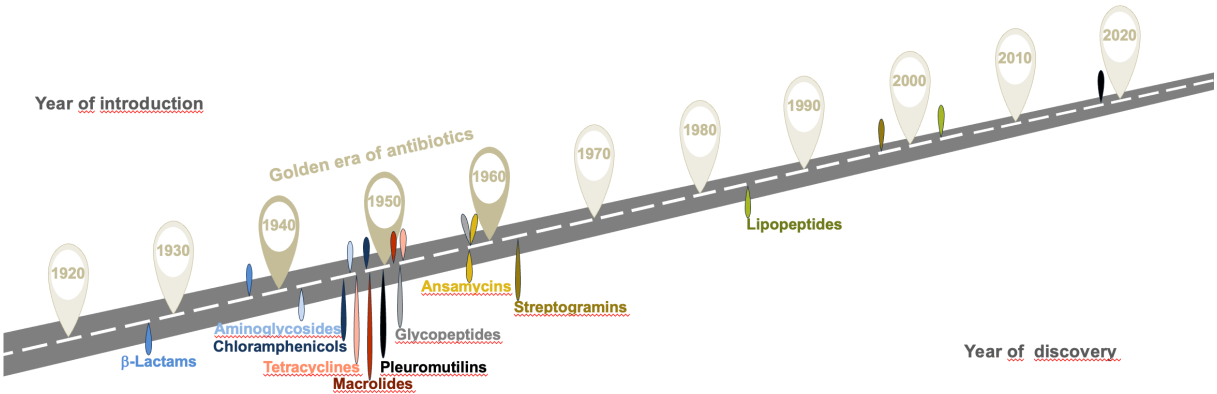
The dearth of new antimicrobials crisis

Miss: why is everyone saying that antibiotic resistance is now the biggest problem facing medicine?



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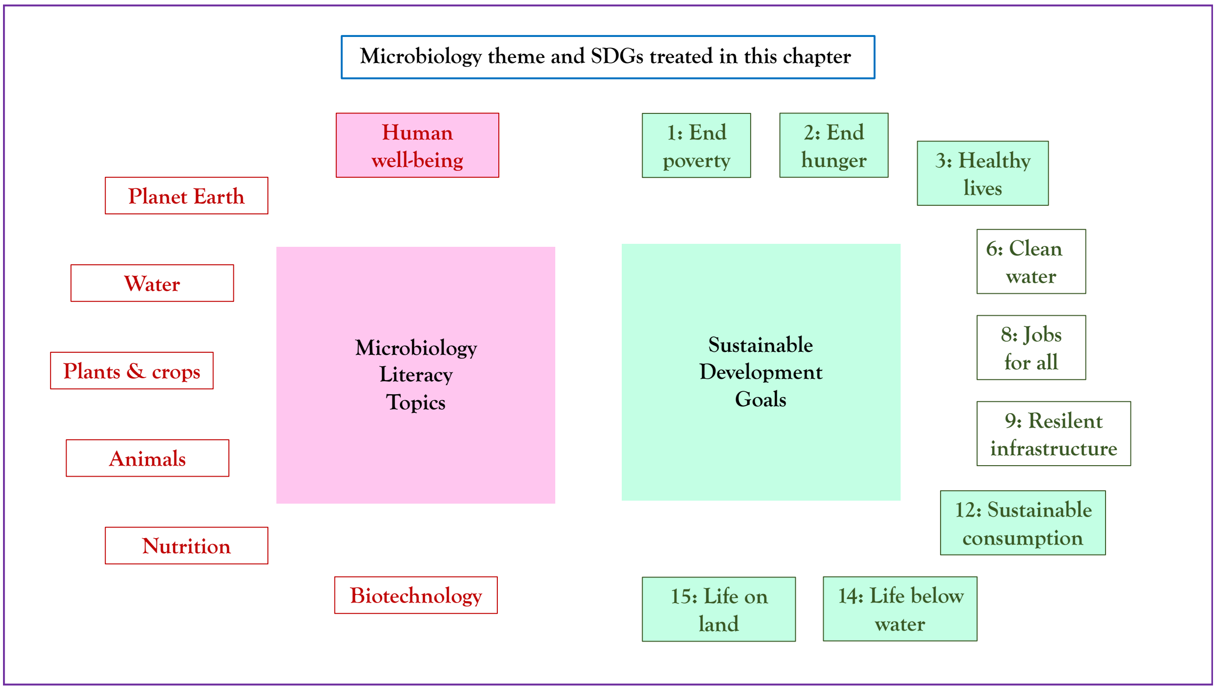
Storyline

