Antibiotics

Mommy, what are those drops you put in my ears when they hurt so much?

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Storyline

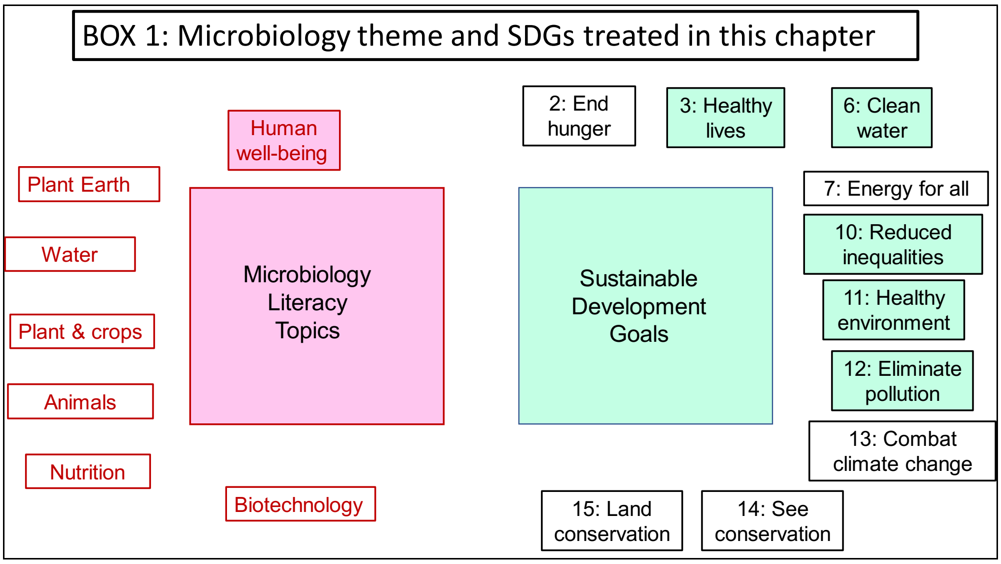
Earache is a common problem, especially in children. There are many possible causes for ear pain, but most frequently, it is caused by a bacterial infection called **otitis**. If these ear infections, like some other bacterial infections, are not treated quickly and properly they can cause serious problems to our organism. To fight bacterial infections, we have learned throughout our history to use substances, whether of natural or synthetic origin, that attack specifically these microbes without affecting our cells. We generically call these antibacterial substances, antibiotics. Antibiotics help us fight bacteria when our immune system is not enough to kill them. Antibiotics are not only used to fight bacterial infections in humans, but also in animals and plants, and their use is currently very widespread. Some antibiotics are also used for nontherapeutic purposes, for instance as food preservatives to prevent bacteria from growing and causing problems by consuming them.

The Microbiology and Societal Context

Good hygiene practices are one of the best ways to protect ourselves from bacterial infections, but although humanity has come a long way in this regard, we remain constantly threatened by bacterial attacks. Even more, although antibiotics are in principle very efficient, bacteria have learned to defend themselves from these substances and, as long as we use them in a massive way, bacteria become resistant and they increasingly stop being effective. The search for new antibiotics and their rational use are envisioned at this moment as two great challenges for human survival.

The misuse of antibiotics promoting an uncontrolled release can also cause environmental problems by polluting soil and waters, and thus affecting the health of many organisms.

On the other hand, unfortunately, not all people of the world have access to good hygienic conditions, and antibiotics do not yet reach all individuals who need them the most, especially the modern and more effective antibiotics, because they are expensive. Thus, the least developed countries with a lower standard of living cannot afford them. There are still too many deaths in the world, especially of children, due to this problem. Access to antibiotics is also a great additional socioeconomic world challenge.



Antibiotics: The Microbiology

1. ***Antibiotic definition. Differences between antimicrobials and antibiotics.*** **Antimicrobial** substances are agents that kill microbes or stop their growth. Antimicrobials are classified according to the microbes they attack, this is, they are named as **antibacterial**, **antiviral**, **antifungal** or **antiparasitic**, depending whether they attack bacteria, viruses, fungi or parasites, respectively. Antibiotics are defined as the antimicrobial substances which are active against bacteria, and thus, we call all antibacterial agents antibiotics.

