CIS\*4020 - Introduction to AMR

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# What is Antimicrobial Resistance (AMR)?

Antimicrobial resistance, often referred to as AMR, is a broad term referring to pathogens (bacteria, fungi, parasites, and parasites) developing natural defence mechanisms against the drugs we use to treat for them. These defence adaptations make it difficult to treat against infections caused by these agents and can lead to an increase in disease spread and mortality. For example, a common ear infection, caused by Strep. pneumonia, can often be resolved in about a week with oral antibiotics, however if the bacteria responsible for the infection has developed antimicrobial resistance to the drug you have been prescribed the infection may not clear up for several weeks or longer, if at all. For minor infections this could mean prolonged symptoms and discomfort, but for more serious infections this could lead to permanent disability or death.

Pathogens, just like all living things, are constantly evolving. Although these organisms are not making conscious decisions to change, changes to their genetic make-up can occur sporadically and by random chance. When a change happens to result in some form of survival benefit (i.e., stronger, faster, more resilient), that change is more likely to be passed down to the next generation since the bacteria has a higher chance of making it to the point of multiplying. Luckily for us, our immune system is equally as clever and can make counter-adaptations in a never-ending cat-and-mouse game of survival. While it may seem like it would take a while to ever come across a beneficial adaptation by randomly changing single lines of genetic code (just as it would take a while to improve computer code by randomly changing lines or commands), it is important to remember that pathogen populations exist in the millions, with each presenting an opportunity to adapt.

In 1928, a London-based scientist, Alexander Flemming, made a discovery that certain mold spores can be used to eliminate bacterial species in a lab setting\*. Shortly after, the practice of prescribing derivatives of these spores (antibiotics) began and revolutionized the medical field. Infections that were once a death sentence could now be resolved with a simple, non-invasive, prescription. Thus began the “antibiotic era”, where for a while, people began to think that bacterial infections were a thing of the past, and doctors were prescribing habitually. Unfortunately for us, the pathogens we thought we had defeated were using the overuse of antibiotics to their advantage and continued to modify their genetics to develop mechanisms of evading our attacks.

Today, many of the earliest discovered antibiotics are becoming increasingly less effective against infections. If we take our ear infection from earlier for example, the bacteria responsible (Strep. pneumonia), is estimated to be resistant to Flemming’s originally discovered penicillin in about 63.5% of cases (Anar et al., 2022). Because bacteria and other pathogens are clever, misuse and overuse of antibiotics are the primary drivers of antimicrobial resistance, as it provides them with more opportunity to develop and pass down defences (WHO 2021).

*\*Fun Fact: Many antibiotics we use today are derivatives of organisms found in soil. So, the phrase ‘rub some dirt in it’ may have some merit.*

# Why is AMR important?

The development of antibiotics has effectively stalled, for biological, economic, and political reasons. Of the 18 largest pharmaceutical companies, 15 have all but abandoned their research efforts into new antibiotics (Ventola, 2015). As a result, the arsenal of antibiotics we currently have is all we will have for the foreseeable future. Therefore, as micro-organisms become more-and-more resistant, we lose more-and-more options for treating infections. Making matters worse, many antibiotics use similar mechanisms of action, therefore when pathogens develop a defence to one attack, it can mean that several drugs of the same class (see ‘nuances of AMR’) or similar classes. Once we lose the effectiveness of an antibiotic to a pathogen, it is virtually impossible to get it back. This means that we are slowly losing the magic bullet that we discovered back in 1928 and are slowly returning to the days where a simple infection can lead to serious consequences.

AMR is often referred to as a slow-moving pandemic. Unlike COVID-19, which hit us hard and fast, AMR is a slow burn. This does not make it any less threatening, as it is estimated that by 2050, we will see 10 million deaths per year because of resistant infections. For context, as of September 8, 2023, Worldometer estimates that COVID-19 has led to just about 7 million deaths total in 2.5 years (Worldometer, 2023). It is estimated that 4.95 million deaths are already attributable to AMR (AMR Collaborators, 2022), which means we are well on track for 10 million by 2050.

# Nuances of AMR

Antimicrobial resistance is a complex problem, and there are several nuances that you should be familiar with for this course. In this course you will only focus on bacterial infections, and therefore the different pathogen types (i.e., bacteria, fungi, parasites, and viruses) will not need to be considered. Entire courses and programs are devoted to understanding all the fine details of AMR, however, for this course there are only a handful of nuances that you should understand to make sense of the data and solve the problem at hand.