Antibiotics play a crucial role in treating bacterial infections such as bronchitis, pneumonia and urinary tract infections by targeting bacteria while minimising damage to human cells. Despite their effectiveness, the rise of antibiotic resistance poses a significant challenge as bacteria develop mechanisms to evade the effects of these drugs. This resistance stems from both natural bacterial defence strategies, and the overuse of antibiotics which accelerates the emergence of resistant strains. In addition, due to high costs of drug development and low profitability, the pharmaceutical industry shows limited interest in developing new antibiotics. Research into new antibiotics is hampered by traditional methods, but advances in genomics and environmental studies offer new hope. Tackling antimicrobial resistance is essential for global health, economic stability and environmental protection, and requires coordinated efforts in research, policy and education.

The Microbiology and Societal Context

The microbiology: bacterial resistance mechanisms; misuse and overuse of antibiotics in humans and animals; hospital-acquired infections; antibiotic residues in the environment; agricultural use of antibiotics and its impact; spread of resistant genes through horizontal gene transfer. *And, peripherally for completeness of the storyline*: lack of new antibiotic development; global travel and trade spreading resistant bacteria. *Sustainability issues*: global public health threat; increased morbidity and mortality; challenges in achieving universal healthcare; economic burden due to longer hospital stays and more intensive care; food security and safety; environmental pollution from pharmaceutical waste; loss of biodiversity



The dearth of new antimicrobials crisis: the Microbiology

1. The vital role of antibiotics in medicine. Bronchitis, pneumonia, urinary tract infection or blood poisoning: all these diseases and many others are caused by bacteria and generally, antibiotics can defeat them.

2. What are antibiotics?"Antibiotics", a Greek term, means "against life", specifically against bacteria. They attack the components or processes of the bacterial cell that differ from a human cell. As a result, antibiotics attack bacteria without causing significant damage to the human cell. This is the principle of *selective toxicity*: high activity towards the target organism, but low activity towards the host, and is the basis of many medicines. Antibiotics are auxiliary policemen assisting the body's own defence system, the immune system, when it cannot successfully fight off the bacteria alone.

3. ***Where do antibiotics originate?*** Antibiotics are chemical compounds. They are either produced by microorganisms (e.g. bacteria or fungi) or by chemical synthesis. Many antibiotics have such a complex structure that they cannot be produced synthetically, but must be isolated from microorganisms. However, antibiotics have evolved as microbial weapons for complex ecological interactions in natural habitats, not for rapidly killing off a pathogen in the context of the human body. Natural antibiotics may therefore not have ideal properties as therapeutic agents, so their structure and properties may need to be tweaked. Therefore, once isolated from a microbe and shown to be efficacious and safe, an antibiotic is usually chemically-modified, or indeed synthesised entirely by chemistry, to become a *microbially-inspired antibiotic*.

4. ***What does antibiotic resistance mean?*** Antibiotic resistance means that a bacterium has become resistant to an antibiotic, so that it is no longer harmed by the antibiotic. Although with the discovery of antibiotics, the battle against disease-causing (pathogenic) bacteria seemed to be won, the golden era of antibiotics ended when pathogenic bacteria became progressively resistant to existing antibiotics, at a time when scientists were discovering fewer new antibiotics (for more information, see also the *AntimicrobialResistanceRogues Portrait Gallery*). As a result, there is an increasing number of cases of people becoming infected with pathogenic bacteria against which all available antibiotics are powerless, with life-threatening consequences. For example, a harmless bladder infection can progress into a threatening kidney-pelvis infection. If this cannot be treated, the bacteria may infect the entire body – sepsis – and the can patient die in a short period of time from multiple organ failure. Doctors are then as helpless as they were 100 years ago. In Europe, it is estimated that 33,000 people die every year from diseases that cannot be cured properly due to antibiotic resistance, and billions of dollars in health care costs are incurred.

