Limiting Antimicrobial Resistance

History of Antibiotics

While most scientists link the beginnings of the era of antibiotics to the discovery of penicillin, there is evidence that ancient cultures used similar types of treatments. For example, ancient China used an antimicrobial substance to fight against malaria, while the red soil in Jordan was used to fight skin infections. The soil was later found to contain antimicrobial bacteria that was effective against skin infections. These traditional remedies were thought to help against infections and diseases, but it took until the 20th century to have the science to back up such medical practices.[1]

The era of the mass-usage of antibiotics began with penicillin, which was important in reducing deaths from infectious diseases. Alexander Fleming is credited with discovering Penicillin in 1928, when he noticed that the mold growing in a dirty petri dish was causing nearby bacteria colonies to die off. Fleming's insistence of the effectiveness of Penicillin helped persuade other scientists to also research into antimicrobials. This was groundbreaking because it opened up a lot more possibilities in medicine and increased life expectancy by being able to treat a variety of bacterial diseases. Penicillin is used to treat ear infections, Listeria, E. coli, salmonella, blood infections, and more. Penicillin's forerunner was Salvarsan, which was developed to fight syphilis. From the 1940s to the 1980s there was a considerable amount of innovation and discoveries regarding antibiotics; however, the research into new antibiotics has been lackluster over the past 30 years.[2]

Antimicrobial Resistance

According to the Center for Disease Control and Prevention (CDC), antimicrobial resistance is when germs, such as bacteria or fungi, develop the ability to destroy the medicine that was designed to kill it. When microorganisms develop resistance to antibiotics they are often referred to as superbugs. Antimicrobial resistance occurs naturally over time due to genetics, but misuse of antibiotics can speed up the process. "They can spread between people and animals, including from food of animal origin, and from person to person. Poor infection control, inadequate sanitary conditions, and inappropriate food handling encourage the spread of antimicrobial resistance."[3]

Resistance develops in several ways. For instance, when someone gets an infection, they take antibiotics to kill the bacteria making them sick. However, if there is a bacterium that is resistant to antibiotics, the bacterium remains in their system. These bacteria can multiply and spread their drug-resistance to other bacteria. Some defense strategies used by drug-resistant bacteria include using enzymes to change or destroy the antibiotic, restrict access of the antibiotic by the bacteria altering their cell wall, and changing the targets of the antibiotic.[4]

Current Issues

---

[1] "A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future." *Frontiers Research Foundation* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109405/.
[2] Ibid
[3] "About Antimicrobial Resistance | Antibiotic/Antimicrobial Resistance | CDC." *Centers for Disease Control and Prevention*. https://www.cdc.gov/drugresistance/about.html.
[4] "Antimicrobial Resistance." *World Health Organization*. https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance.

Resistance to antibiotics and antimicrobial treatments is causing a crisis and threatens to return the world to the pre-modern era of medicine in which diseases were difficult to defeat. Diseases that we can "cure" today, might not be curable in the future. Medical procedures such as surgery or chemotherapy become very dangerous without the availability of dependable antibiotics.

Innovating Antibiotics

While it's not difficult to find substances that kill bacteria, it is common for these substances to be harmful to humans. When a potential antibiotic is discovered, it must be thoroughly tested to ensure that it is not dangerous to the public. The time from discovery to being available for public use can take 10-20 years. In addition, it is very costly to develop these new antibiotics. Making new antibiotics is not a lucrative investment because the new, innovative antibiotics are saved for serious cases so that they can maintain their effectiveness. This means that companies that produce a new antibiotic will not make a high profit off of their new antibiotic, or it will take a very long time for them to get a return on their investment. All of the antibiotics that have been introduced in the past 30 years are just variations of already existing drugs, showing that pharmaceutical companies have not been focusing too much on developing better antibiotics.[5]