2. ***The principle of selective toxicity.*** A guiding principle in the search for new medicines used to treat infectious diseases is *selective toxicity*, i.e. the toxicity of the medicine for the infectious agent – fungus, bacterium, etc. – compared with the toxicity for human cells. Ideally, the medicine should effectively kill the infectious agent but have no effect on us. Selective toxicity is based on differences between us and the pathogen: a medicine with good selective toxicity inhibits an essential activity of the cells of the infectious agent, which is different to the activities of our cells. To identify such differences, and hence potential targets for new medicines with high selective toxicities, it is essential to study the basic structure and metabolism of the cells of microbes and humans. Because bacteria have a very different cellular structure from human cells, and a rather different suite of enzymes responsible for metabolism, it is relatively easy to find medicines that have a strong effect on bacteria but little or no effect on humans, i.e. a high selective toxicity. On the other hand, cancer cells are simply human cells whose growth and multiplication are no longer regulated: they multiply rapidly and eventually take over. The basic structure and metabolism of cancer cells are essentially the same as those of all human cells, so it is difficult to find medicines with selective toxicity for cancers. Cancer medicines therefore target the property of fast growth of cancer cells, but are still to some extend toxic for all cells. This is why we may feel sick and our hair falls out when we are treated with anti-cancer medicines (chemotherapy).

3. ***Disinfectants and antiseptics.*** Some antimicrobial substances are non-selective and can affect many different microbes, but others are highly selective and only affect a specific type of microbe. Some non-selective antimicrobials are **disinfectants** such as bleach, and

antiseptics such as alcohol. Disinfectants are mainly used on non-living surfaces, air or liquids to prevent the spread of illness, whereas antiseptics are applied to living tissue or skin to reduce the possibility of infection.

BOX 2: Brief history of antibiotics. The natural sources of antibiotics.

Antibiotics have been used for millennia to treat infections, although it was not until very recently that we learned that infections were caused by bacteria. Interestingly, moulds and plant extracts were used to treat infections in different civilisations such as the ancient Egyptians, who applied mouldy bread to infected wounds. Small amounts of a tetracycline antibiotic have been found in human skeletons in Nubia (today, the region of Southern Egypt and Northern Sudan) and those from the time of the Roman occupation of Egypt, but the origin of this antibiotic has not been demonstrated. John Parkinson, an English pharmacist, was the first person to document in his book Theatrum Botanicum, published in 1640, the ancient knowledge of using moulds to treat infections. Pyocyanase, discovered by Rudolph Emmerich and Oscar Löw, two German physicians, was the first antibiotic drug to be used in hospitals in the 1890s. The bacterium then called *Bacillus pycyaneus* (now renamed as *Pseudomonas aeruginosa*) produces a green-blue pigment named pyocinin, that provides the color to a bacterial extract called pyocyanase that contained a mixture of compounds and enzymes effective against extremely pathogenic bacteria, such as those that caused cholera, typhoid fever, diphtheria, and anthrax. This antibiotic, although effective, was very toxic and therefore was only used for a short time. In 1909, Paul Ehrlich, a German physician, who can be considered as the father of modern antimicrobial chemotherapy through his works with antibacterial dyes, discovered that a chemical called arsphenamine containing arsenic was an effective treatment for syphilis. However, the word 'antibiotics' was first used over 30 years later by the Ukrainian-American microbiologist Selman Waksman, who discovered many modern antibiotics, such as streptomycin and neomycin. Antibiotics revolutionized medicine in the 20th century, but mainly after the discovery of penicillin in 1928 by Alexander Fleming, who demonstrated its utility during the second world war. The second half of the 20th century is considered the golden age of antibiotics. Most of the modern antibiotics were initially discovered as natural products derived from Actinomycetes and fungi, but thereafter they have been chemically modified to improve their antibacterial activities and pharmacological properties.

4. ***Antibiotics can kill bacteria or inhibit bacterial growth.***

Our body's defence systems are normally capable of defeating most infections on their own. But when bacteria take over and dominate, we need help fighting the infection. Antibiotics reduce the number of disease-causing microbes infecting our body and help our defences win the battle.

