above, can you think and discuss things that would no longer be possible, or much more dangerous or difficult, without working antibiotics. Examples include bowel surgery, childbirth, cosmetic surgery, chemotherapy for cancer treatment, intensive food production (plant and animal based) and dentistry.

The Evidence Base, Further Reading and Teaching Aids

World health Organisation Fact Sheets: https://www.who.int/health-topics/antimicrobial-resistance
Society for Applied Microbiology Fact Sheets:
https://sfam.org.uk/knowledge/policy/priority-areas/antimicrobial-resistance-amr.html

Glossary

AMR – Antimicrobial resistance
Pathogenic – Disease causing
Synthetic – Produced in a laboratory by humans