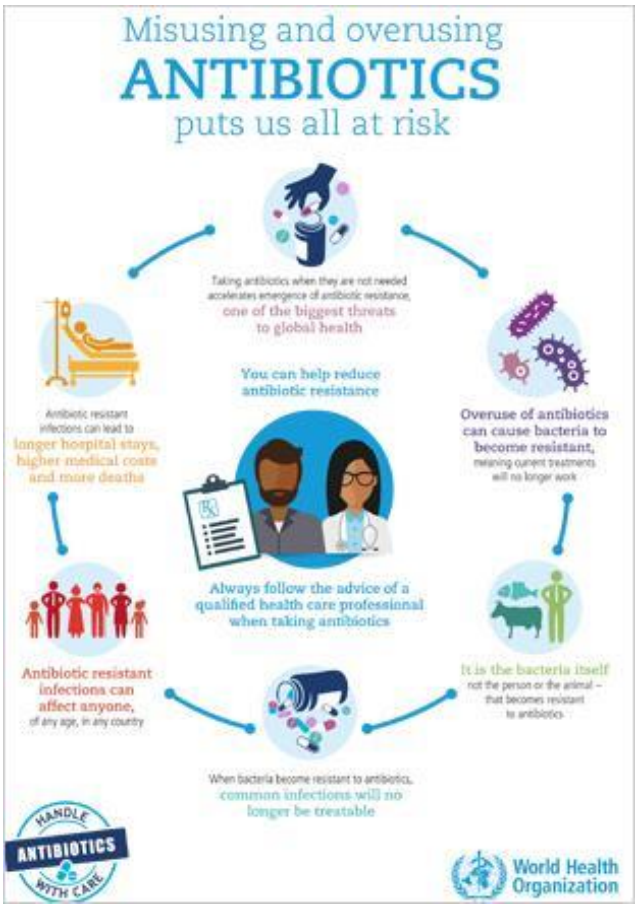
Overuse and Misuse of Antibiotics

Misuse of antibiotics by patients and doctors is rampant. Doctors overprescribing antibiotics is a major cause of increasing resistance to antimicrobials. Specifically, some doctors are prescribing antibiotics for viral infections instead of just bacterial infections.[6] It is important to recognize that antibiotics only target bacterial infections and not viruses. Viruses and bacteria are very different on a molecular level with respect to their cell wall composition and the presence or absence of a lipid bilayer, amongst many other variables. On the other hand, many patients do not take their antibiotics as prescribed.[7] Instead of taking the antibiotics until they finish the amount prescribed, many people stop taking their medication once the symptoms are eliminated. This is dangerous because it can allow for the bacteria to develop better defenses to antibiotics, which will cause the antibiotic to be less effective or completely ineffective in killing that bacteria.[8] This phenomenon increases a patient's susceptibility to contracting a more serious infectious disease that will not be able to be treated with the previous antibiotic used. Instead, a stronger and potentially dangerous antibiotic will have to be used to fight the infection.[9]

While it is remarkable that stronger antibiotics exist, the use of such strong antibiotics actually increases the chance of acquiring another more serious bacterial infection. Another infection could be contracted because the use of stronger antimicrobial therapies has a larger range of targets for the destruction of bacteria, which will include the elimination of normal flora in the body that works synergistically with us to maintain health and compete with harmful pathogens.[10]

---

[5] "Owed to Nature: Medicines from Tropical Forests." *Rainforest Trust*. https://www.rainforesttrust.org/owed-to-nature-medicines-from-tropical-forests/.
[6] "How to Stop Antibiotic Resistance? Here's a WHO Prescription." *World Health Organization*. https://www.who.int/mediacentre/commentaries/stop-antibiotic-resistance/en/.
[7] Ibid
[8] Ibid
[9] Ibid
[10] Ibid



Potential Solutions

Educational Programs: One cause of antimicrobial resistance is people who take their antibiotics, but stop taking them when they feel better. In order to fully kill off the diseases, the antibiotic needs to be taken for its entire course. Additionally, it is important that doctors are properly trained in knowing when to prescribe antibiotics and when to let the immune system fight it off.[11] Educating both the doctors and the patients on how to prescribe and take antibiotics is crucial to preventing antimicrobial resistance.[12] The World Health Organization (WHO) aims to provide increased awareness and education regarding antimicrobial resistance. Their awareness campaign was created with the goal of "raising awareness of antimicrobial resistance and promoting behavioral change through public communication programs that target different audiences in human health, animal health, and agricultural practices as well as consumers is critical to tackling this issue."[13]

Reforms to the Drug Research Process: Countries with the highest investment in medical studies such as the United States, the United Kingdom, and France have laws that make the research process for new drugs very lengthy. A potential antibiotic has to be tested repeatedly in order to measure side effects and its effectiveness. The Food and Drug Administration (FDA) in the United States, for example, has a 5-step Drug Development process:

