The Antimicrobial Resistance Crisis

Daddy: Why do you always insist on line-caught fish for supper?

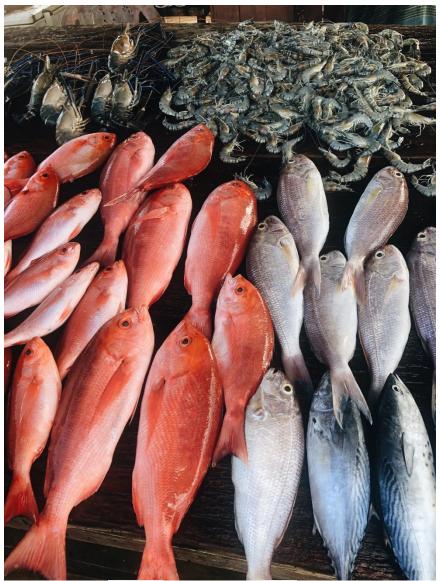


Photo by <u>Marina Akimova</u> from <u>Pexels</u>

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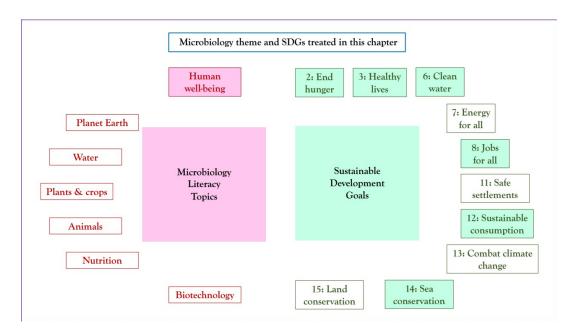
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Storyline

Getting sick is a normal and sometimes frightening part of life. In developed nations, if someone gets infected by a pathogen, it is mostly an inconvenience that can be tackled by a trip to the doctor and getting a course of an antimicrobial chemotherapeutic (often called antibiotic see Box). Sometimes, antimicrobial chemotherapeutics don't work because the microorganism has developed antimicrobial resistance (AMR). This means that if a person gets an infection and it can't be treated, they can become very ill and may even die. This has implications for families who may lose family members, and for society where death may threaten social cohesion. This is also the case if people require longer time periods to recover from infection. Because of AMR, some infections are now untreatable and this is predicted to get worse into the future. It important to highlight that antimicrobial chemotherapeutics are not only used to treat infection but also to prevent infection. Hospital procedures such as surgery or cancer chemotherapy come with high risk of infection, and so antimicrobials may be administered for prevention. Although rising AMR places us all at risk, our most vulnerable (e.g. the elderly, immunocompromised or poor) with reduced immunity are most at risk. AMR limits our options for treating a variety of illnesses and is not an easy problem to manage. It is linked to processes in human medicine, food production (animal and plant) and environmental pollution and so is defined as a One Health problem that traverses human, animal and environmental ecosystems. Therefore, future interventions that aim to minimise the effects of AMR will need to consider its impact in all of the One Health domains. As a result, AMR and interventions are linked to multiple Sustainable Development Goals.

The Microbiology and Societal Context

The microbiology: antibiotic therapy; antibiotic prophylaxis; non-clinical use of antimicrobials; AMR; AMR transmission and ecology. *Sustainability issues*: end hunger; healthy lives; clean water; economy and employment; antibiotics as growth promoters for food animals; conservation of marine resources.



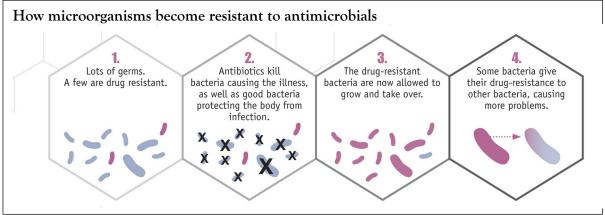
Antimicrobial or antibiotic?