## Classes of antibiotics

Antibiotics, used to treat bacterial infections exist in families, called classes. Antibiotics of the same class use common mechanisms of action to combat bacterial species and were often derived from a common ancestor drug. There are several reasons for why we have multiple drugs per class, but the details are not important for this class. Therefore, as mentioned above, when a bacterial species develops resistance to an antibiotic’s method of attack, it is usually observed that drugs of the same class will similarly become less effective. Below is a figure outlining the most common antibiotic drug classes, however in this course we have removed all drug names and replaced them with pseudonyms. Drug classes have also been given fake names, but the relationships in the data should remain. Each drug in the dataset has been given a name with a letter and a number; the letter corresponds to the drug class, and the number is used to differentiate it from other drugs in the same class (i.e., Drug B3 and Drug B7 are members of the same family).

A chart of the different classes of antibiotics

Description automatically generated

Figure 1. Common classes of antibiotics and when they were discovered. \*\*Just for interest. <https://www.compoundchem.com/2014/09/08/antibiotics/>

Now, let's address a critical concern: the development of resistance. When a bacterial species becomes resistant to one antibiotic's method of attack, it frequently exhibits resistance to other drugs within the same class. This phenomenon occurs because antibiotics in the same class typically share similar mechanisms of action. For instance, if bacteria develop resistance to an antibiotic like Drug B3 (where B denotes the drug class), other antibiotics within the B class may also become less effective against those resistant bacteria. This is why a tiered approach to antibiotic usage is crucial in the battle against AMR.

### The Tiered Approach to antibiotics

Tier 1: First-Line Drugs: These are the initial antibiotics prescribed for common infections. They are broad-spectrum antibiotics effective against a wide range of bacteria. First-line drugs are generally safe and well-tolerated. Their widespread use helps combat common infections effectively while minimizing the risk of resistance development.

Tier 2: Second-Line Drugs: When first-line drugs are ineffective or specific factors require an alternative, second-line drugs come into play. These antibiotics may have a narrower spectrum of activity or may be more potent. They serve as valuable alternatives when needed.

Tier 3: Last-Resort Drugs: Last-resort antibiotics are the most critical and potent. They are reserved for severe infections that do not respond to first or second-line treatments. Using last-resort drugs is a measure of last resort, considering their potential for more significant side effects and higher costs.

Responsible antibiotic usage involves matching the right tier of antibiotic to the severity of the infection. By using the lowest effective tier, we reduce the risk of resistance development and preserve the effectiveness of last-resort antibiotics for the most severe cases. Understanding the tiered approach to antibiotic usage is paramount in the fight against AMR. By deploying antibiotics strategically and reserving critical drugs for the direst situations, we can slow the pace of resistance and ensure that our antibiotic arsenal remains potent when confronting the most challenging infections.

## Infection Charcteristics (i.e., type and location)

Companion animals, such as cats and dogs, can contract a variety of infections, and these infections can manifest in different ways. Some common types of infections include skin and soft tissue infections, urinary tract infections, respiratory infections, and gastrointestinal infections. The type of infection often determines the clinical symptoms and the appropriate treatment approach. Moreover, the location of the infection within the animal's body can greatly influence its severity and the choice of treatment. For instance, a skin infection may present as a localized rash or abscess, while a urinary tract infection affects the urinary system. Understanding the type and location of infections in companion animals is essential for veterinarians to diagnose and treat these conditions effectively. In the context of AMR, the type of infection and its location can impact the choice of antibiotics and susceptibility patterns. Some bacteria are more commonly associated with specific types of infections, and this knowledge is valuable when analyzing susceptibility testing data and developing strategies to combat AMR in cats and dogs.

## Bacterium Characteristics

One fundamental classification among bacteria is the division into two groups: Gram-negative and Gram-positive. This distinction is based on the structure of their cell walls and has significant implications for AMR.

### Gram-Negative Bacteria

These bacteria have a double-membrane cell wall, making them more resilient. They often pose substantial challenges in treating infections because their outer membrane acts as a fortress, preventing antibiotics from penetrating. Notable Gram-negative bacteria include Escherichia coli and Pseudomonas aeruginosa. Due to their complex cell structure, they tend to exhibit diverse resistance mechanisms.

### Gram-POsitive bacteria

In contrast, Gram-positive bacteria have a simpler cell wall structure, making them somewhat more vulnerable to antibiotics. However, don't let their apparent vulnerability fool you. They can develop resistance through various mechanisms. Staphylococcus aureus and Streptococcus species are prominent examples of Gram-positive bacteria commonly found in companion animals. Understanding the differences between these two groups is essential because susceptibility patterns can vary. For instance, antibiotics effective against Gram-positive bacteria might not work as effectively against Gram-negative ones and vice versa.

### Transfer of Resisatnce genes

Bacteria, like all living organisms, are constantly trying to adapt for survival. When faced with antibiotics, they employ various strategies to outsmart these drugs. One of these strategies involves transferring resistance genes horizontally among themselves.

**Imagine this**: Bacteria of different species or even the same species but with varying resistance profiles come into contact. They can exchange genetic material, including resistance genes. This exchange can occur through mechanisms such as plasmids, transposons, and conjugation.

