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Authors
Malhi, Sahil
Bao, Vinh-Dan

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Sahil Malhi and Vinh-Dan Bao

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Sahil Malhi and Vinh-Dan Bao

School of Natural Sciences, University of California, Merced

Abstract

Antibiotics were produced to treat and prevent infections caused by pathogens such as bacteria. They are known to be one of the most significant medical breakthroughs in the history of medicine. Antibiotic resistance occurs when pathogens can survive against antibiotics. One key issue that leads to increased resistance is the overuse and improper use of antimicrobial drugs. As a society, it is important to look towards antibiotics and other antimicrobial drugs and use them with advice from public health officials that can allow us to use the strength of antibiotics if an infection ever does arise. Another reason antibiotic resistance is a prominent issue is due to the various mechanisms pathogens have to spread genetic information in a process known as horizontal gene transfer. Horizontal gene transfer is the transfer of genetic information between organisms and allows for resistant pathogens to spread their resistant traits leading to an increase in resistant organisms. Currently, the best thing to do is spread awareness, learn about the mechanisms that spread it such as horizontal gene transfer, and learn how to continue to battle this issue.

Keywords: Horizontal Gene Transfer, Antibiotic Resistance, Multi-Drug Resistance Bacteria (MDR), Transformation, Bacteriophage

Glossary

Bacteriophages: They are viruses that only infect bacterial cells (Kasman & La Donna Porter, 2022)

Horizontal Gene Transfer: The transfer of genetic information such as DNA between organisms (Burmeister, 2015)

Pathogenic: An organism that has the ability to cause disease (Pirofski & Casadevall, 2012)

Transduction: is the transfer of genetic information through bacteriophages that inject hybrid DNA from one bacterium to another (Schneider et al., 2021)

Transformation: is the process of foreign DNA being uptaken from the environment by a pathogen and incorporated into the cell's genome (Lorenz et al., 2023) Conjugation- Is the transfer of genetic information through direct contact from one donating bacterium to a receiving bacterium in one direction (Virolle et al., 2020)

The Evolution and Spread of Antibiotic Resistance in Microorganisms

Antibiotic Resistance is an evolutionary process that occurs when microorganisms can survive against antibiotics, a drug designed to battle microorganism infections (CDC, 2022). Antibiotic resistance is an important topic due to its impact on human healthcare, livestock, and other industries that help contribute to our health and safety. Antibiotics have been a cornerstone of the healthcare industry when it comes to battling microbial infections for the past 70 years (Uddin et al., 2021). While antibiotics have been one of the greatest medical inventions in the last century, it is important to realize that they are used against microorganisms that are always evolving. This is due to these microorganisms, such as bacteria, obtaining resistance to certain drugs through foreign DNA uptake from their environments or mutations. This is an important topic in 2023 due to the overuse of antibiotics, not only in the medical field, as one of the first options for all infections but also the use of antibiotics in our food industry. The higher usage of antibiotics increases the rate of selection for antimicrobial-resistant organisms. As a result, the adapted organisms will spread and thrive, defending themselves against antibiotics (Mancuso et al., 2021). Without effective antibiotics at our disposal, there will be a decrease in the effectiveness of this drug type, which will see an increase in severe cases of infections and which will lead to more deaths. With over 700,000 people dying every year from antibiotic-resistant microorganisms, awareness must be spread on this topic, as infections will have a detrimental effect on the human population over time (Mancuso et al., 2021).

The Evolution of Antibiotics

Antibiotics are used to help battle bacterial infections that can occur in many ways. The first antibiotic used was in 1910, known as Salvarsan (Hutchings et al., 2019), igniting the revolution of modern medicine with a breakthrough of a drug class such as antibiotics. Salvarsan was the first antibiotic that showed positive trials in being able to kill microorganisms (Christensen, 2021). Salvarsan was the lead antibiotic during this period, until the creation of penicillin in 1929 (Uddin et al., 2021), a safer alternative antibiotic to salvarsan due to the less toxic contaminant possibilities that salvarsan contained. Penicillin treatment was not used till 1945 but when it was released, it was known as a breakthrough of antibiotics. During this period, the spread of a sexually transmitted bacterial infection called syphilis was at its peak (CDC, 2023). However, because penicillin had recently hit the market, it was used as the prime medication to help battery this infection (Christensen, 2021). It was even stated that the worries of using Salvarsan and the toxicities that may be associated with it worried individuals more than the infection itself. This fear of toxicity was one of the primary reasons the alternative antibiotic, penicillin, became popular as it was a safe alternative for antibacterial purposes and was a significant finding for the medical field during this time (Scully, 2014). Penicillin and other antibacterial drugs are still used to help treat syphilis showing the breakthrough in medicine that occurred during the 20th century (Tampa et al., 2014).