The term antibiotic is often used in the popular media. Traditionally, it means a chemical produced by one microorganism to inhibit the growth of or kill another microorganism. Penicillin is one such antibiotic that is produced by a blue-green fungus called *Penicillium notatum* and in nature is used to outcompete bacteria in soils for better access to nutrients. In the late 1930's, penicillin was purified from the fungus and repurposed for use in treating bacterial infections in humans and animals. Since then, scientists have discovered many antibiotics produced by microorganisms and developed ways of chemically synthesising them and modifying them. Modified antibiotics are called semi-synthetic antibiotics.

Most antibiotics are antibacterials, meaning they inhibit or kill bacteria and so the World Health Organisation and others use the term antibiotics to mean those chemicals used in therapy to treat bacterial infections. Antimicrobial chemotherapeutics are a broader category of chemicals used in therapy to kill microorganisms which include viruses, bacteria, fungi and protozoa. Chemicals that specifically target these classes of microorganisms are called antivirals, antibacterials, antifungals and antiprotozoals.

It is important to note that antimicrobial chemotherapeutics must be non-toxic to humans and animals and have few to no side effects. Good antimicrobial chemotherapeutics are selectively toxic. That is, they kill or inhibit the infecting pathogen and not the cells in the host. They are said to have high *selective toxicity*, in contrast to some other drugs, like anti-cancer agents, which have low selectivity and hence have side effects.

1. AMR is a natural consequence of the selection pressure imposed by use of antimicrobials. Microorganisms grow quickly and will naturally change through mutation of their DNA which contains genes coding for all the things needed to grow and divide. Mutations occur randomly and may have no effect or may change a microorganism such that it may become less or more able to survive in its environment. Where antimicrobials are present, a mutated microorganism that survives better in their presence will outgrow others and become dominant. This process is called evolution, where in this context, the microorganism has evolved resistance to an antimicrobial with the gene(s) responsible called resistance gene(s). Evolution occurs naturally but it is the selection pressure from the presence of the antimicrobial which dictates which of the microorganisms survive better by inhibiting the growth of or killing those that are sensitive.



CDC public health library (https://phil.cdc.gov/Details.aspx?pid=16883)

Microbes are abundant in all environments, including soil and water, and in and on humans and animals. Wherever antimicrobial chemotherapeutics are used, selection of AMR microorganisms will occur. For example, when antibiotics are used by people in agriculture, microorganisms in the gut of animals may evolve to become resistant and be selected. Put simply, the more antimicrobial chemotherapeutics are used in any environment, the more likely that AMR will occur, and the more prevalent AMR becomes. This increases the likelihood that AMR will spread across environments, such as in hospitals containing sick and vulnerable people. Additionally, some microorganisms can share their resistance genes (see above image).

All this means that that resistance can evolve in any microorganism, including those that don't cause disease, which can share their resistance genes with those that cause disease, making them difficult or impossible to treat. As a result, we need to think about AMR beyond human health, because AMR in animals and the environment contributes to its impact on human health. We need to think of ways to minimise AMR in all environments and ways to minimise the movement of resistant microorganisms and genes across environments (e.g. from animals into humans or environment into animals – see below).

2. *Rising AMR means more death, illness and a lower quality of life.* Infectious diseases have always been a scourge on humanity with epidemics and pandemics responsible for numerous deaths over history. In the early 1900's, deaths from pneumonia, tuberculosis, diarrhoea and diphtheria were commonplace, disproportionately impacting infants and children. Sanitation, hygiene, vaccination and antimicrobial chemotherapeutics substantially reduced deaths and sickness from infectious disease. From when antimicrobial chemotherapeutics were first implemented, US deaths reduced by approximately 220 for every 100,000 people. In comparison, all other medical technologies such as cancer treatments, surgery or drugs treating conditions such as diabetes or cardiovascular disease have reduced deaths by approximately 20 for every 100,000 people. And remember, antimicrobial chemotherapeutics are often used to support these other medical treatments.