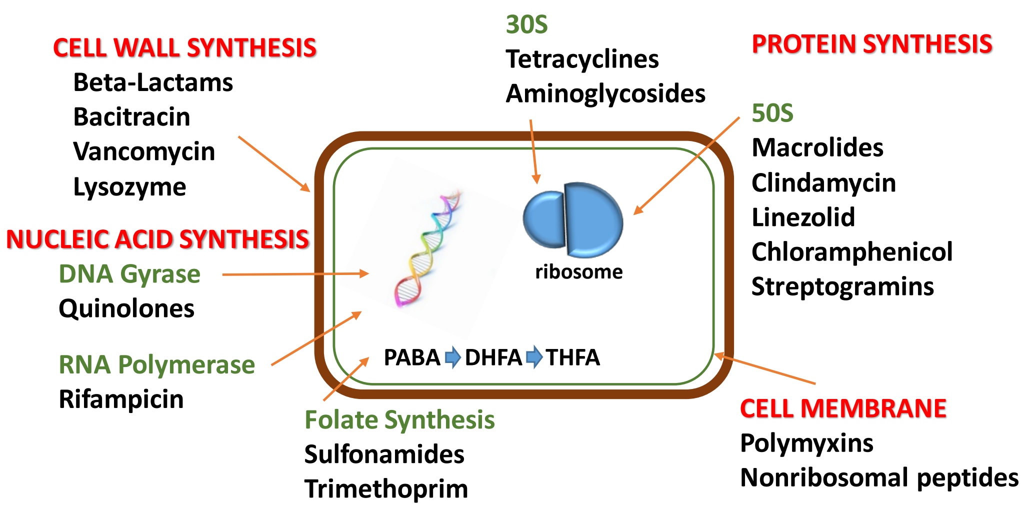
Antibiotics are commonly classified as bactericidal (lethal) or bacteriostatic (inhibitory) agents, based on their antimicrobial mechanism of action. Bactericidal antibiotics can destroy bacteria by inducing bacterial cell lysis, whereas bacteriostatic antibiotics simply stop or slow down multiplication of bacteria, without killing them. In the latter case, the assistance of phagocytic blood cells from our immune system is required to permanently eliminate the bacteria that are not killed from the body. Bacteriostatic antibiotics are therefore thought to be less effective without an efficient immune response. Nevertheless, both types of antibiotics are really very efficient.

At some point in clinical practice, bactericidal and bacteriostatic antibiotics were combined trying to improve their efficacy and increase the spectrum of activity, but what a surprise when the clinician realized that these combinations can be counterproductive. The reason is that bactericidal antibiotics are most effective at killing actively-growing bacteria, so when they stop growing because they are inhibited by bacteriostatic antibiotics, they are no longer killed by bactericidal antibiotics. The combination stops the infection in its tracks and symptoms disappear, so antibiotic therapy is halted. The non-growing bacteria can then resume growth, and restart the infection/disease process.

The best known bactericidal antibiotics are the beta-lactam antibiotics (penicillins (penams), cephalosporins (cephems), monobactams, and carbapenems). Other bactericidal antibiotics are vancomycin, fluoroquinolones, daptomycin, metronidazole, nitrofurantoin, co-trimoxazole, or telithromycin. The best example of a bacteriostatic antibiotic is the old sulfonamides, that were the first broadly effective antibacterials used systemically since the late 1930s (Prontosil, Bayer AG), which paved the way for the antibiotic revolution. Other well-known bacteriostatic antibiotics are tetracyclines, spectinomycin, trimethoprim, chloramphenicol, macrolides and lincosamides.

Aminoglycosidic antibiotics, such as streptomycin, neomycin, gentamycin or kanamycin are usually considered bactericidal, although they may be bacteriostatic for some bacteria.

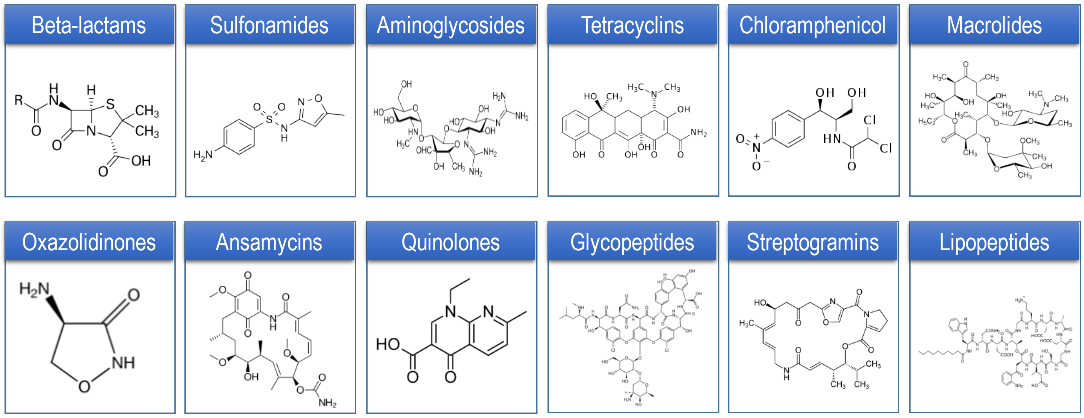
BOX 3: Mechanisms of action of antibiotics



5. **Broad and narrow spectrum activity of antibiotics.** Depending of the mechanism of action, antibiotics can be also classified with a narrow or a broad spectrum of activity. **Narrow-spectrum** antibiotics are only active against a limited number of bacterial strains. **Broad-spectrum** antibiotics instead act on a wider range of bacteria.

Narrow-spectrum antibiotics are preferred when you know the bacterium causing the disease, since the negative effects on other – good – bacteria (non-disease causing) are more limited. However, broad-spectrum antibiotics are often used when you do not know the cause of disease, or when it is difficult for doctors to diagnose the disease-causing bacteria in time, or when knowledge about how to correctly treat an infection is lacking. In these cases, antibiotics kill good and bad bacteria and, while killing the bad bacteria may stop the infection, killing the good ones might ultimately have side effects in the patient.