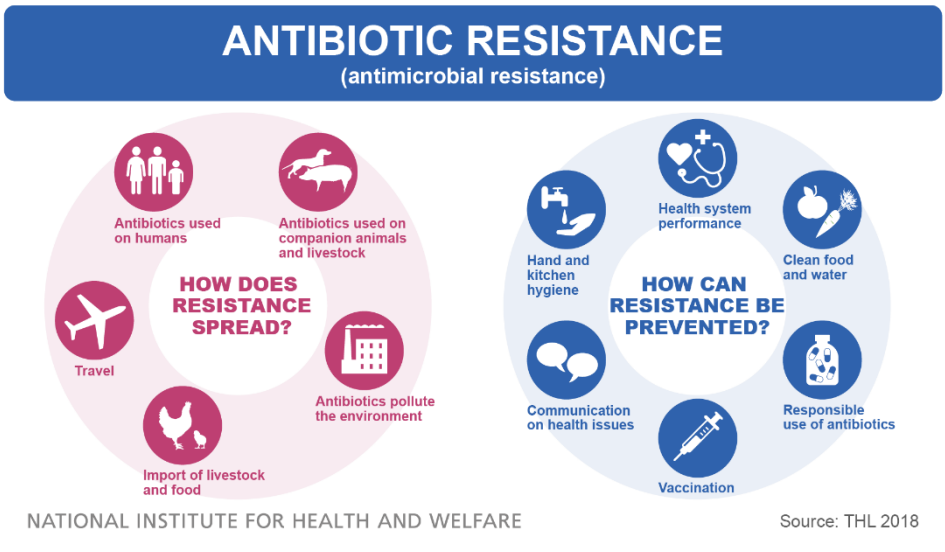
1. **Discovery and Development:** research begins in a laboratory;
2. **Preclinical Research**: drugs undergo laboratory and animal testing to answer basic safety questions;
3. **Clinical Research**: drugs are tested on people to make sure they are safe and effective
4. **FDA Review**: review teams thoroughly examine all of the submitted data and make a decision regarding its approval
5. **FDA Post-Market Safety Monitoring**: monitors safety once the drug is available for use by the public.[14]

---

[11] Ibid
[12] "A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future." *Frontiers Research Foundation*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109405/.
[13] "Awareness and Education." *World Health Organization*. https://www.who.int/antimicrobial-resistance/global-action-plan/awareness/en/.
[14] "The Drug Development Process." *U.S. Food and Drug Administration*. FDA. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process.

From discovery to drug, this process takes between 10 and 20 years. All of the antibiotics brought to the market in the past three decades have been different variations of the same medications discovered prior to 1984. Suggested solutions for streamlining this process include exploring the potential for vaccines to combat against infection, and take action to ensure that "industry and government work together to test promising treatments and bring them to market[15]."

Environmental Protections for Rainforests: Many antibiotics come from the natural world, with the rainforest serving as a crucial source. With thousands of acres of rainforest being cleared every day, and thousands more being degraded, many species are becoming extinct or at risk of becoming extinct before we can even discover them.[16] For example, in 1987 the U.S. National Cancer Institute led a plant collection expedition to Borneo. Among the samples the Institute took, was a promising substance that seemed to be effective against HIV. Sadly, when researchers went back to take more samples, they couldn't find any remaining trees that contained the special substance.[17] Luckily, more samples were found years later in Singapore; however, this story shows that there are several plant species out there that could be beneficial to medical science but they have not been discovered yet, or that there are plants being destroyed before they can be effectively researched. Cutting down the rainforests reduces biodiversity and could be killing off new cures for diseases.[18]



Limiting the prescription of antibiotics: Sometimes, doctors may prescribe antibiotics to a patient thinking they have a bacterial infection when they actually have a viral infection. In this scenario, the antibiotics are not actually effective against viral infections. This can also allow the bacteria within the patient's body to build up resistance against the antibiotic that they were prescribed. Additionally, the antibiotic kills good bacteria, putting the patient at risk for additional infections. The unnecessary prescription of antibiotics can be limited by doctors performing the correct tests to confirm a bacterial or viral infection before signing onto prescriptions.[19] Risks of antibiotic overuse or overprescribing include, "not only increases in antibiotic resistance, but [also] increases in disease