AMR affects all type of infections, including those caused by viruses, fungi, bacteria and protozoa with some now being untreatable or difficult to treat requiring longer stays in hospital increasing healthcare costs. It's important to appreciate the effect of AMR on our future in terms of impact on families, society and the economy. If AMR is not properly managed, it is predicted that 10 million lives each year will be lost by 2050 and cost a cumulative US\$100 trillion in global production.

3. AMR is made worse because of increasing global demand for meat and seafood. Global consumption of meat and seafood has risen dramatically over the last 20 years in line with population growth and an increasing food demand. Apart from having impacts on climate change and ecosystem degradation, agriculture is a driver of AMR. Sometimes, animals get sick and need to be treated with antimicrobials. Where animals are grown in high density, infectious disease can easily spread amongst animals requiring more use of antimicrobials. In some discouraged practices, antimicrobials are added into feed as so-called growth promoters to prevent infection and to stimulate production. This is not only in agricultural food animal husbandry but also in aquaculture.

In some industries, antimicrobial use is optimised through antimicrobial stewardship programs which provide alternatives to antimicrobials and advice on when best to use them. In countries where resources are limited, the administration of AMR stewardship programs is

limited and antimicrobials are still used without appropriate regulation. Unrestricted use of antimicrobials in food production has a number of major concerns.

a. AMR can emerge and amplify in animals and spread between them. In some instances, AMR pathogens affecting both animals and humans can emerge and cause infectious outbreaks. In other instances, AMR bacteria and genes can move into the microbiomes of farm workers or people who consume the meat, who then act as reservoirs for movement of AMR genes into an infecting pathogen.

b. Antimicrobials can contaminate meat and, when consumed by people, select for AMR in their microbiomes.

c. Manure from food-producing animals used in soils as fertilizer to grow food crops (e.g. vegetables, fruit, grains) may contaminate them with antimicrobials and AMR bacteria, causing AMR selection in soils and movement of AMR into humans through the food chain.

In a world where food is readily traded across borders, AMR in one part of the world can easily move into another part and is one of many reasons why tackling AMR must be a global collaborative effort. Infectious diseases do not respect borders and where there is trade of food and movement of people, AMR will spread.

4. Suboptimal and inappropriate use of antimicrobial chemotherapeutics in human *medicine makes AMR happen faster.* Although antimicrobials are life-saving drugs that should be prescribed whenever necessary, their use in human medicine is the biggest driver of AMR. Decisions on when and how to use antimicrobials in healthcare vary from country to country with many having antimicrobial stewardship programs to reduce unnecessary use. Some countries do not have restrictions and antimicrobials are available over the counter where consumers may make uninformed decisions on antimicrobial use. Antimicrobial stewardship programs assist prescribers make good decisions on selection of antimicrobial for an infection and whether to use it or not. Even with stewardship programs, the selection of an antimicrobial is complex and dependent on multiple factors such as cause of infection, what is known to be effective against the infection and prescriber knowledge. Diagnosis of the infection is important in deciding if an antimicrobial should be used. Some infections like colds are selflimiting and do not require an antimicrobial. As microorganisms become resistant, antimicrobials that once worked may not work anymore and so antimicrobial sensitivity tests are carried out to determine which may work. Sensitivity tests take days, delaying treatment and sometimes forcing prescribers to prescribe antimicrobials in a non-optimal fashion. In some instances, poor antimicrobial prescribing may be due to pressure from patients who feel comforted by taking a drug for an infection (e.g. colds) where it may not have an effect. This is rooted in a misunderstanding over how antimicrobials work with public education campaigns having some benefit in shifting this perspective. On the other hand, prescribers may feel obliged to prescribe an antimicrobial if they are unsure of the diagnosis and want to cover all options. The decision to prescribe an antibiotic is often difficult with prescribers forced to make decisions with limited information although, this can be improved with faster diagnostic and sensitivity tests and antimicrobial stewardship programs.

