Farm to Fork - Antibiotic Resistance in Agriculture

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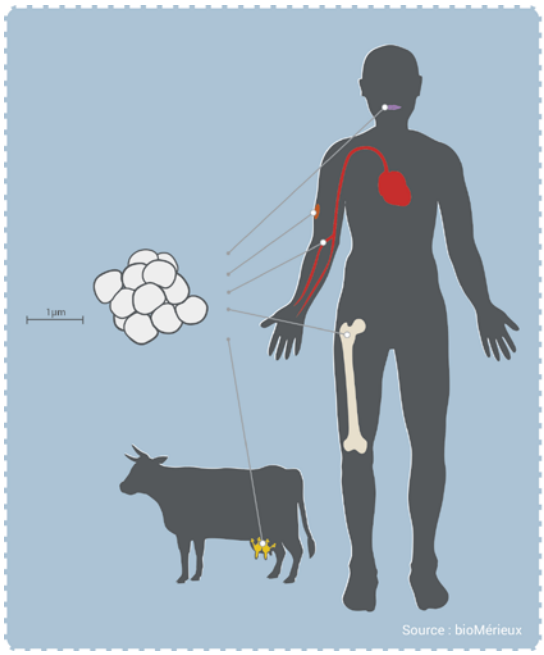
The cows lay on their sides, cadaverous, surrounded by a swarm of flies waiting to consume their next meal. A stench permeates the air, foreboding the god of death.
Farmers despise this part of the day, but they know not what is killing their livestock, their lifeblood.

This could be the bleak fate of agriculture, where bacteria have developed total resistance to the antibiotics we use to treat cattle, causing epidemics like the one above as well as in the people that consume it. With the world's population projected to reach 10 billion by 2050, safe food is needed for all those new mouths to feed.

But firstly, what are antibiotics?

Antibiotics are medications that destroy or slow down the growth of bacteria, treating diseases caused by them such as bronchitis and conjunctivitis as well as preventing infections during surgery. They play a crucial role in healthcare today, helping to treat billions of people and animals annually. However, the "Review on antimicrobial resistance" predicts that 10 million lives per year could be put at risk due to increasing threat of antimicrobial resistance. As many people will die from antimicrobial resistance as the leading cause of death today: coronary heart disease.

How did antibiotic resistance become such a widespread issue?



Most frequent infections caused by *Staphylococcus aureus*

The bacterium *Staphylococcus aureus* - which can turn into the infamous "MRSA" (methicillin-resistant *S. aureus*) - is part of the normal microbial flora of the skin and nests in about 30% of human noses. Depending on the type of strain and the immune system of its host, it can cause skin, soft tissue, bone and even bloodstream infections.

- In hospitals, it is the most common cause of surgical wound infections.
- In livestock, it affects the skin of animals causing a variety of illnesses such as mastitis, a common infection of the mammary glands in dairy cows.

Staphylococcus aureus is increasingly resistant to antibiotics such as methicillin and vancomycin.

Fig 1. MRSA in humans and animals

Following the commercialisation of antibiotics, people have used antibiotics improperly, such as by taking inadequate amounts of antibiotics, improper treatment of antibiotic-containing waste and unrestricted feeding of antibiotics to animals. The last reason is especially significant, as 80% of the world's antibiotics are used to treat livestock. Disconcertingly, many of those antibiotics such as tetracyclines, aminoglycosides, β-lactams, lincosamides, macrolides, pleuromutilins, and sulphonamides have the same mode of actions or belong to the same general classes as those used in humans. Since many bacteria species can cross from animal to human (known as a zoonotic disease), this poses a threat to modern medicine.

Since 1970, farms have employed antibiotics in antibiotic prophylaxis, preventing livestock from falling ill in modern farms where they are kept in high-density environments with poor hygiene, often injured by the caging.
Furthermore, antibiotics have been found to help animals grow faster and bigger, increasing the inertia to move away from their inclusion in animal feed.

Antibiotics are only partially broken down in digestion and a large amount is excreted by animals through urine and manure, which if used to grow vegetables, would leave antibiotic resistant bacteria on farms. If improperly washed before consumption, it could cause illnesses in people. Some countries such as Vietnam and China, utilise integrated agriculture aquaculture systems, where livestock farms are located near aquaculture farms, with the animal droppings being used to "fertilize" the water, promoting algae growth. This algae is then consumed by fish which are later eaten by people. This system could cause antibiotic resistant bacteria to spread to fish, which is worrying since the bacteria will not be killed through cooking, in many fish species such as salmon and tuna that can be eaten raw.