[15] "Why Is It so Difficult to Discover New Antibiotics?" *BBC News*. https://www.bbc.com/news/health-41693229.
[16] "Owed to Nature: Medicines from Tropical Forests." *Rainforest Trust*. https://www.rainforesttrust.org/owed-to-nature-medicines-from-tropical-forests/.
[17] Ibid
[18] Ibid
[19] "How to Stop Antibiotic Resistance? Here's a WHO Prescription." *World Health Organization*.

severity, disease length, health complications and adverse effects, risk of death, healthcare costs, re-hospitalization, and the need for medical treatment of health problems that previously may have resolved on their own."[20]

Limiting the use of antibiotics on livestock and produce: Like in humans, giving antibiotics to livestock will kill most bacteria, but resistant bacteria can still survive. when these animals are slaughtered and processed, "resistant germs in the animal gut can contaminate the meat or other animal products."[21] Misuse of antibiotics by farmers can lead to increased antibiotic resistance, as they are spread through the food chain and the environment. This can unintentionally lead to the general population being exposed to an increased number of antibiotics, while bacteria can become stronger and more resistant to antibiotics. In 1991, Namibia became the first African nation to ban the use of antibiotics in the commercial beef industry. According to Rosa Katjivena, quality assurance executive of the Meat Corporation of Namibia, "the health risks are our biggest concern because the overuse of antibiotics leads to the development of 'superbugs' [antibiotic resistant bacteria]. Methicillin-resistant Staphylococcus aureus (MRSA), as well as some salmonella strains have become resistant because of the practice of overuse of antibiotics."[22] Because of this ban, farmers are improving the condition in which their livestock are kept. Focusing on animal welfare, farmers increase the space animals have, keep their pens clean, and ensure they have clean water. "Vaccinating animals against infectious diseases is another safe, effective, and affordable method that can reduce the need for antibiotics."[23]

Case Studies

Resistance in Malaria

According to the Center for Disease Control, malaria is "a serious and sometimes fatal disease caused by a parasite that commonly infects a certain type of mosquito that feeds on humans."[24] Nearly half of the world's population is at risk, however transmission primarily occurs in South Asia and Sub-Saharan Africa, because the temperature, humidity, and rainfall produce an environment that allows these mosquitoes to thrive. In these areas with high rates of transmission, "the most vulnerable groups are young children, who have not developed immunity to malaria yet, and pregnant women, whose immunity has been decreased by pregnancy."[25]

Antimalarial drug resistance is best defined as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug in doses or higher than those usually recommended but within tolerance of the subject."[26] The drug must "gain access to the parasite or the

---

[20] "Overuse and Overprescribing of Antibiotics." *Center for Infectious Disease Research and Policy*. http://www.cidrap.umn.edu/asp/overuse-overprescribing-of-antibiotics.
[21] "Food and Food Animals | Antibiotic/Antimicrobial Resistance | CDC." *Centers for Disease Control and Prevention*. https://www.cdc.gov/drugresistance/food.html.
[22] "Namibia's Ban on Antibiotics in Healthy Animals Drives Meat Exports." *World Health Organization*. https://www.who.int/news-room/feature-stories/detail/namibia-s-ban-on-antibiotics-in-healthy-animals-drives-meat-exports.
[23] Ibid
[24] "CDC - Malaria - About Malaria." *Centers for Disease Control and Prevention*. https://www.cdc.gov/malaria/about/index.html.
[25] Ibid
[26] "Drug Resistance in Malaria." *World Health Organization*. https://www.who.int/csr/resources/publications/drugresist/malaria.pdf.

infected red blood cell for the duration of time necessary for its normal action."[27] Major causes of antimalarial drug resistance include the following:

- "Unusual genetic structure of malarial parasites in regions known for antimalarial drug resistance"[28]
- Counterfeit or inadequate treatments
- Unregulated or poorly administered drug use
- Antimalarial drug use without a complementary combination treatment

Great strides have been made towards the eradication of malaria by improving accessibility to antimalarial treatments, however resistance to these treatments puts this progress at risk. Currently, resistance to available antimalarial drugs has been confirmed in two out of four human malaria parasite species- *Plasmodium falciparum* and *P. vivax*- but this number is at risk of rising.[29] One potential solution to combating antimalarial resistance is reducing pressure on the drugs, which could be achieved by improving the system in which malaria is diagnosed. Current method of diagnosis result in individuals receiving unnecessary treatment, however "basing treatment on the results of a diagnostic test...would result in the greatest reduction of unnecessary malarial treatments and decrease the probability that parasites are exposed to subtherapeutic levels of [the] drug."[30]