5. Suboptimal and inappropriate use of antimicrobial chemotherapeutics in veterinary medicine makes AMR happen faster. Owning a pet provides a multitude of benefits including companionship, exercise and a sense of responsibility. Pets can become infected with a number

of pathogens and when this happens benefit from a trip to the veterinary hospital. Antimicrobial chemotherapeutics used in human medicine are also used in veterinary medicine and therefore, contribute to the AMR problem. Generally, factors governing prescribing decisions made by veterinarians overlap with practitioners such as the cause of the infection and pet owner expectations. However, there are some differences that are worth highlighting to help provide an understanding of the prescribing contexts. For example, the costs of diagnostic and sensitivity tests are usually covered by pet owners rather than through nationalised healthcare schemes and if unaffordable, limit the information available to veterinarians in making an optimal prescribing decision. Additionally, while antimicrobials stewardship programs are being developed for veterinary practices, these are not as advanced as those in human medicine. Finally, pets produce waste that may contain unmetabolized antimicrobials and AMR microorganisms (See AMR pollution below) that contribute to AMR and its spread.

6. *AMR is a One Health issue and will require multi-pronged interventions in human, animal and environmental ecosystems.* As we've learned, AMR can emerge in human, animal and environmental ecosystems and will be selected where antimicrobials are used. This means AMR increases and therefore more likely to spread. As humans regularly come into contact with animals and their environment, picking up AMR microorganisms probably happens regularly. Spread from person-to-person can then easily occur.

This does not mean that once someone picks up a resistant microbe, they will keep it forever. Some antimicrobial resistances come with a metabolic burden. That is, they confer a selective advantage when antimicrobials are present but a selective disadvantage when antimicrobials are absent. Therefore, reducing antimicrobial use not only lowers the selection pressure for spread of AMR, but can also result in the loss of some existing resistances in some microbes.

Most global and national AMR mitigation strategies aim to reduce use of antimicrobials and stop spread of AMR microorganisms and genes. If we consider that AMR is occurring a variety of contexts, then we need to find ways of minimising AMR in all these contexts. This requires a One Health approach that means working collaboratively with all stakeholders (e.g. industry, consumers, policy makers) that have influence over AMR to effectively incorporate best practices that minimises AMR. This is a massive undertaking when you consider all the stakeholders involved and the variety of different interactions they have with one another. If we consider food production alone, then stakeholders will include farmers, veterinarians treating livestock, abattoirs, food distributors and consumers.

One example of how an interaction between stakeholders in food production can result in unforeseen increase in the use of antimicrobials are consumers demanding cheap meat in a supermarket. Supermarkets place pressure on farmers which may drive animal rearing practices (e.g. growing animals at high density) that encourage the use of antimicrobials. This is one example but similar complexities can be imagined in veterinarian care of pets (see above) or in AMR pollution (see below).

Interventions may involve governments producing enforceable guidelines on how antimicrobials should be used in food production, others may include educating stakeholders such as consumers on how demand for cheap meat drives antimicrobial use and AMR. Whilst interventions are important, they must be done in collaboration with affected stakeholders and in a respectful way such that it recognises and thus minimises, the impact of AMR interventions on livelihoods.

7. Antimicrobial and AMR pollution helps AMR spread faster. Antimicrobials and AMR bacteria and genes are emerging as pollutants. When humans and animals are given antimicrobials, approximately 50% or more is passed through the body unmetabolized and enters into waste streams. Additionally, waste from hospitals and antimicrobial manufacturing plants contain high concentrations of antimicrobials. Without treatment, these antimicrobial pollutants exert selection pressure in wastewater pipes and treatment plants, and in the environment if not removed. Apart from driving AMR, antimicrobial pollution may disrupt the function of microorganisms in natural environmental ecosystems. AMR bacteria and genes in human and food-producing animal waste, including that from aquaculture, can spread AMR into the environment and wild animals through gene sharing where they can act as reservoirs. Even with excellent control of AMR spread in healthcare environments, AMR can readily reenter from these reservoirs.

