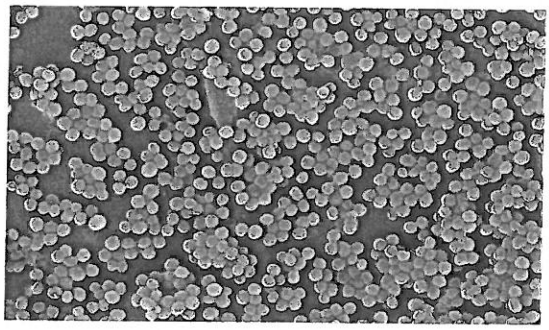
What is antibiotic resistance?



Bacteria

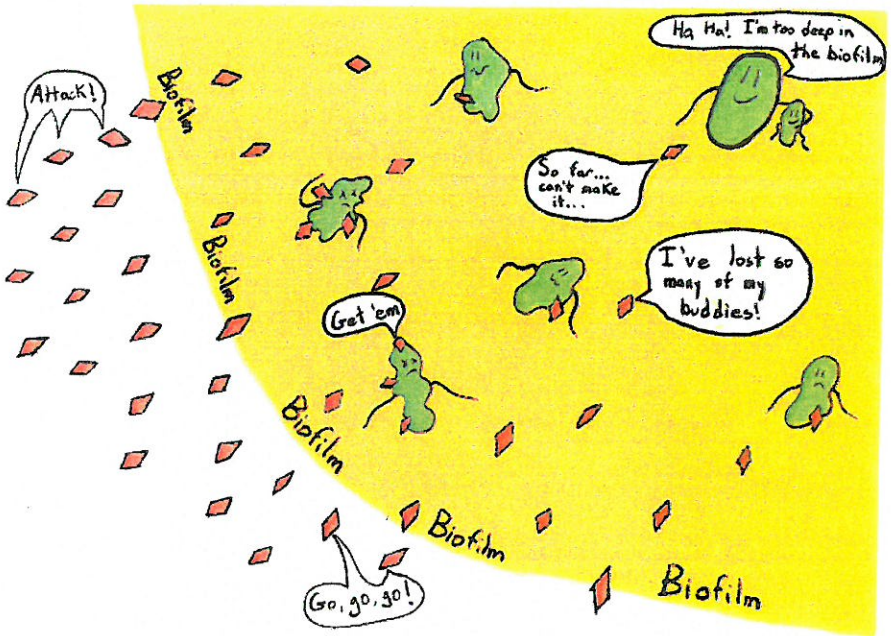
Antibiotic resistance describes a bacteria's ability to survive while being exposed to antibiotics.

How does antibiotic resistance develop exactly?

When a bacteria is exposed to antibiotics there are three possible outcomes - they will die, they will stagnate (not multiply), or they will multiply. Three main factors will predict which is more likely to happen; antibiotic concentration, bacterial mutation, and bacterial genetic exchange.

Antibiotic concentration

Generally, the more antibiotic getting to a bacteria will cause it to stagnate/die, and less antibiotic will allow it to multiply. Some bacteria live within a "biofilm", which is a jelly-like substance where thousands of bacterial cells are suspended inside (think raspberry seeds in raspberry jelly). It's sort of like a big, thick energy shield. The antibiotic has to move (diffuse) through the biofilm to reach all of the bacterial cells. Some cells that are buried deep within the biofilm are exposed to only a fraction of the antibiotic that reaches the surface.