BOX 4: Main classes of antibiotics



6. ***Administration of antibiotics.*** Antibiotics can be administered **topically** on body surfaces (skin, mucosa, etc.) or **systemically**, that is, distributed into the circulatory system so that the entire body is affected. Topically administered medicines are applied as drops, ointments, sprays, powders, or creams. These antibiotics can in some cases be combined with antiseptics, as for instance in the treatment of skin wounds.

In the case of systemic antibiotics, administration can take place via oral administration (absorption of the drug through the gastrointestinal tract) or parenteral administration (generally injection, infusion, or implantation).

The first penicillins used were the so-called natural penicillins (penicillin G (benzylpenicillin) and penicillin V (phenoxymethylpenicillin)) that are the primary products obtained by growing (cultivation) *Penicillium* in large vessels called fermenters (fermentations). These penicillins presented some problems, not only because of the low spectrum of activity, but also because of the limited ways of administration. These problems immediately led to the search for new penicillin derivatives that could be useful to a wider range of infections and that can be highly efficient through oral administration. The isolation of 6-aminopenicillanic acid (6-APA), which is the core part of penicillin, opened the way for chemical modification and the preparation of the current semisynthetic penicillins.

Many antibiotics currently used are **semisynthetic** compounds derived from the natural ones. A good example of this is amoxicillin, which alone or in combination with clavulanic acid is one of the most frequently used oral penicillins worldwide.

In general, antibiotics are organic molecules of low molecular weight (<1000 Da), but there are larger molecules. Lysozyme (approx. 14 kDa) is a polypeptide enzyme discovered by Alexander Fleming in 1921 that digests the bacterial cell wall. Lysozyme is abundant in human secretions (e.g., tears, saliva, etc.), but also in other biological fluids and tissues of many living organisms. For instance, it is very abundant in hen eggs to protect them against bacterial infections. Thus, this protein is a natural antibiotic produced by us, that is also used in medicine. There are also other polypeptide antibiotics, such as polymyxin, bacitracin, actinomycin, etc., but these are smaller than lysozyme and made in a different way. Thus, lysozyme is now classified as an enzybiotic.

BOX 5: Other uses of antibiotics for animals, plants or food preservation. Environmental issues

Apart from the antibiotics used in veterinary medicine for the treatment of animal diseases, an enormous amount of antibiotics is currently used in food animal production. In this case, antibiotics are used to improve feed utilization and to increase animal growth rates, resulting in a reduced food production cost. Moreover, it also reduces the production of excrements and thus, its use decrease the pollution problems caused by animal husbandry. Currently, millions of kilograms of clinically important antibiotics are used yearly on livestock farms, that might correspond about to 80% of the total antibiotic market. Probably, tetracyclines, penicillins and sulphonamides are the most widely used antibiotics in this sector. Other antibiotics, such as tylosine, that have been recommended for this sector because they are not used currently for human treatments, are not always used because of their higher cost.

Antibiotics can be also used to control some bacterial diseases of plants. The antibiotics most commonly used for this purpose are oxytetracycline and streptomycin. Antibiotics applied to plants account for only a small fraction of the total global market because antibiotics are expensive and can be only used on high-value vegetable/fruit crops, as well as in some ornamental plants, where the investment can be recouped. This is also due to the fact that bacterial diseases of plants are less prevalent than diseases caused by fungi or viruses. Prophylactic (disease prevention) treatments of plants are limited in efficacy, and a therapeutic use is very ineffective. Most applications are by spray treatments. In the open field, the massive use of antibiotics administered by sprays causes environmental problems because the antibiotics that do not directly land on the plant leaf target contaminate the ground, and thence are transported by rain to surface waters and aquifers. Furthermore, animals in contact with the treated plants can ingest these antibiotics.