Chemotherapeutic antimicrobials are mostly antibiotics (see Box) which are chemicals produced by microorganisms to outcompete each other. Over millions of years, microorganisms have evolved resistance and, in most cases, problematic pathogens contain AMR genes that have been relocated from environmental microorganisms. Research has found substantial diversity of AMR genes in soil and aquatic environments indicating a vast reservoir. AMR genes in microorganisms from humans and animals are mostly associated with DNA called mobile genetic elements which are primed to capture *new* AMR genes as they evolve and travel from microorganism to microorganism. Therefore, AMR pollution increases the likelihood that AMR genes resistant to new antimicrobials will be captured and relocated into pathogens.

8. Antimicrobials affect microbiomes. Historically, there has been a sense that antimicrobials are a silver bullet that fight infection and don't have side effects. Apart from driving AMR, chemotherapeutic use of antimicrobials can impact your natural microbiome. Although antimicrobials are selective in that they target microorganisms and not your cells, they are not so selective that they will not affect the natural microorganisms in and on your body. This is why doctors sometimes recommend a probiotic to minimise the effect of the antimicrobial on the microbiome. A healthy microbiome is important for digestion, preventing infection and building immunity. As such, taking a course of antimicrobials can cause an upset gut and in infants, disrupt normal development of the microbiome. Some antimicrobials cause such detrimental impacts on the host microbiome that it can leave people susceptible to a dangerous gut infection caused by a bacterium called *Clostridium difficile*. In many instances, restoration of the microbiome through a faecal transplant is the only treatment.

9. Government funded research is essential for improving AMR. Most global and national AMR strategies rely on preserving our current antimicrobials through optimal use, preventing spread of AMR and developing new antimicrobials and non-antimicrobial treatments. Currently, research into new antimicrobials is being largely driven by government funding because most pharmaceutical companies have determined that it is not a profitable venture. Discovering and developing new antimicrobials is costly and the return-on-investment is low in comparison to other pharmaceuticals. Drugs such as those used in managing chronic conditions (e.g. blood pressure) are taken regularly by patients and provide a constant source of income. In comparison, antibiotic treatments typically last for 5-10 days, and are 'one-off'. Moreover, resistance to a new antimicrobial chemotherapeutic develops within 1-2 years which restricts its effectiveness, and hence its use and profitability. As a result, the cost for development of new antimicrobials will need to be borne by government funding.

While there will always be a use for antimicrobials in the foreseeable future, other nonantimicrobial treatments will need to be developed to replace and reduce antimicrobial use, and these will also require governmental funding. Vaccines are one such option which can protect people from being infected by priming their immune system to kill the infecting pathogens. Another option is bacteriophage therapy. Bacteriophage are viruses that attack and kill bacteria which can be administered to treat infections. There are other promising technologies but before they can be used for treatment, more research is required to ensure its safety and efficacy.

Relevance for Sustainable Development Goals and Grand Challenges

Microorganisms are part of the biosphere and AMR is a direct result of the selection pressure applied by human use of antimicrobial chemotherapeutics. As a result, AMR is directly linked to 6 SDSs (*microbial aspects in italics*), including:

- Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture (ensure sustainable food production systems and implement resilient agricultural practice that increase productivity and productions, that help maintain ecosystems). The use of antimicrobials in food production to protect from disease addresses the issue of food security, but only in the short-term as resistance will emerge. Additionally, antimicrobials provided in feed in low doses have growth promotion activity in livestock. Because of AMR, use of antimicrobials in food production. Additionally, antimicrobials impact soil and water ecosystem function. In developing nations where food is limited, the decision to use antimicrobials is contextual. Ending hunger is a need that is immediate whereas AMR is a consequence that occurs later. Antimicrobial stewardship programs and modified agricultural practices have had extensive success in some countries without affecting productivity.
- Goal 3: Ensure healthy lives and promote well-being for all at all ages (*Reduce mortality and end epidemics of infectious disease and, support research and development of vaccines and medicines for infectious disease*). As AMR worsens, mortality and morbidity from infectious diseases will increase. It will also heighten the risk of other medical procedures that rely on antimicrobials to prevent infection. Increased morbidity will increase the economic health burden. Support into the research and development of new vaccines, antimicrobials and treatments, and more rapid antimicrobial sensitivity tests, will be pivotal in attaining this SDG. AMR is global and spreads across borders so new technologies will need to be accessible in all countries.
- Goal 6: Ensure availability and sustainable management of water and sanitation for all (access to safe and affordable drinking water, adequate sanitation and hygiene and, reducing water pollution). Unpolluted water that does not spread AMR requires infrastructure that improves sanitation by effectively treating human and animal waste. Water with polluting antimicrobials can encourage AMR in those that drink it. Most developed countries have well developed wastewater treatment systems where waste is treated before being released into the environment. Wastewater treatment systems act as a barrier to the spread of especially intestinal microbes, many of which are AMR. Many developing countries do not have this infrastructure so there is no barrier, with the resulting increase in the spread of AMR to the microbiomes of local people.