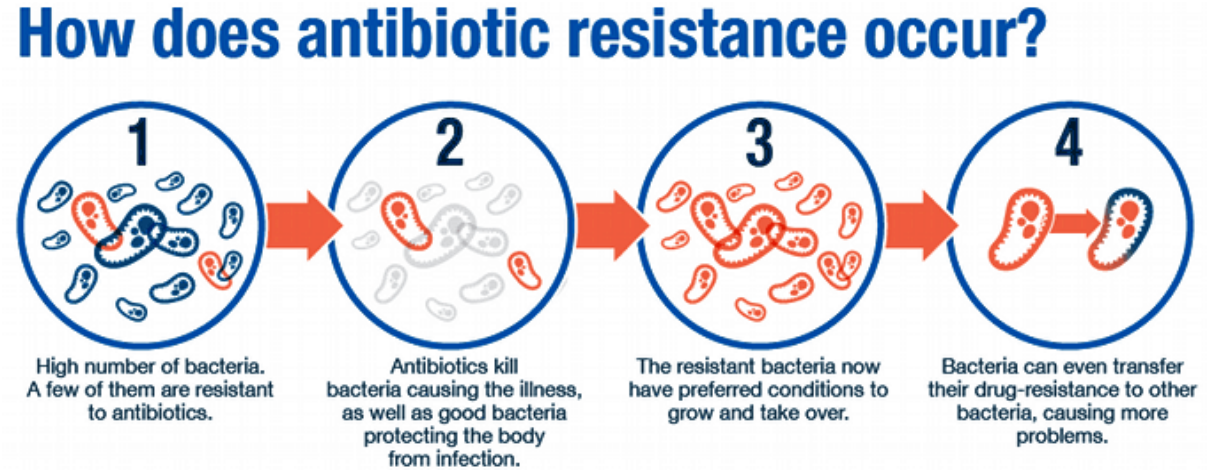


Fig 2. Antibiotic resistance process

With little regulation in less developed countries, farmers often atimes use antibiotics improperly, without consultation from veterinarians. Farmers would look to "experienced" peers who are also likely unaware of the threat of antibiotic resistance. Aside from possibly misdiagnosing viruses as bacteria caused diseases, they may administer dosages that are too high or too low. For instance, effluent from farms contain bacteria and antibiotic residues,

which is often carelessly discharged into waterways. The antibiotic residues are in low concentration that places a selective pressure on the population, killing off those that are susceptible while inducing mutations in others. These antibiotic resistant bacteria could spread to communities down the waterways.

Bacteria can mutate rapidly under stress, mutating to mitigate the mechanism of action of antibiotics, executing resistance by either modifying or altering the target sites (ribosomes) antibiotics bind to, with the help of ribosomal protection proteins which bind to the ribosomes, preventing the binding and interference of protein synthesis. Bacteria can also neutralise antibiotics by producing enzymes that add acetyl or phosphate groups to a precise site on antibiotics, rendering them ineffective.