The creation of new antibiotics has continued to this day as it is still a vital tool used to help battle and prevent bacterial infections. While researchers wish the same antibiotics could forever be the golden pill that can protect us, evolutionarily it is known that this is far from the truth. This is due to the evolutionary ability of microorganisms to find resistance to these antibiotics through various mechanisms. This is why the development of new drugs such as antibiotics is vital to stay ahead in the battle against these pathogens. The terrors in the medical world that have led to a worldwide health issue is the breakthrough of drug-resistant bacteria.

These types of pathogens can survive against a variety of medications preventing the curability from infections. There is a growth of multi-drug resistant bacteria, also known as MDR bacteria, that are resistant to various antibacterial medications that exist today (Butler & Paterson, 2020). Pathogenic resistance to antimicrobial drugs such as antibiotics is only going to increase and if the development of new drugs does not increase, the future battles against these infections will become worrisome. It is well known that pathogens, such as MDR bacteria, are ahead in the race which is prompting immediate attention toward the development of new drugs (Ardal et al., 2019).

Evolutionary Mechanisms that lead to Antimicrobial Resistance

Antibiotic resistance is known as the ability of various pathogens, once susceptible to antibiotics and other antimicrobial agents, to survive against treatments and continue to survive and reproduce. Pathogens such as bacteria have various mechanisms that allow them to eventually gain resistance to drugs such as antibiotics which can all be detrimental to society as antibiotics are one of the key ways to battle or prevent infections. The processes in which antimicrobial agents work often are regarded as the process of destroying the structural integrity of microbial cells and the cellular components, leading to pathogen death or prevention of growth (Baquero & Levin, 2020). One of the most common mechanisms that allow bacteria to survive antibiotics is known as the ability of the Efflux Pump: a pump in bacteria that removes antibiotic molecules from the cell preventing cell death which leads to keeping the bacteria alive (Wu et al., 2023). Other mechanisms that show importance involve the process of horizontal gene transfer. Knowing this, it is important to look at ways in which pathogens have been able to become resistant to antimicrobial mechanisms of action of antibiotics and other antimicrobial drugs use, as well as looking at ways pathogens can spread these resistant traits in the form of genes transfer while learning how mutations are often the driving force that led to resistance.

How Mutations Lead to Antimicrobial Resistance

Mutations are one of the main ways resistance in organisms such as bacteria occurs. Mutations are random and occur at high rates in bacteria, more mutations mean a higher chance of producing change, which randomly can end up being a mutation that helps protect them from antimicrobial drugs. Understanding the mechanisms in which antimicrobial drugs act, and how certain mutations allow for microorganisms to defend themselves which will allow us to understand how to counteract this resistance wave. Pathogens that contained these traits in the past were not selected evolutionarily as protection from antibiotics was never needed, but modern medicine has started battling against these pathogens. As natural selection states, the fittest will survive and thus microorganisms with antibiotic-resistant traits will survive. Mutations randomly occurring that lead to pathogens containing thicker cell walls, various enzyme inhibitors, and other counteracting mechanisms that battle against antibiotics lead to resistance. Many antibiotics act on the cell wall, as a form of destroying the pathogen's structure and disrupting the colonies so they can no longer grow. A mutation that leads to a thicker cell wall preventing the disruption allows pathogens to survive against antibiotics, which leads to resistance. The more pathogens are being exposed to antimicrobial agents, the more selection the environment will have, also known as selective pressure, and the faster possible beneficial mutations will be selected for, increasing the speed at which pathogens can become resistant against antimicrobial agents stating the importance of understanding overuse (Mancuso et al., 2021). This is why providing awareness regarding overuse is one of the key goals the public health department should dial in on, many individuals do not know how medications such as antibiotics work and look at them as the golden pill that will cure them every time but this increases the selective pressure leading to an increase in selection for antibiotic-resistant organisms.