- Goal 8: Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all (*promote economic growth, productivity and innovation, enterprise and employment creation*). Economic growth is contingent on a healthy workforce and so having effective antimicrobials for clinical medicine is important. Left unchecked, AMR will continue to increase morbidity and mortality which will weaken a nation's economic power. Research into new therapies or technologies that reduce AMR will result in new innovations, enterprise and therefore employment. As policies are put in place to optimise use of antimicrobials, a One Health approach requires us to engage with affected stakeholders to minimise loss of employment. For example, a reduction of antimicrobial use in Dutch agriculture was paired with veterinarians promoting preventative healthcare to replace therapeutic healthcare, thereby maintaining employment.
- Goal 12: Ensure sustainable consumption and production patterns (achieve sustainable production and use/consumption practices, reduce waste production/pollutant release into the environment, attain zero waste lifecycles, information people about sustainable development practices). Infectious outbreaks in agriculture are promoted by poor practices that attempt to maximise productivity by maximising animal growth and the density of animals grown on a piece of land. This is driven by economic demand for cheap meat. Apart from environmental damage, these practices drive the use of antimicrobials to control disease or promote growth and thus, drive AMR. Animal waste contaminates the environment with AMR and unmetabolised antimicrobials.
- Goal 14: Conserve and sustainably use the oceans, seas and marine resources for sustainable development (*reduce marine pollution*). Marine environments are often the end point of human and animal waste. Antimicrobials impact the ecological function of these environments by inhibiting or killing microorganisms. Many marine microorganisms play important roles in nutrient cycling and, as the base of the food web, support the growth of higher marine organisms. AMR waste can also constitute an exposure risk to those that recreationally use coastal beaches (e.g. swimming). People that use marine waters for fishing are at risk if the fish have been exposed to AMR waste and are consumed.

Potential Implications for Decisions

1. Individual decisions relating to the AMR crisis

a. Asking the doctor for an antimicrobial and placing unnecessary pressure for a prescription. Is this request based on fear or on the doctor's diagnosis? (i.e. some patients feel comforted by having a treatment for an illness that will resolve itself).

b. Eating less meat. The more demand for meat, the more pressure to use antimicrobials.

c. Eating sustainably produced meat where antimicrobials are not used unnecessarily (costs more but has greater health and environmental benefits).

d. Deciding to own a pet. Weighing up benefits of pet ownership resulting in antimicrobial use in veterinary care.

e. Practicing good hygiene. Reducing the spread of infectious diseases to minimise antimicrobial use.

f. Activism. Encouraging policymakers to fund programs that reduce AMR and research for identifying new antimicrobials and therapies.

2. Community policies relating to the AMR crisis

a. Introduction of antimicrobial stewardship programs

b. Campaigns and educational activities on the dangers of AMR and how to minimize it.

3. National policies relating to the AMR crisis

a. Healthcare costs associated with people requiring hospitalisation and other costly therapies.

b. Economic costs associated with people unable to carry out work-related duties.

c. Impact of intervention relating to restricting antimicrobial use and AMR spread on livelihoods.

d. Costs associated with improving wastewater infrastructure to reduce AMR spread.