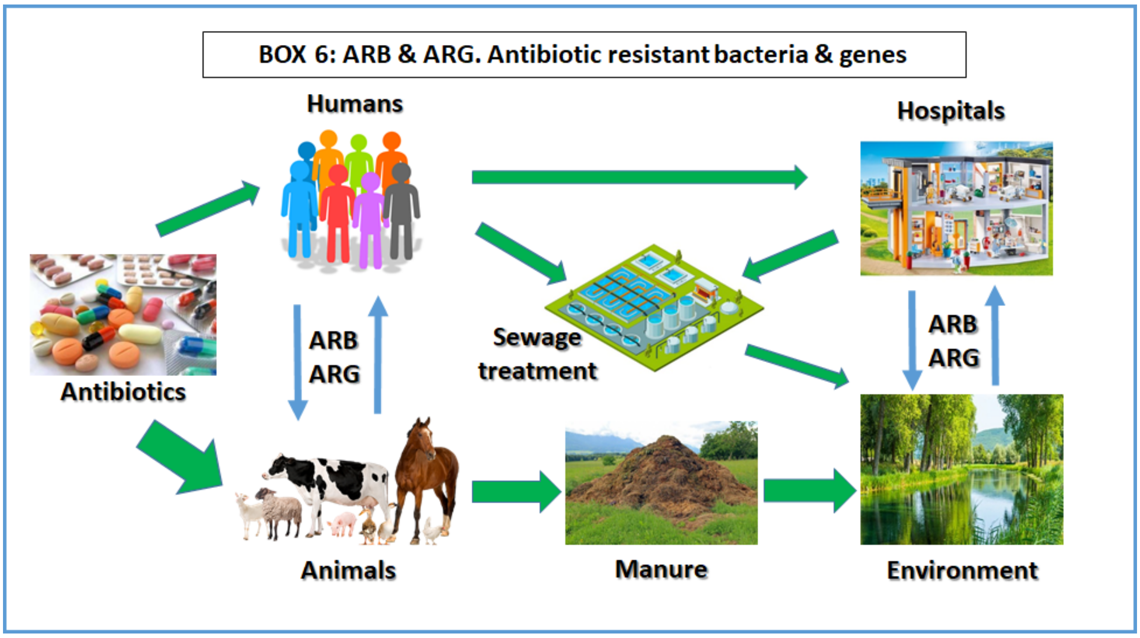
Several synthetic chemical substances including nitrates/nitrites, sulfites, sodium benzoate, propyl gallate, and potassium sorbate are used as conventional preservatives of food to prevent its oxidation, and resulting deterioration of flavour, as well as the proliferation of microbes. But other natural antimicrobial compounds of various origins have been also developed for food preservation. These compounds act on bacteria and fungi and can be considered as antibiotics. Moreover, some clinical antibiotics alone or in combination with antifungal substances, have been also authorized as preservatives for biological products, although their use is not universally accepted as preservatives in all countries. Broad-spectrum antibiotics such as nisin are commonly used for this purpose. Nissin (E 234), a polycyclic antibacterial peptide produced by the bacterium *Lactococcus lactis*, is currently an authorised food additive in the EU. Antibiotics in food are useful in reducing the risk of alteration of raw red meat, raw fish, shrimp tails, whole or lumpy, raw eviscerated poultry and vegetables. Antibiotics slow down the development of pathogenic bacteria and normal heat-resistant flora in foods such as custard, cheese and milk, killing vegetative cells and spores. Antibiotics applied to food in very small doses, lower than the prophylactic ones, can prolong the good state of fresh food for several days, but they need the help of low temperatures, i.e. without refrigeration they do not ensure long term preservation.

7. ***Resistance to antibiotics.*** Bacteria can develop the ability to defeat the drugs designed to attack them and become resistant to the antibiotics. In fact, many microbes produce antibiotics and avoid being killed themselves by simultaneously producing a

resistance system, so-called *producer resistance*. Resistance can be a natural property due to specific genes encoded in the genome, as is the case for *producer resistance*, or can be generated by a genetic mutation. The resistance can be also acquired by transfer from other bacteria by multiple genetic mechanisms, collectively called horizontal gene transfer (**transformation**, **conjugation**, **transduction**). **Plasmid**-mediated transmission of resistance antibiotic genes is the most common route for acquisition of genetic material from other bacteria. Plasmids are extrachromosomal DNA molecules that are physically separated from chromosomal DNA and can replicate independently. Plasmids can carry many genes including those conferring antibiotic resistance. This means that many genes that confer resistance to antibiotics are encoded in plasmids that can be transferred to other bacteria.

Depending of the antibiotic, bacteria can be resistant through different mechanisms. In some cases, bacteria inactivate the drugs. Bacteria have enzymes that modify the antibiotic molecule, rendering it inactive. This is the case of beta-lactamases that degrade the beta-lactam antibiotics. In other cases, the enzymes add chemical groups to the antibiotics (e.g., acetylation, phosphorylation) to inactivate them. This is the case of the transferases that inactive chloramphenicol and aminoglycosides. Another mechanism is by restricting the uptake of the drug, by changing the cell membrane so that it does not permit entry. This is the case for tetracyclines. Alternatively, bacteria can expel drug molecules that enter the cell, by increasing their transport from inside to outside by producing so-called efflux systems. This is the case for macrolides. Finally, bacteria can modify the cellular target of the antibiotic, to reduce its ability to bind the drug and hence be affected by it. This is the case of beta-lactam antibiotics when a mutation results in reduced binding of the antibiotic to its target, a penicillin-binding-protein that is an essential component of the cell envelope.