Resistance in *Escherichia coli*

E. coli bacteria typically live in the intestines of healthy people and individuals, and most varieties of the bacteria are harmless or simply cause mild diarrhea. You can be exposed to the more harmful strains, particularly E. coli O157:H7, by consuming contaminated water or food, including raw vegetables and undercooked beef.[31] In the United States, for example, recent E. coli outbreaks have been linked to prior contamination of ground beef and romaine lettuce. Individuals who are at a high risk for E. coli include young children and older adults, individuals with weakened immune systems- such as those being treated for AIDS, cancer, or to prevent the rejection of an organ transplant, or those who take medication to reduce their levels of stomach acid.[32]

Antimicrobial resistance in E. coli has developed primarily through genetic mutations. The World Health Organization has reported up to 50% resistance for these treatments in its regions- Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific[33]. Additionally, they have confirmed that "patients with infections caused by resistant *E. coli* strains carry a risk of poorer clinical outcomes and come more health-care resources than patients with infections by *E. coli* strains susceptible to third-generation cephalosporins or fluoroquinolones."[34]

International Action Against Antimicrobial Resistance

---

[27] Ibid
[28] "Malaria Drug Resistance." *Infectious Diseases Data Observatory*. https://www.wwarn.org/about-us/malaria-drug-resistance.
[29] "CDC - Malaria - Malaria Worldwide." *Centers for Disease Control and Prevention*. https://www.cdc.gov/malaria/malaria_worldwide/reduction/drug_resistance.html.
[30] "Drug Resistance in Malaria." *World Health Organization.*
[31] "E. Coli." Mayo Clinic. *Mayo Foundation for Medical Education and Research*. https://www.mayoclinic.org/diseases-conditions/e-coli/symptoms-causes/syc-20372058.
[32] Ibid
[33] "Antimicrobial Resistance Global Report on Surveillance." *World Health Organization*. https://bit.ly/2B38NKF.
[34] Ibid

Antimicrobial Resistance is a new phenomenon that the international community is just beginning to address. In the past five years, the United Nations and World Health Organization (WHO) have held several debates and organized ministerial meetings about this issue. For example, WHO is collaborating with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) to promote best practices to avoid the emergence and spread of antibiotics. They are working to help member nations develop their own national plans of action to combat antimicrobial resistance. Generally, these programs entail limiting the use of antibiotics while also improving global access to quality medications.[35] In order to spread awareness on antimicrobial resistance, WHO recognizes an annual antibiotic resistance awareness week. Additionally, WHO has partnered with Drugs for Neglected Diseases Initiative (DNDi) to develop up to four new treatments by 2023 by improving existing antibiotics and speed up the research process of new medicines.[36]

In 2015, WHO launched the Global Antimicrobial Resistance Surveillance System (GLASS), to "support global surveillance and research in order to strengthen the evidence base on antimicrobial resistance[37]." The program initially will focus on "surveillance data on human priority bacterial pathogens considered the greatest threat globally and progressively incorporate information from other surveillance systems related to antimicrobial resistance in humans[38]." In the early years of this system, GLASS plans to primary support countries in developing their own effective antimicrobial resistance surveillance systems.

Questions to Consider

- What incentives can be instituted in order to make the process of developing new antibiotics more appealing and efficient?
- How should the international community go about educating doctors and the general public on the dangers of misusing and overusing antibiotics?
- What actions should be taken to reduce the use of antibiotics in livestock?
- How can international programs be improved to ensure that their goals of eliminating antimicrobial resistance are achieved?

---

[35] "FAO/OIE/WHO Tripartite Collaboration on AMR." *World Health Organization*. https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/.
[36] "How to Stop Antibiotic Resistance? Here's a WHO Prescription." *World Health Organization*. https://www.who.int/mediacentre/commentaries/stop-antibiotic-resistance/en/
[37] "Global Antimicrobial Resistance Surveillance System (GLASS)." *World Health Organization.* https://www.who.int/glass/en/.
[38] Ibid