Antibiotics traveling through biofilm

Bacterial mutation

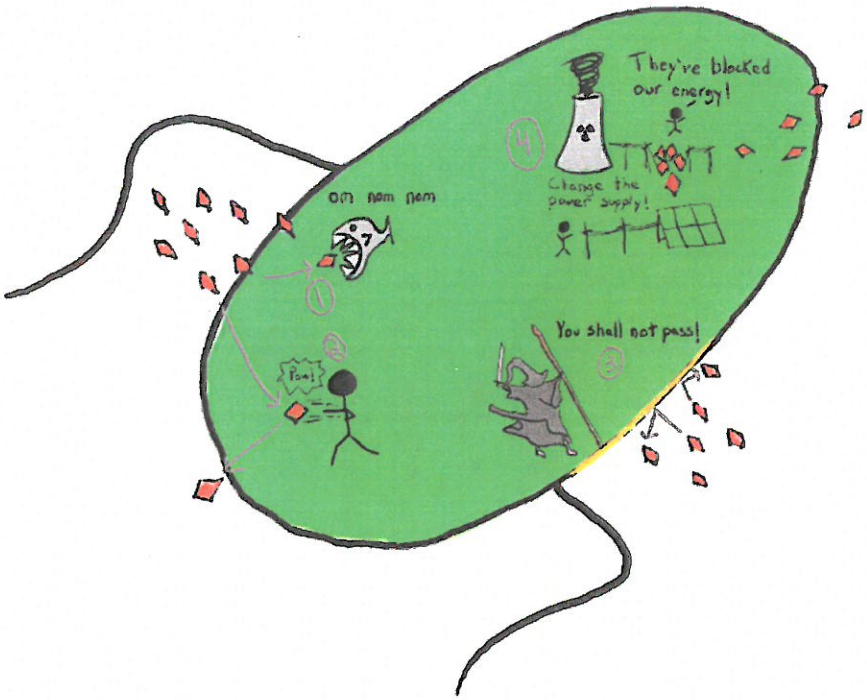
When bacterial cells replicate, there is a small chance the new bacterial cell will not be exactly the same as the original bacterial cell. We call these errors in the copied cell a mutation. In one bacterial cell, the cell wall could be slightly different, in another an enzyme works poorly, and so on. Mutations are key to the idea of evolution, and all of the diversity you can see in nature came from a series of many mutations over hundreds of thousands of years. In animals, it can take centuries or millennia for a species to adopt a mutation which helps it survive (and sometimes these mutations create entirely new species). It takes this long in animals because it takes years for most animals to grow up and reproduce.

Bacteria on the other hand can multiply within hours, allowing for more mutations to occur over a shorter period of time. These mutations (such as a change to the bacteria's cell wall) can make it difficult for the antibiotics to enter the bacteria or stick to it, making the antibiotic less effective at hurting or killing the bacteria.

There are four common mutations bacteria undergo to become resistant to antibiotics:

1. Enzymes in the bacteria eat and deactivate antibiotics.
2. Antibiotics are ejected from the bacteria.
3. The bacterial wall prevents antibiotics from entering.

4. The bacteria adopts a new way of processing energy (as some antibiotics interfere with the energy process).



Bacterial mutations to fight antibiotics

These little mutant bacteria may thrive where the non-mutant bacteria die, and new antibiotics (or more of the same antibiotic, if the mutants are only slightly resistant) must be used to kill them.

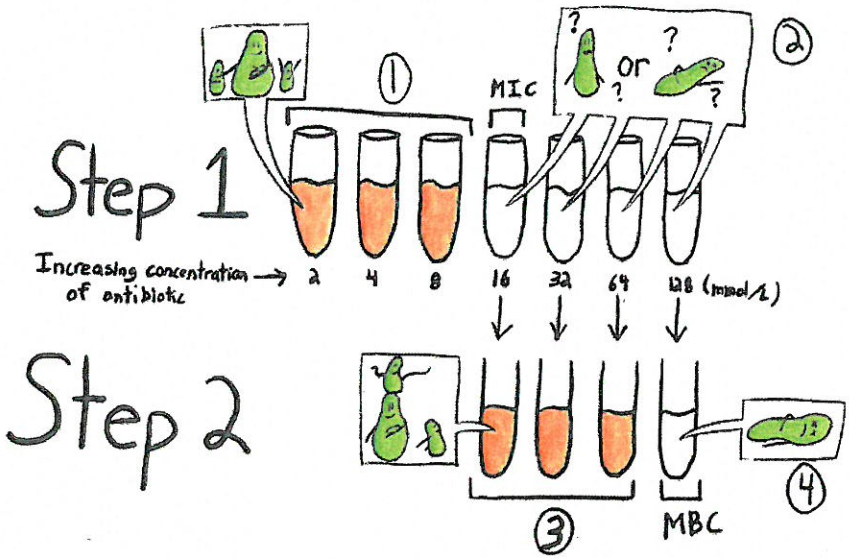
Humans continue to search for new antibiotics to help the immune system, and bacteria continue to have mutant members in their colonies that can potentially resist antibiotics!