Pupil Participation

1. Class discussion on why AMR is a One Health issue.

- a. Class discussion on factors driving the AMR crisis.
 - i. In human healthcare
 - ii. In animals including food production
 - iii. In the environment

2. Pupil stakeholder awareness

a. Rising AMR will make it harder to meet the SDG on healthy lives particularly in developing countries. What are some other global actions we could take to minimise death from infection in developing countries besides use of antimicrobials.

- b. Where would you like to see governments spend money to help manage AMR?
- c. What are some easy choices you can make to help minimise AMR?
- d. People sick for longer and unable to carry out duties such as work that brings in income. What are the consequences for the family?
- e. People sick for longer and unable to carry out duties such as looking after other family members. What are the consequences for cohesiveness of family unit and mental health?
- f. People dying increasing the level of fear of infection. What are the possible consequences for how people spend time with one another and for developments such as stigma associated with others being ill?
- g. Fear of activities associated with injury or higher risk of illness. What are the possible consequences (e.g. swimming in polluted aquatic environments)?
- h. Disproportionate impact of AMR on developing countries that have underresourced healthcare systems. What are the possible consequences?

3. Exercises

a. Now that you know that antimicrobial use leads to AMR, do you think these drugs should be used for pets? If so, why? If not, why?

b. What options exist to minimise use of antimicrobials in food production?

c. In developing countries, children are dying from a lack of access to antimicrobial chemotherapeutics. How do you think developed countries should help?

d. Come up with a list of interventions for minimising AMR and then rank them. Consider the costs of having to implement each intervention.

e. Come up with 1-2 messages for communicating AMR to your friends and family. How would you present it in a pamphlet?

The Evidence Base, Further Reading and Teaching Aids

For additional reading, there are some excellent reports on AMR that is targeted toward a broad audience. These include:

O'Neill, J. 2016. Tackling drug-resistance infections globally: Final Report and Recommendations. The Review on Antimicrobial Resistance.

https://amr-review.org/sites/default/files/160525 Final%20paper with%20cover.pdf

The executive summary (4 pages) is sufficient however, the reader may choose to read chapters for more detail.

World Health Organisation. 2015. Global action plan on antimicrobial resistance.

https://ahpsr.who.int/publications/i/item/global-action-plan-on-antimicrobial-resistance

Glossary

Antimicrobial chemotherapeutic: Chemical that inhibits or kills infecting microorganisms and is used in medicine to prevent or treat infections.

Antimicrobial resistance: When a microorganism changes and becomes resistant to a chemotherapeutic.

Antimicrobial sensitivity test: A laboratory test that test the sensitivity of a microorganism against a specific antimicrobial.

Antimicrobial stewardship program: Procedures and guidelines that promote optimal use of antimicrobials.

Bacteriophage: A virus that infects bacteria and uses it to replicate itself.

Epidemic: A disease affecting people above normal incidence within a population, community or region.

Evolution: Change in the heritable characteristics of living organisms over time.

Faecal transplant: When faecal material from a healthy person is transplanted into another to promote a healthy gut microbiome.

Hygiene: Behaviours that preserve health (e.g. hand washing).

Infection: When a microorganism causes disease in a human or animal.

Microbiome: The total microorganisms that make up a particular environment (e.g. gut microbiome).

Microorganisms: Microscopic organisms that are observed using microscopy.

Mobile genetic element: Genetic material (DNA) that can move between cells or between DNA locations.

One Health: A concept that recognises that human, animal and environmental health are linked.

Pandemic: When an epidemic breaks geographic boundaries such as country borders or water borders separating continents.

Pathogen: An agent that causes disease in humans or animals.

Probiotic: A supplement containing healthy and safe live microorganisms.

Resistance gene: DNA sequence coding a gene that gives resistance to an antimicrobial(s).

Sanitation: Procedures and measures used by governments to protect public health (e.g. disposal of sewage)

Selection pressure: A pressure that favours s characteristic(s) in a population over another.

Vaccination: A preparation administered to people and animals that primes their immune system to protect against pathogens.