The Spread of Antimicrobial Resistance through Gene Transfer

While mutations are a strategy for antimicrobial resistance, the alteration would not matter if the associated genes that allow for this resistance to occur do not get passed onto offspring or other pathogens. The goal of microbial organisms is to survive and reproduce. Having resistant genes is considered step one as it will allow them to survive the antimicrobial drugs. Again, it is imperative that they pass along these traits. This is where pathogens can acquire genes through horizontal gene transfer from pathogens with these genes. Locations with abundant nutrients, varying survivability of pathogen species, and selective pressure of antimicrobial drugs will be some of the more significant areas where gene transfer will occur. A notable example of such an area in the soil is manure (Lima et al., 2020). There are three gene transfer mechanisms known as transformation, transduction, and conjugation, all of which help spread genetic information and continue the evolutionary battle against antimicrobial resistant organisms. Being able to acquire such genetic information leads to the incorporation of resistant traits. These species are more likely to survive during selective pressure and will continue to survive and adapt to their environments.

Horizontal Gene Transfer: Transformation

In horizontal gene transfer, one of the mechanisms by which genes are transferred from bacterial pathogens in the same environment to another is known as genetic transformation.

Transformation is a form of DNA uptake from the environment in which bacteria can incorporate the DNA and use the genetic coding for their own use, as shown in Figure 1 below Lorenz et al., 2023). This process was discovered by Frederick Griffth in 1928 showing the world of microbiology that bacteria can incorporate DNA from the external environment (Villa et al., 2019). Knowing the process of gene transfer, and specifically transformation, allows us to understand the difficulty of stopping the spread of resistant genetic material. DNA in the environment as free-floating fragments that instruct the activation of resistance-obtaining genes continues to make the battle against resistant organisms tougher. From an evolutionary perspective, this mechanism is one of the main reasons as to why it is so difficult to create antimicrobial drugs to battle these strains as the strains are always changing, mutating, and transferring genetic code. Knowing this information, the next step research can take is to learn about ways to block the uptake of DNA from the environment, opening a new pathway to battle antibiotic resistance.

Horizontal Gene Transfer: Transduction

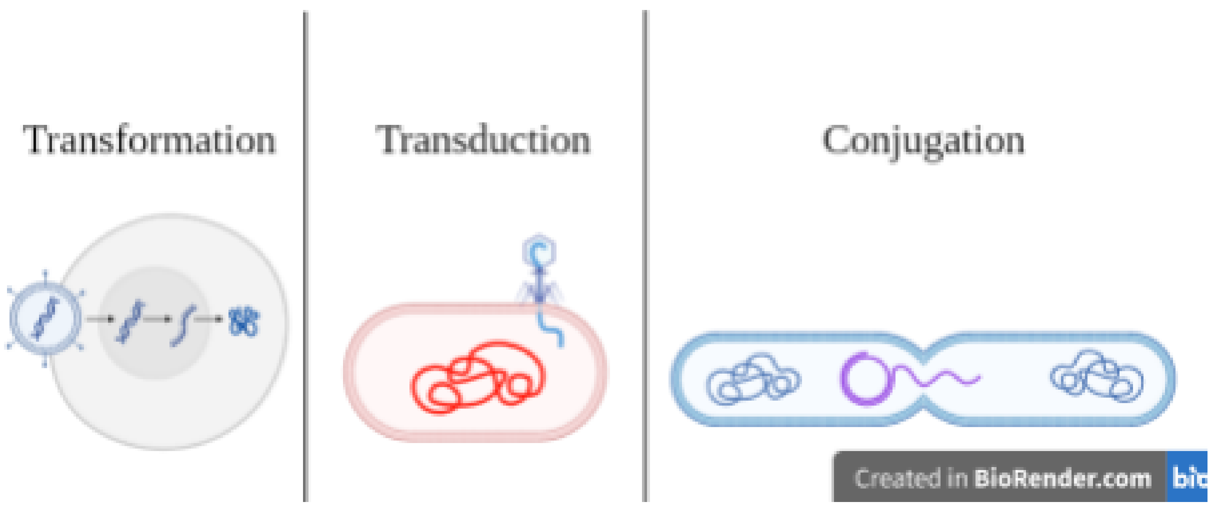
Transduction is the transfer of genetic information (DNA) through phages such as bacteriophages that infect host cells and transfer DNA, also known as the transfer of DNA between bacteria through mediators like viruses. The DNA that is being transferred is known to be a form of hybrid DNA, some of which is from the bacteriophage's viral genome and the rest being the DNA from bacteria. This DNA is being transferred by a tube used by other bacteria which is shown in Figure 1 (Schneider, 2021). This mechanism was discovered in the 1950s and is known as one of the major methods at which bacteria can adapt to the selective pressures of the ever-changing environment (Chiang et al., 2019). Evolutionarily, bacteriophages can transfer DNA from one bacterium to another, allowing for the continued transfer of resistant genes that allow for the survival of the species. During selective pressure, the surviving bacteria are attacked by bacteriophages which leads to the spread of DNA, often by the bacteria that contain resistant genes. This process is random, and bacteriophages are not searching to transfer this hybrid DNA into specific bacteria, this is all a random process from start to finish. It is understood that this matter starts with bacteriophages being the root cause of this gene transfer so research must look towards methods at which could prevent the injection of the hybrid DNA into bacteria, looking at a different avenue to battle antibiotic resistance, one of which is to use bacteriophages to our advantages (Burrowes et al., 2014).