Bacterial genetic exchange

A curious habit of bacteria is that they love to share information when they meet, like two old friends at the park. This happens even between two different bacterial species. As a result, once a single bacterial species has managed to resist antibiotics with a gene(s), that gene(s) can get copied and passed around to other bacteria. It's like passing around a juicy bit of gossip - as more meetings occur, more and more bacteria learn how to resist an antibiotic!

How do we measure antibiotic resistance?

In order to pick the best antibiotic for treating the infection, its useful to know how effective the antibiotic would be at preventing a bacteria from growing or simply killing the bacteria. You can do an experiment to figure it out! You can even see how resistant bacteria is to antibiotics by running the same experiment multiple times using a variety of antibiotics.



Finding MIC and MAC

Step 1:

Place a tiny but **equal** amount of bacteria into a series of test tubes full of clear, nutritious bacterial broth (chicken soup for the bacteria!). Next, put increasing amounts of antibiotic into the test tubes (doubling the antibiotic concentration as you go). Now wait 24 hours.

1. Some of the tubes have turned cloudy! The concentration of the antibiotic in these tubes are too low to prevent the bacteria from multiplying.

2. Some of the tubes are still clear! The concentration of the antibiotic in these tubes are high enough to prevent the bacteria from multiplying. The lowest concentration of an antibiotic needed to stop bacteria from multiplying is called the **Minimum Inhibitory Concentration (MIC)**. In the diagram above, the MIC is the first clear test tube. But wait! Are the concentrations of the antibiotic in these clear tubes enough to kill the bacteria or just stop them from multiplying? We can find out!

Step 2:

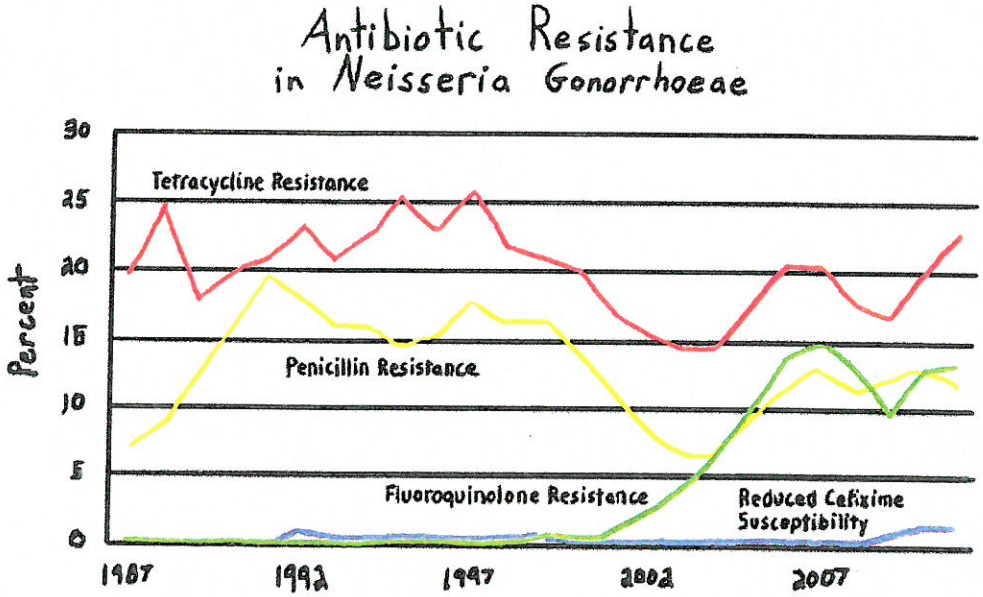
Take a small sample of fluid from each of the clear test tubes in step 1 and put each sample into a new test tube filled with broth. Do **not** put antibiotics in these new test tubes. Once again wait 24 hours. Note: There will be a bit of antibiotic carried in the sample from step 1, however not enough to affect the results in step 2.