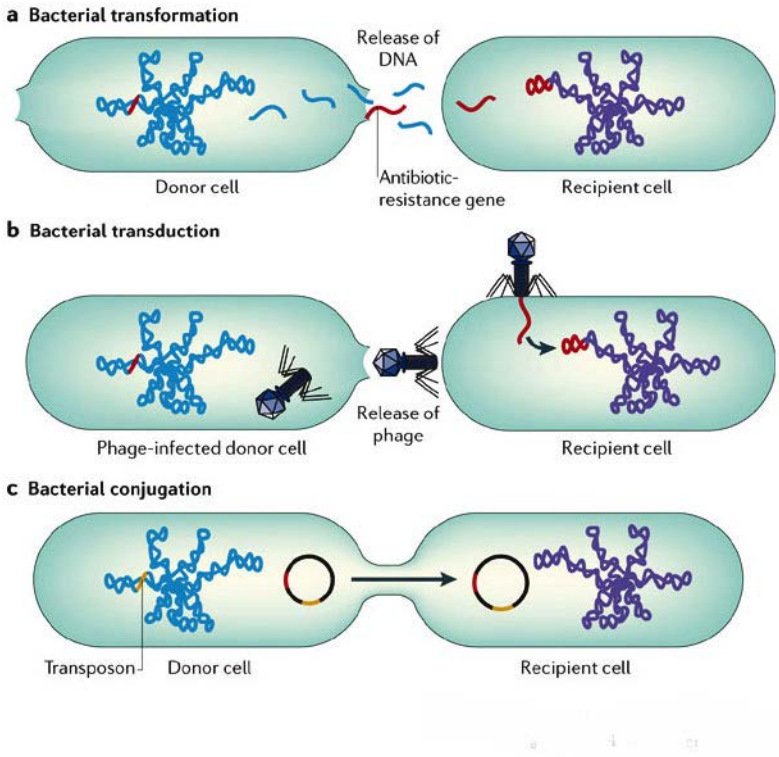


Fig 3. Different ways of HGT

Bacteria can acquire foreign DNA coding resistance through horizontal gene transfer (HGT). HGT takes the form of either transformation, conjugation or transduction. In transformation, bacteria take up free fragments of DNA, often in the form of plasmids, found in the environment like in dead bacteria. In conjugation, two cells unite temporarily through a pilus, exchanging a plasmid. In transduction, a bacteriophage infects a donor cell, taking some of its DNA, before transmitting it to another cell.

HGT is of particular concern, as it means that if a few bacteria cells mutate to resist the antibiotic, through rapid division and HGT, within a few generations, the whole farm could be resistant to the antibiotics used.

In our globalised world today, this means that a resistant gene could spread around the world and hurt our ability to treat the disease.

What threat does it pose to man?

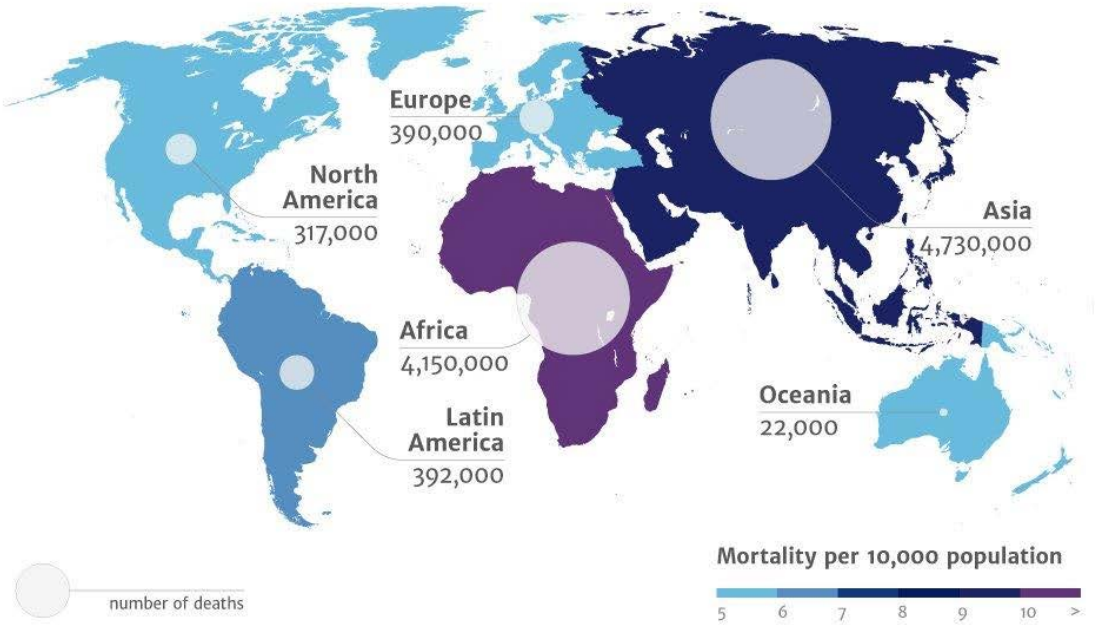


Fig 4. Deaths attributed to antimicrobial resistant bacteria infections

Less developed countries have drastically increased their consumption of antibiotics in agriculture as they are bountiful and cheap. Improper management lead to the spread of resistant bacteria, which is dangerous as in many of these countries, food prepared by street vendors is often unhygienic and contaminated with bacteria, causing many people to fall ill. Underdeveloped healthcare systems would only be able to treat patients with common, low cost antibiotics which the bacteria are immune to. Critically important antibiotics are often more expensive and many lives have been lost due to this fact.

Poorly educated farmers could also fail to adhere to practices such as withdrawing antibiotic-infused feed from animals that are due to be slaughtered. Since antibiotics tend to accumulate in edible animal organs such as the chicken's gizzards, heart, liver, kidney, ample time has to be given for these antibiotics to be excreted. Consumers could have allergic reactions to the antibiotics used and bioaccumulate, posing health risks such as diarrhoea and abdominal pain.