5. ***Where does resistance come from?*** Bacteria are fast growing organisms that have existed on earth for more than 3 billion years. Scientists were able to demonstrate that bacteria which had not previously come into contact with modern medicine exhibit resistance against certain antibiotics. Microbes have thus developed defence strategies long before antibiotics became used in medicine. Why?

On one hand, antibiotics are based on natural substances, which have also existed since time immemorial. Bacteria produce antibiotics to inhibit the activities and success of competitors. But they also need to protect themselves from the antibiotic they produce, otherwise they would commit suicide. So a resistance mechanism is an essential part of antibiotic production. On the other hand, to be successful, competitors must also become resistant, and so develop resistance mechanisms that disarm the effect of the antibiotics.

There are a number of different types of antibiotic resistance mechanisms (see the *AntimicrobialResistanceRogues Portrait Gallery*) and most can be readily transferred among bacteria, including of course the pathogenic bacteria.

In addition, the use of an antibiotic always sets mechanisms of evolution in action: under the pressure of antibiotics, bacteria develop mutations, causing antibiotic ineffectiveness. This is the "development of resistance". The increasing number of resistant pathogenic bacteria is a vicious circle humans cause: the more antibiotics we use, the more the number and range of resistant bacteria increases.

6. ***Why is there an insufficient industry interest in antibiotics research?*** Despite the clear need for more antimicrobial agents, only few antibiotics are coming onto the market; the last completely new class of antibiotics was discovered in the late 1980s (antibiotic class defines a set of related antibiotics). This is because, on the one hand, scientists believed to have almost won the fight against bacteria. On the other hand, the discovery and the market launch of antibiotics is often not profitable for pharmaceutical companies. According to a study surveyed in 2017, developing an antibiotic costs around $1.5 billion. Conversely, the average revenue from the sale of an antibiotic is around $46 million per year, which is nowhere near enough to cover the investments.

7. ***The process of developing new antibiotics.*** The discovery process starts with basic research to identify organisms producing antibiotics. Sometimes discoveries take interesting turns and end in unexpected places. It is rather easy to discover substances attacking bacteria in the laboratory. However, this does not necessarily mean that those substances are also effective in the human body without harming it: they may have poor *selective toxicity*.

Promising substances proceed to clinical trials, where scientists evaluate their safety and efficacy in humans. Usually conducted in three phases, clinical trials are even more expensive and complex; they require resources, infrastructure and expertise that only large pharmaceutical companies can provide. The final phase and the experiments required after launching a new antibiotic account for more than 80% of the costs. Another big challenge in the approval process for antibiotics to treat highly resistant bacterial infections is that, so far, only a relatively small number of patients have these infections, making it difficult to meet the requirements for participation in large traditional clinical trials.

The last step before physicians can legally prescribe the new antibiotic is the registration of the drug at the governmental drug agency. Approval procedures, which are usually lengthy and involve many regulatory hurdles, increase costs and time. Statistically, only one in five drugs for infectious diseases that reaches the first phase of testing in humans is approved by the Food and Drug Administration (FDA). Assessment of the pipeline dated March 2021 shows 43 new antibiotics in development that are expected to be effective against the majority of resistant bacteria. Of the 43 antibiotics in development, 15 entered phase 1, 13 phase 2 and 13 phase 3. Historically, about 60% of drugs entering phase 3 received marketing authorisation.

8. ***Antibiotics have become the Cinderella of drug discovery.*** Of the around 38 companies that have antibiotics in clinical development, only two are among the 50 top-selling pharmaceutical companies that formerly dominated this field; more than 95 % of the products in development today are being researched by small companies. Companies responsible for developing one in three new antibiotics in the last decade have gone bankrupt and many private and venture capital companies have exited the field.

As a result, a lot of money is spent on marketing. Despite these efforts, it can be very difficult to get physicians and health systems to buy and use the new antibiotics. They are kept in reserve for only the serious disease progressions because it is feared that they will promote resistance. New antibiotics are treated as “last resort” drugs to combat serious diseases. This practice decreases the use of new antibiotics and reduces the return on investment.