3. Some of the test tubes have turned cloudy! The bacteria is growing again! This means the concentration of the antibiotic in step 1 didn't kill the bacteria, just stopped it from multiplying.

4. Some of the test tubes are still clear! This means the concentration of the antibiotic in step 1 killed the bacteria. The lowest concentration of an antibiotic needed to kill the bacteria is called the **Minimum Bactericidal Concentration** (MBC). In the diagram above, the first clear test tube in step 2 is the MBC.

Once you know the concentration of an antibiotic needed to stop a bacteria from growing (MIC) or living (MBC), you need to know whether that concentration can be safely given to a person. If so, then we would say that a bacteria is "susceptible" to an antibiotic, and if not, then we would say that a bacteria is "resistant" to an antibiotic. The goal is to pick an antibiotic that will be effective against the bacteria causing an infection, but won't hurt a patient or destroy their healthy ecosystem of bacteria.

How resistant have pathogens become?



Antibiotic resistance of pathogens graphed over time

Over the years some bacteria have become more resistant to antibiotics than others. Here's a quick glance at some of the most common and/or concerning resistant bacteria:

- **Carbapenem-resistant enterobacteriaceae (CRE):** Some strains of CRE are incurable and are resistant to all antibiotics. Patients who have bloodstream infections with CRE have a mortality rate of 50%. While these infections are rare, researchers are very concerned about the spread of CRE.
- **Clostridium difficile (C. difficile):** This bacteria usually invades after antibiotics have ruined the normal bacterial ecosystem of the gut, and can cause symptoms like painful, bloody diarrhea and fevers. It's often found in hospitals and group homes, and frequently is fatal for the elderly. This bacteria is naturally resistant to many antibiotics and generates spores that are particularly tough to kill.
- **Neisseria gonorrhoeae:** This bacteria is the cause of the second most common infection (Gonorrhoeae) in North America and can lead to serious reproductive complications. While at one time it was thought to be extremely easy to treat, now ~30% of infections are resistant to an antibiotic.

How do you prevent bacteria from developing antibiotic resistance?

To limit antibiotic resistance, it's important to limit the exposure that bacteria all over the planet (inside of us, within animals, and living in the environment) have to antibiotics. two ways you can help make sure bacteria are not getting overexposure to antibiotics are:

- Taking antibiotics responsibly: Take antibiotics only if you have a bacterial infection (not a virus), and pick one that is narrow spectrum so that it doesn't kill off your healthy bacterial ecosystem. Ask your healthcare professional to help you make these choices. Similarly for animals - narrow spectrum antibiotics should be used to treat bacterial infections, rather than indiscriminate use among healthy animals. Being really selective in how we use antibiotics keeps them from becoming obsolete.
- Trash antibiotics responsibly: Disposal of antibiotics should be done in a way that minimizes the exposure of bacteria living in the environment to the antibiotic. For example, you shouldn't crush antibiotics or flush them down the toilet. That gives the antibiotics direct access to bacteria living in the soil and water. Instead, two options are to either give them back to a pharmacist for disposal or to put them into a sealed plastic bag and toss it into the trash.

References

Silver, L. L. (2011). Challenges of Antibacterial Discovery. Clinical Microbiology Reviews, 24(1), 71–109. doi:10.1128/CMR.00030-10