Plasmids, for instance, are small, circular DNA molecules separate from the bacterial chromosome. They can carry resistance genes and are easily shared among bacteria. When a bacterium acquires a plasmid containing resistance genes, it gains the ability to withstand antibiotics, potentially leading to AMR. This ability of bacteria to transfer resistance genes horizontally means that even if one bacterial strain develops resistance, it can quickly share this trait with others, fostering the spread of resistance within a bacterial community. This phenomenon emphasizes the interconnectedness of AMR across various bacterial species and highlights the importance of surveillance and understanding resistance patterns, especially within bacterial families.

# What makes AMR in cats and dogs important?

Understanding AMR in companion animals, such as cats and dogs, holds significant importance in the context of "One Health." This term underscores the interconnectedness of human, animal, and environmental health and emphasizes the need for a comprehensive approach to address health issues in all these domains. AMR in companion animals has far-reaching implications. When companion animals develop AMR, antibiotic-resistant bacteria can potentially enter human households. Due to close contact between pets and humans, there's a risk of transmitting these resistant bacteria, potentially leading to infections in both pets and their owners. Humans and animals often share the same antibiotics. When antibiotics become less effective in animals due to AMR, it reduces the available options for treating human infections. This shared pool of antibiotics means that responsible antibiotic use in companion animals is crucial to preserve these medications' effectiveness for treating infections in both animals and humans.

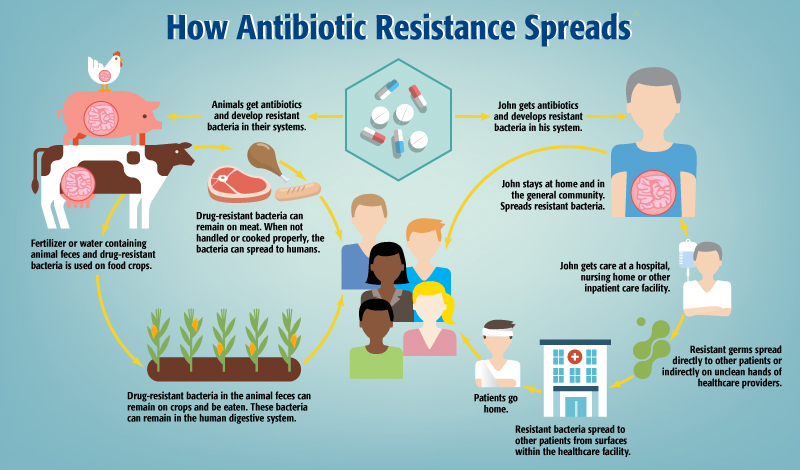


Figure 2. Visual explaination of the One Health cycle of aMR spread between humans, animals and the environment. <https://www.biomerieuxconnection.com/2018/07/12/explain-antimicrobial-resistance-friends-family-infographics/>

# How do we test for AMR?

This section is intended to give you some background on how we determine whether bacteria are resistant to antibiotics. This information is strictly to provide context. In the data you will be working with, the test results have resulted from an automated machine detection system. The simplified process of testing looks something like this:

1. A sample is taken from the infection site of the infected animal. This could mean taking a sample of urine, a swab from an ear or a sample of puss from an infected wound. Sample collection is performed by the veterinarian. The sample is then packaged and sent into a lab.
2. When the sample arrives at the lab, the first step is to determine which pathogen(s) are present. This is done in a variety of ways. This name of the identified bacterium is recorded.
3. A small, standardized amount of the bacteria are then prepared at a specified concentration.
4. Small amounts of the bacteria are then introduced to varying concentrations of a given antibiotic solution.
5. The mixture of bacteria and antibiotic are then monitored to determine if the bacteria are still growing, and if so, how much are they growing. If the bacteria are still growing, then they are likely resistant to the antibiotic. Based on the concentration of the drug required to prevent growth (called the ‘Minimum Inhibitory Concentration (MIC)), each drug is recorded as being either resistant (R), intermediate (I), or susceptible (S). See example table below for what these test results may look like.

When a bacterium is categorized as "Susceptible" (S) to a specific antibiotic, it means that the antibiotic is effective in inhibiting the growth of that bacterium. In practical terms, this suggests that the antibiotic can be used as a treatment option for infections caused by this bacterium. When a bacterium is classified as "Intermediate" (I), it implies that the antibiotic's effectiveness against that bacterium is uncertain or variable. The antibiotic may inhibit bacterial growth, but it might not do so reliably or may require higher doses. A bacterium is labeled as "Resistant" (R) when it is not effectively inhibited by the antibiotic being tested. This implies that the antibiotic is unlikely to be successful in treating infections caused by this bacterium.