Sometimes, bacteria have multiple resistance mechanisms for the same antibiotic, which gives higher levels of resistance and allows bacteria to tolerate higher concentrations of antibiotics. This is why doctors often prescribe an antibiotic in a very high dose, both to inhibit moderately resistant bacteria causing the infection, and to prevent some residual growth that might allow mutations to accumulate or resistance to be acquired from other, resistant bacteria.



8. ***Misuse of antibiotics.*** Resistance of microbial pathogens to an increasing number of antibiotics is becoming a serious problem. Antibiotic-resistance in bacteria keeps growing, putting more and more lives in danger and this is mainly due to the misuse of antibiotics. Antibiotic resistance happens when the bacteria mutate the antibiotic target such that the target no longer responds to the molecule designed to bind to it. The more we subject bacteria to the presence of antibiotics, the more opportunities we give them to prepare and consolidate these resistance mutations.

When we do not use the correct dose of antibiotic, that is, when we use a sub-lethal dose or we use antibiotics for less time than recommended by the doctor, we are giving bacteria an opportunity to mutate and generate resistance to the antibiotic. It often happens that when we are taking antibiotics and already feel good, we stop taking them, although the disease has not completely subsided. This reduces the concentration of the antibiotic in the tissues and some bacteria that are still alive and that have developed a moderate resistance to the antibiotic can be selected and stay hidden for a next chance. Antibiotics should be taken for as long as the doctor has prescribed them.

When the antibiotic treatment has finished, if still some tablets/pills remain in the box, it is important not to dispose of the antibiotics by pouring it down the drain or flushing it down the toilet. This causes an environment problem and also contributes to development of bacterial resistance. Leftover antibiotics can be dropped off in pharmacies to be safely destroyed.

Self-medication is the use of medicines on our own initiative without any intervention by the doctor (neither in the diagnosis of the disease, nor in the **prescription** or supervision of the treatment). Unfortunately, self-medication of antibiotics is a common habit in our society and is not without risks. Sometimes we reuse the antibiotics from an unfinished box stored in the medicine cabinet. We assume that the new infection is the same as the last one for which these antibiotics were very good for me, but most likely the pathogen may be different and these antibiotics could not be effective or very little effective. In addition to the risk that the infection cannot be stopped because it is not the correct antibiotic, it can make the pathogen more resistant to this antibiotic. Antibiotics should never be taken on your own initiative without the supervision of a doctor.

To treat viral infections with antibiotics is a frequent case of misuse. Antibiotics do not kill viruses since these compounds do not recognize as targets the components of the viruses or their mechanism of replication. The machinery and mechanism of replication of viruses are very different from that of bacteria and thus, antibiotics cannot affect virus development. Antibiotics kill bacteria because they were developed to target their specific life processes. For instance, penicillin blocks the formation of bacterial cell walls by acting on specific enzymes that are required to synthesize them. Because viruses do not have the same walls of bacteria, penicillin cannot kill viruses. Only in some specific cases, when the viral infection co-occurs with a bacterial infection, or facilitates a secondary bacterial infection, can the use of antibiotics be justified.

9. ***Side effects of antibiotics.*** All medications, including antibiotics, may cause side effects. A side effect is an unwanted reaction of the body that occurs in addition to the intended therapeutic action of a medicine. Some critical side effects may interfere with the possibility to finish the treatment. When used appropriately, antibiotics are generally safe producing only few side effects. Side effects of antibiotics can range from mild **allergic reactions** to severe and debilitating adverse events. Some common side effects include: i) mild skin rash or other allergic reactions; ii) soft stools, short-term **diarrhoea**; iii) upset

stomach, nausea; iv) loss of appetite; v) fungal (yeast) vaginal infections or oral thrush. More severe side effects include: i) severe allergic reaction that results in difficulty breathing, facial swelling (lips, tongue, throat, face); ii) severe watery or bloody diarrhoea, as for example caused by *Clostridium difficile*; iii) stomach cramps; iv) yeast infections in the mouth or vagina.

The use of antibiotics, in particular broad spectrum oral antibiotics, might heavily disrupt the ecology of the human microbiome. A **dysbiosis** of microbiome may affect vital functions such as nutrient supply, vitamin production, and protection from pathogens. Dysbiosis of the microbiome has been associated with a large number of health problems. Typically, a strong antibiotic treatment causes diarrhoea and might lead in extreme cases to a severe *Clostridium difficile* infection.