As previously mentioned, since front-line antibiotics can no longer be used, more expensive medicines have to be used, which in the US alone, costs $2 billion per year. These antibiotics run the risk of resistance themselves with greater use. Moreover, organ transplants, caesarean sections and chemotherapy become more dangerous as antibiotics cannot be used to prevent infection in these immunocompromised patients.

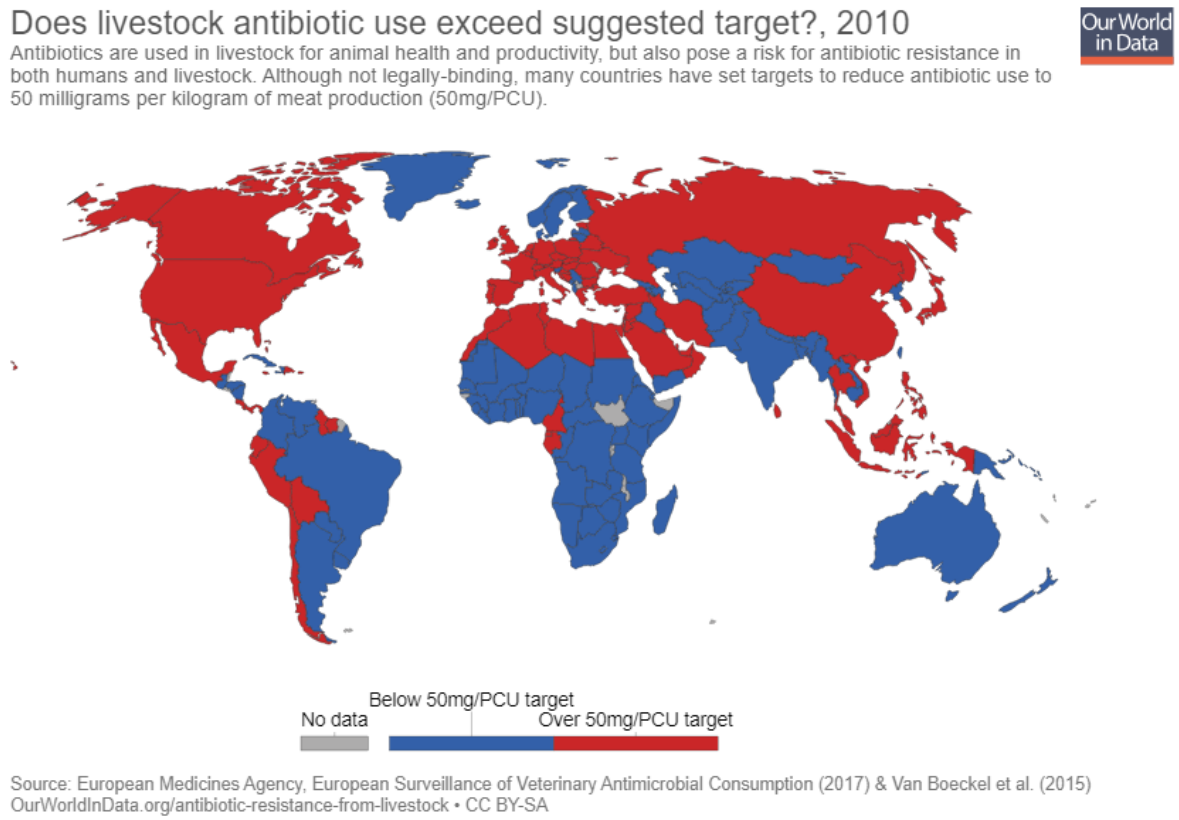


Fig 5. Excessive use of antibiotics in livestock around the world

If antibiotics continue to be used indiscriminately by man, bacteria would become resistant to most of them. This could put mankind back to the medieval ages where simple infections that antibiotics defend against today could prove to be life-threatening.

Now, what could we do to prevent widespread antibiotic resistance from becoming a reality?

Broad spectrum antibiotics are antibiotics used to treat a large range of bacterial infections. Farms often employ them in animal feed to prevent the greatest possible range of infections that their livestock could contract. However, this practice increases antibiotic resistance in bacteria, especially so for these important drugs used in medicine. As such, it would be useful to educate farmers on the proper use of antibiotics, with laws regulating that antibiotics have to be prescribed by veterinarians and only allowing them to be used to treat animal infections.