Importantly, compared to other drugs, antibiotics are taken only for a short period of time. Therefore, antibiotics are financially less interesting than medicines that are taken for years. Additionally, there is the risk that bacteria become resistant to the newly developed antibiotic and the financial investment will not pay off in the end. These circumstances discourage the pharmaceutical industry from investing in antibiotics research; companies have steadily divested their antibiotic research teams in favour of those working in areas that are not "easier" but have higher commercial value. In oncology, for example, the potential of nearly 800 new products was explored in 2014, of which about 80 % were potentially "first-in-class". In comparison, fewer than 50 products were in the antibiotic pipeline. This switch has been reflected in the rate of new approvals; in oncology, twice as many drugs have been approved since 2010 as in the 2000s, demonstrating the impact of a significant and sustained industry effort on a scientifically challenging but commercially lucrative disease area.

Only a very tiny proportion of venture capital funds are used for antibiotic development; of the $38 billion in venture capital invested in pharmaceutical R&D between 2003 and 2013, only $1.8 billion went to antimicrobial research.

However, these costs must also be considered from another angle. Antibiotic resistance leads to an increase in treatment costs due to longer hospital stays, higher spending on antibiotics and treatment, and indirect costs to family and society. Leading health organisations predict that antibiotic resistance will soon become the most serious problem facing medicine with disastrous economic consequences and human suffering. There clearly needs to be a paradigm change in the financing and economics of antibiotic discovery and development.

9. ***How can we accelerate the discovery of new antibiotics?*** Existing hurdles notwithstanding, research into antibiotics has re-intensified in recent years, as the problem of antibiotic resistance has become more acute. In particular, smaller companies and funding agencies have made it their goal to develop new antibiotics. However, to make drug development profitable a more radical approach is required.

Historically, the discovery of antibiotics has been based on screening for inhibition of the growth of a target microbe. This has been a highly successful approach leading to the isolation of many useful compounds that formed the basis for the treatment of infectious diseases. Scientists especially exploited the genus *Streptomyces* for decades in search for new drugs. However, this approach is becoming increasingly frustrating, because it leads to (re-)discovery of inhibitors that are similar or identical to those already known.

The traditional approach is based upon the ability to grow organisms on standard substrates under laboratory conditions. However, the number of microorganisms that scientists can culture is limited compared to the true diversity of microbial life. The recognition that most microbial species from the environment cannot be cultured using conventional microbiological methods has led to the development of new approaches, which allow the growth of slow-growing microorganisms. These isolates are also able to produce (new) bioactive substances.

Another method of uncovering new microorganisms is sampling/searching unusual habitats, such as the deep sea or cave systems, that have not thus far been explored, or at least fully explored. The study of fascinating examples of complex symbiotic interactions of microbes and their environments has also resulted in the identification of novel antibiotics. Such studies have also revealed the importance of these inhibitory molecules in shaping environmental niches.

Despite these successes, it is unlikely that most environmental microbes can be cultured under laboratory conditions soon. Therefore, it is necessary to develop alternative methods for obtaining active compounds. The revolution of next generation sequencing methods has now resulted in a shift from traditional screening methods towards genomic-based approaches. Mining microbial genomes has revealed the true potential of many organisms to produce antibiotics. Even well probed genera have been shown to be able to produce on average 10 times more compounds than have so far been detected in the laboratory. Moreover, massive whole genome sequencing projects have revealed that many more species than were previously suspected specify novel compounds that are awaiting discovery. Now the challenge is to effectively mine the huge amount of available data, prioritize the most promising gene clusters, and develop effective ways to produce and characterise encoded compounds. This is the classical idea of genome mining: predicting and isolating natural products based on genetic information without a structure in hand. Plenty of tools are available to enable researchers to computationally mine genetic data. These techniques have rapidly evolved during the last decade and are currently an important part of drug discovery efforts.

10. ***Summary.*** Antibiotic resistance is a critical global problem because it leads to increased mortality and prolonged illness due to harder-to-treat infections, limits treatment options and compromises the safety of surgical interventions and medical procedures including treatment with immune depressives. Resistant bacteria spread easily, posing a public health risk and an economic burden through increased medical costs and lost productivity. The development of new antibiotics is slow, exacerbating the problem. In addition, the use of antibiotics in agriculture contributes to resistance and affects human health. This problem threatens both developed and developing countries, underlining its urgent and widespread impact

Relevance for Sustainable Development Goals and Grand Challenges

Antibiotic resistance significantly impacts global health and sustainable development. It threatens global health by reducing the effectiveness of treatments for infectious diseases, leading to higher morbidity and mortality rates. The economic burden from increased healthcare costs, prolonged hospital stays, and reduced productivity also poses a challenge to economic growth and poverty reduction efforts. In agriculture, the misuse of antibiotics affects food security and safety, leading to potential risks in food supply chains. Additionally, antibiotic residues in the environment contribute to resistance in natural microbial communities, disrupting ecosystems and threatening biodiversity. Addressing antibiotic resistance is crucial for achieving sustainable development goals and tackling grand challenges in global health, such as developing new treatments, ensuring health security, and promoting responsible use of antibiotics to protect public health and the environment.