Relevance for Sustainable Development Goals and Grand Challenges

- **Goal 3. Ensure healthy lives and promote well-being for all at all ages.** Antibiotics are essential medicines to guarantee a healthy life and promote well-being in all ages, but especially in children and the elderly. Bacterial diseases continue to be one of the highest mortality causes in the world. Antimicrobial resistance is a missing topic in the Sustainable Development Goals (SDGs). The World Health Organization (WHO) has warned that 10 million people could die each year from antimicrobial resistance starting in 2050. Infectious diseases kill over 17 million people a year including about 9 million deaths in young children. Nearly 50,000 men, women and children are dying every day from infectious diseases; many of these diseases could be prevented or cured for as little as a single dollar per head. Some major diseases, such as cholera, pneumonia, and tuberculosis are making a deadly comeback in many parts of the world, despite being preventable or treatable. Pneumonia killed 4.4 million people, about 4 million of whom were children.
- **Goal 6. Ensure availability and sustainable management of water and sanitation.** Many studies have shown that water is increasingly contaminated with medications, both prescription and over-the-counter. Other studies have shown that many antibiotics can be detected in samples of water. Antibiotics and other drugs get into the water by several ways. Our bodies only metabolize a fraction of the antibiotics that we take, and the rest is excreted in urine or faeces, or sweated out. This all ends up in our sewers and eventually, after being treated at wastewater plants, is discharged back into rivers and other bodies of water. The livestock industry which has long used antibiotics to make animals grow faster and keep them alive from getting sick, is a big contributor to antibiotic pollution of waters. Another way is to flush expired or non-used antibiotics down the drain.

In general, the levels of antibiotic residues in drinking water are minute and do not represent a risk to human health. However, antibiotic residues can be found at higher levels in waste water, surface waters, agricultural runoff and water used for aquaculture (farms of fish, muscles, seaweed and other marine species). This can contribute to increased bacterial resistance to antibiotics. Antibiotics must be used more prudently, but in most of the world, improving water, sanitation and hygiene is also critically important. If we can ensure cleaner water and safer food everywhere, the spread of antibiotic resistant bacteria will be reduced across the environment, including within and between people and animals.

- **Goal 10. Reduce inequality within and among countries.** It is very important to ensure that people everywhere have access to essential medicines like antibiotics. The WHO has a Model Lists of Essential Medicines and Essential Medicines for Children as part of the campaign for universal health care around the world. The most recent lists include antibiotics for minor or serious infections using the Access-Watch-Reserve (AWaRe) classification, with the goal of optimizing their use and reducing antibiotic resistance without restricting access. Access group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens, while also showing lower resistance potential than antibiotics in the other groups. Watch group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the critically important antimicrobials for human medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Reserve group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. The WHO promotes universal access to health products by reinforcing their selection and supply chains. The WHO works with governments to create strategies for measuring, monitoring and managing medicine prices that fit regional contexts and health care systems.

- **Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable.** Although antibiotic resistance in bacteria was primarily driven by imprudent use of antibiotics in human and veterinary medicine, growing evidence suggests that environmental factors may be of equal or greater importance to the spread of antibiotic resistance, especially in the developing world.

For instance, if a two-year-old child living in poverty in a city of a developing country gets sick with a common bacterial infection, there is more than a 50 per cent chance an antibiotic treatment will fail. Somehow the child has acquired an antibiotic resistant infection – even to drugs to which they may never have been exposed. Unfortunately, these little kids might also live in a city with limited clean water and inadequate waste management, bringing them into frequent contact with faecal matter or other type of animal or human wastes. They are regularly exposed to millions of bacteria containing antibiotic resistant genes, including multi-resistant bacteria that are very difficult to treat. These stories are unfortunately very common, especially in places where pollution is high and clean water is scarce.

- **Goal 12. Ensure sustainable consumption and production patterns.** It is necessary to promote the responsible consumption of antibiotics to combat antibiotic resistance of bacteria. Sustainable use implies optimal prescribing and consumption of these drugs in a way that slows the growth of overall pathogen resistance, thereby maximizing the wellbeing of humans now and in future. It also encompasses lowering both 'appropriate' and 'inappropriate' demand for antibiotics. The growth of antibiotic resistance has resulted essentially from a widespread use of antibiotics. Thus, efforts must be made to ensure a restricted and sustainable use.

Good preventive medical care for animals, which involves an optimal animal environment, a good animal management, an adequate breeding population and an adequate food supply, reduces the risk of diseases. The spread of infectious diseases is reduced through biosecurity measures on farms and with restricted and controlled trade in live animals. Healthy animals do not need to be treated with antibiotics. The risk of developing and spreading antibiotic resistant bacteria is reduced in this way and thus, it benefits both animal and public health.

A synergistic approach between access strategies, quality of antibiotics, diagnostics for low-resource settings, measures to encourage fair and sustainable decision-making, and helping to search for optimal therapeutic and dosing strategies, are key instruments for a sustainable use of antibiotics. A successful integration of these strategies depends on effective governance mechanisms and accurate evaluation systems at regional, national, regional and international levels.