Biosecurity measures can be put in place such as sterilizing farm personnel and ensuring that effluent from farms also have to be treated, to prevent antibiotic residues and bacteria from being released into the environment.

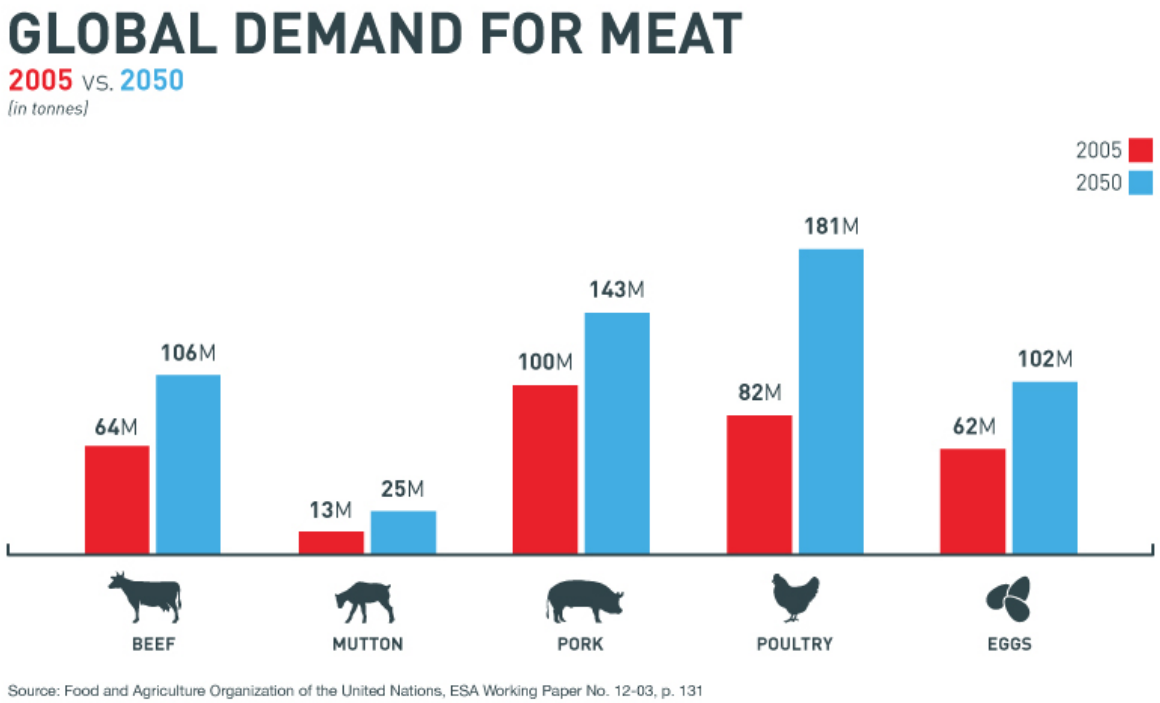


Fig 6. Increasing global demand for meat

As countries become more and more affluent, consumers have increased the demand for meat. However, by reducing consumption of meat, there would be fewer livestock farms, lowering the usage of antibiotics, giving rise to fewer mutations. Consumers can also choose to support farms that are “free range” where the animals are kept in more sanitary conditions that reduce bacterial growth and transmission of disease, that warrants less antibiotic use.

The main alternative to antibiotic prophylaxis is the use of vaccines to prevent infection in livestock. To be used in food producing animals, vaccines have to be safe, effective, easy to use, and cost-effective, but most vaccines today lack in one of these areas. Regardless, research has demonstrated that by vaccinating Danish pig herds against *Lawsonia intracellularis*, the causative agent of ileitis, oxytetracycline consumption has been reduced by 80%, also decreasing the number of pigs treated, improving productivity measures such as average daily gains and carcass weights.

There have been recent breakthroughs such as small molecules that render bacteria ineffective without killing them, relieving the selective pressure that drives the growth of resistant strains or using bacteriophages, which are viruses that attack bacteria, but these solutions have not gone through clinical trials.

In conclusion, antibiotic resistance in bacteria is only set to become worse and mankind has to take steps to maintain the efficacy of our antibiotics. Governments, producers and medical experts around the world have to work hand in hand to improve awareness and

understanding of antimicrobial resistance, strengthen surveillance and research on antibiotics, to reduce the incidence of infection in livestock, preventing the excessive use of antimicrobial medicines and to fund sustainable research in countering antimicrobial resistance.