Potential Implications for Decisions

1. ***Individual***

a. Deciding on the necessity of antibiotics for minor infections, considering the potential for natural recovery and alternative treatments.

b. Understanding the importance of completing the prescribed course of antibiotics to prevent the development of resistance.

c. Avoiding self-medication and ensuring antibiotics are only taken when prescribed by a healthcare professional.

d. Educating oneself about the differences between bacterial and viral infections to better understand when antibiotics are necessary.

e. Taking measures to prevent infections, such as maintaining good hygiene, getting vaccinated, and practicing safe food handling, to reduce the need for antibiotics.

f. Recognizing the signs of antibiotic side effects and seeking medical advice if they occur, to ensure appropriate management and avoid unnecessary continuation of the medication.

g. Being aware of the potential impact of antibiotic use on the microbiome and considering probiotics or other supportive measures to maintain gut health.

2. *Community policies*

a. Implementing local guidelines for the responsible use of antibiotics to reduce the development and spread of resistance.

b. Promoting community awareness programs on the dangers of antibiotic resistance and the importance of adhering to prescribed treatments

c. Encouraging public health initiatives that focus on preventive care and the reduction of infections through improved hygiene and vaccination

d. Ensuring proper disposal of unused or expired antibiotics to prevent environmental contamination and misuse

e. Facilitating access to rapid diagnostic tests in local clinics to ensure antibiotics are prescribed only when necessary

f. Collaborating with local schools to incorporate education on antibiotic resistance and proper use into health curriculums

g. Supporting local initiatives to reduce the use of antibiotics in agriculture and veterinary practices, which can contribute to resistance in human populations

3. *National policies*

a. Developing and enforcing regulations on the use of antibiotics in both human medicine and agriculture to curb resistance.

b. Investing in healthcare infrastructure to support rapid diagnosis and appropriate treatment of bacterial infections, minimizing unnecessary antibiotic use

c. Ensuring access to clean water and sanitation to reduce the spread of infections and reliance on antibiotics

d. Funding research and development of new antibiotics, alternative treatments, and rapid diagnostic tools

e. Promoting sustainable agricultural practices to reduce antibiotic use in livestock, thereby decreasing environmental pollution and resistance spread

f. Considering economic incentives and support for pharmaceutical companies to invest in antibiotic research and development, ensuring a steady pipeline of new treatments

Pupil Participation

1. Class Discussion of the Issues Associated with Antibiotic Use

a. Discuss the role of antibiotics in modern medicine.

b. Explore the consequences of antibiotic resistance.

c. Understand how antibiotics impact personal health and the environment.

2. ***Pupil Stakeholder Awareness***

a. Antibiotic use has both positive and negative consequences for global health and sustainable development. Which of these are most important to you personally/as a class?

b. Can you think of anything that might be done to reduce the negative consequences of antibiotic resistance, especially in healthcare and agriculture?

c. Can you think of anything you might personally do to promote responsible antibiotic use and reduce the spread of resistance?

3. ***Exercises***

a. Role-Playing Exercise: Imagine you are a healthcare provider. How would you explain the importance of completing an antibiotic course to a patient?

b. Debate: Divide the class into two groups to debate the pros and cons of using antibiotics in livestock. Discuss the impact on human health, animal welfare, and the environment

c. Creative Project: Design a public awareness campaign aimed at educating your community about the dangers of antibiotic resistance and the importance of responsible antibiotic use

d. Community Engagement: Organize a school event where students educate parents and community members about antibiotic resistance and how they can contribute to mitigating the issue

e. Field Trip: Visit a local pharmacy or healthcare facility to learn about their antibiotic stewardship programs and how they manage antibiotic prescriptions and disposal

The Evidence Base, Further Reading and Teaching Aids

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