Horizontal Gene Transfer: Conjugation

The third form of horizontal gene transfer is known as conjugation, stated to be one of the more prominent methods of gene transfer out of the three mechanisms that support the creation and survival of drug-resistant bacteria (Bello-López et al., 2019). Unlike the previous two, conjugation requires contact between the two cells where one is transferring and the other is receiving as this is a unidirectional process shown in Figure 1 (Bello-Lopez et al., 2019). Having a method that transfers genes that code for resistant traits through direct contact, the genetic information will reach the inside of the cells at a high percentage compared to DNA being free-floating in the environment to be absorbed such as in transformation. What makes conjugation so strong can stem from the fact that the receiving cell is not only gaining genetic information to gain resistance, but these cells acquire the ability to become a transferable cell. In other words, they can attach to other cells and transfer their genetic information to others consequently continuing the spread of resistance genes and keeping the bacterium alive (Bello Lopez et al., 2019) Using this information, research on antimicrobial drugs must look toward a method at which they could block conjugation from occurring as it prevents the spread of genetic information which can lead to resistant colonies of bacteria. Additionally, it may also be possible to use it with antibiotics as 'you' would then be able to battle the pathogen and prevent the spread of resistant genetic information (Graf et al., 2018). Finding a way to not only block conjugation but all three of these gene transfer methods will allow for a transformational change for the better in the battle against resistance.

Figure 1

The figure below represents the three Horizontal Gene Transfer mechanisms.



Beginning with transformation, DNA starts outside the cell in the environment and is uptaken and incorporated by the cell, allowing the external DNA to be processed and encoded. The second part shows transduction where a bacteriophage injects the Hybrid DNA; here the bacteriophage injects the DNA which the receiving cell can now incorporate into its genetic information. Finally, bacterial DNA is transferred from one cell to another, in a unidirectional route, spreading DNA that can be used by the receiving cell. These images were created by me, Sahil Malhi, and placed on this page using Biorender's illustration tool.

Conclusion

Bringing awareness of antibiotic resistance is one of the most important topics in the 21^{st} century. Antibiotic resistance is an important topic due to its impact on human healthcare, livestock, and other industries that help contribute to our health and safety. This global health issue of antibiotic resistance is going to get more awareness as time goes on as people begin to realize the detrimental effects overuse has led to. There is significant scientific importance on this topic as antibiotics are the cornerstone of medical systems, everywhere from treating infections to preventing them. They have saved millions of lives and will continue to do so. If society does not continue to find new ways to battle antimicrobial resistance, it is projected that by the year 2050 ten million deaths could result from the inability to fight bacteria.

With the CDC spreading the importance of this topic, stating the danger of antibiotic resistance as one of the top problems to public health, this is not something new. A report in 2022 by the CDC also stated the increasing initiative the United States of America is taking to learn more about ways to stop this global health danger (CDC, 2022). By knowing the mechanisms that pathogens use to gain resistance and spread these traits, research must focus on using this knowledge to win this battle against antimicrobial resistance. Research must continue to understand the mechanisms that allow these microorganisms to survive, reproduce, and spread their genetic information, to one day slow them down and allow us to be ahead in the battle from a medical standpoint. The newly published findings indicate the possibility that a new class of antibiotics known as Dynobactin that have shown the ability to be effective against resistant strains, but research must continue to produce increased findings, as well as other effective antibiotics as the battle against resistance will never stop (Miller et al., 2022). Medical research must continue to ask not only about how to produce new antimicrobial medications but also how to spread more information about the proper use of these drugs. The mechanisms that allow these organisms to spread their resistance must be countered. Still, society must also learn how to effectively use antimicrobial drugs with knowledge regarding overuse. This could help slow the spread of resistance and allow researchers more time to create new counters to these pathogens. Asking questions about how to use the knowledge will let us advance our knowledge about resistance.

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