Potential Implications for Decisions

1. ***Individual.*** It is important to convince people not to flush expired or non-used antibiotics down the drain. In addition, it is also necessary to avoid self-medications, especially in those cases, as the viral infections, where the use of antibiotics is nor useful at all.

2. ***Community policies.*** Everyone involved in the food chain, and especially those involved in raising animals for food, should feel responsible for ensuring that the development and spread of antibiotic resistant bacteria due to food producing animals has to be kept to a minimum. Keeping healthy animals in proper facilities with good hygiene is essential for a minimal need for antibiotics in animal husbandry.

3. **National policies related to antibiotics.** Taking into account that antibiotics are a public good, it is necessary to preserve them for our future generations. Thus, a sustainable use must be at the forefront of public policy. It is important to regulate at national and international levels the consumption of antibiotics in agricultural practices. Carrying out public awareness campaigns for the rational and sustainable use of antibiotics is a mission of the state authorities. Raising awareness of the fact that unused antibiotics must be deposited in clean areas such as pharmacies is also essential to avoid pollution of wastewater.

Pupil Participation

1. ***Class discussion of the issues associated with antibiotics.*** Find the list of AWaRe antibiotics established by WHO and discuss it.

2. ***Pupil stakeholder awareness***
   a. Can you propose different ways to reduce the use of antibiotics on animal farms?
   b. How many boxes or vials for antibiotics can you find open or unused in the medicine cabinet at home? What should you do with those boxes and vials?
   c. Why should we not take antibiotics when we have the flu?

3. ***Exercises***
   a. Create a list of all beta-lactam antibiotics that are currently in clinical use.
   b. Find the antibiotics approved for clinical use during the last five years.
   c. Name some examples of broad- and narrow-spectrum antibiotics.

The evidence base, further reading and teaching aids

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Glossary

Allergic reactions – Immune system responses to normally harmless substances (allergens), causing symptoms like rash, itching, swelling, or breathing difficulties.

Anaphylaxis – A severe, life-threatening allergic reaction that can cause difficulty breathing, a drop in blood pressure, and shock.

Antibacterial – A substance that kills or inhibits the growth of bacteria.

Antibiotic – A type of antibacterial drug used to treat bacterial infections.

Antifungal – A drug or agent that kills or inhibits the growth of fungi.

Antimicrobial – A broad term for substances that kill or inhibit the growth of microorganisms, including bacteria, fungi, viruses, and parasites.

Antiparasitic – Drugs or agents that target and eliminate parasitic organisms (e.g., protozoa, helminths).

Antiseptics – Substances applied to living tissue to reduce or prevent infection by killing or inhibiting microorganisms.

Antiviral – Drugs or agents that prevent viruses from replicating or spreading in the body.

Bactericidal – A substance that kills bacteria directly.

Bacteriolytic – A substance that kills bacteria by breaking down or dissolving their cell walls.

Bacteriostatic – A substance that inhibits the growth and reproduction of bacteria without necessarily killing them.

Broad-spectrum – Refers to antibiotics or antimicrobials effective against a wide variety of microorganisms.

Conjugation – A process in which bacteria transfer genetic material (such as plasmids) directly from one cell to another.

Diarrhea – Frequent, loose, or watery bowel movements, often caused by infections or digestive disturbances.

Disinfectant – A chemical used on non-living surfaces to kill microorganisms.

Dysbiosis – An imbalance in the normal microbial community of the body (e.g., gut microbiota), often linked to disease.

Enteral – A route of drug administration that uses the gastrointestinal tract (e.g., oral, sublingual, rectal).

Intramuscular (IM) – A method of injecting medication directly into a muscle.

Intravenous (IV) – A method of delivering medication or fluids directly into a vein.

Narrow-spectrum – Refers to antibiotics or antimicrobials that target a specific type or limited group of microorganisms.

Nephrotoxicity – Toxicity or damage to the kidneys caused by a substance or drug.

Otitis – Inflammation or infection of the ear.

Plasmid – A extrachromosomal DNA molecule within a cell that is physically separated from chromosomal DNA and can replicate independently. They are most commonly found as small circular, double-stranded DNA molecules, but they can be also large and linear. Some plasmids can carry genes for antibiotic resistance.

Prescription – Authorization from a healthcare professional to dispense a specific medication.

Semisynthetic – A substance partly derived from natural compounds and partly created through chemical synthesis.

Systemically – Refers to treatment affecting the whole body, usually via the bloodstream.

Topically – Refers to applying a substance directly to a specific area of the body (e.g., skin, eyes).

Transduction – Transfer of bacterial genetic material from one bacterium to another via a virus (bacteriophage).

Transformation – Process in which bacteria take up foreign genetic material (DNA) from their environment.