Antimicrobial susceptibly testing (AST) is typically performed multiple times against a panel of different drugs. On average, a submitted sample may be tested against 12 or so different drugs of the same or differing classes. This provides the veterinarian or doctor with a results sheet indicating which drugs are likely to be effective for the patient and which will likely not clear up the infection.

Table 1. example of antimicrobial suscpetibility test results.

|  |  |  |
| --- | --- | --- |
| Tracheal aspirate: *Pseudomonas aeruginosa* | | |
| Antibiotic | Minimum inhibitory concentration | Interpretation |
| Aztreonam | 8 | S |
| Ceftriaxone | >32 | R |
| Cefepime | 2 | S |
| Ciprofloxacin | <= 1 | I |
| Gentamicin | 2 | S |
| Meropenem | <= 0.5 | S |
| Piperacillin/Tazobactam | <= 4/4 | S |

# The problem to be solved

Susceptibility testing can be expensive and lead to treatment delays for pet owners. Consequently, many veterinarians and pet owners bypass this testing and opt for a broad-spectrum medication, hoping it will do the job. However, if the infection is resistant, this approach is ineffective, and they often must resort to a more potent medication later. Veterinarians typically select antibiotics based on their past experiences with similar infections, advice from seasoned colleagues, or established guidelines. Keep in mind that bacteria with the same name are not always identical and although may show similar resistance patterns to each other, may not always. For example, one infection caused by *E. coli* may be susceptible to amoxicillin while another may be resistant. This is why individual-level testing is important.

Our aim is to encourage veterinarians to make data-driven decisions by giving them a tool to visualize patterns of antimicrobial resistance specific to their cases. To make this possible, a commercial laboratory in New York State has supplied us with four years' worth of data (from 2019 to 2022) on antimicrobial susceptibility test results\*. Each dataset entry represents a sample previously submitted to the lab by a veterinarian, originating from a canine or feline patient. This data includes patient descriptors (like age, infection site, and sample source), spatiotemporal information (such as State, County, ZIP code, year, and month), and susceptibility test results for approximately 50 different antibiotics.

**Scenario:** a client brings in their pet with an infection, but they can't afford to wait for susceptibility testing before starting treatment. Instead of relying solely on their past experiences, the veterinarian opens your dashboard to determine which drugs are likely to be effective based on specific details about the patient's condition, which may include location, time of year, species, and the type of bacteria involved. Remember, the veterinarian may have no idea which bacteria is present in the infection, since this is information, they would typically receive from the lab during testing. Therefore, a useful component of the dashboard would be the ability to see which bacteria are commonly present in similar infections.

*\*this is a hypothetical scenario, and all susceptibility test results are synthetically generated.*

# DEscription of the data

|  |  |  |
| --- | --- | --- |
| Variable name | Description | Example |
| id | Deidentified patient identification number. | 969167 |
| state | State from which the sample originated. | New York |
| county | County from which the sample originated. | Suffolk |
| zip\_3\_level | ZIP code from which the sample originated (truncated to 3 digits for privacy) | 117 |
| order\_year | Year that the sample was submitted. | 2020 |
| order\_month | Month that the sample was submitted. | 7 |
| species | Species from which the sample originated. (Patient species) | CANINE |
| panel\_name | The type of test panel the sample was tested against. When a sample is submitted, the veterinarian can select from a list of panels to test against. The choice of panel is dependent on several biological factors. | AEROBIC CULTURE |
| assay\_name | The type of test assays the sample was tested against. For this course, can be treated as like panel\_name. assay\_name, unlike panel\_name is a mandatory field. | Aerobic Culture |
| remark | Section for veterinarian or lab to make notes about the patient. | NA |
| site | Site on the animal from which the sample was taken from. | CLOSED ABCESS OVER R EYE… |
| source | The method of sample collection used to obtain the sample. | EYE |
| org\_standard | FILLED IN BY LAB: the identified bacterial species found in the sample and used in susceptibility testing. | *E. coli* |
| age\_year | Age (in years) of the cat or dog from which the sample was taken from. | 6 |
| R1, H1, W1, N5, … Y1 | FILLED IN BY LAB: Susceptibility test results. | S, R, I, TF (to follow), N/I (not interpretable). **NOTE:** not all samples are tested against every drug, therefore the majority of test columns will be NA for a given row. |

# Documents

|  |  |
| --- | --- |
| ‘CIS4020AMRData.csv’ | Antimicrobial susceptibility testing data for NY State (2019-2022), csv file. |
| ‘CIS4020AMRData. | Antimicrobial susceptibility testing data for NY State (2019-2022), parquet file. Opened with ‘read\_parquet()’ from the ‘Arrow’ package. |
| ‘CIS4020DrugTiers.csv’ | Data key with a complete list of the antibiotics included in the testing data and their respective tiers. |

# References

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