Journal of Academic Inquiry and Knowledge Volume 2024 (4) 130-147
ISBN 979-8-9888908-2-9

Rethinking Antibiotics: Antibiotic Side Effects and Alternatives

Li Cheng Liu

New Jersey

Rethinking Antibiotics: Antibiotic Side Effects and Alternatives

Humans have known of the dangers of infection since ancient times. Although ancient societies did not understand the technicalities of infection, such as miasma theory, they learned of the threat presented by exposed wounds. Pharmacology was abandoned as the world transitioned from the medieval to the early modern (Tracey & DeVries, 2015). This would have drastic consequences, as many bacterial plagues have left their mark. Until the twentieth century, bacteria and their related ailments—tuberculosis, bacterial pneumonia, bubonic plague, and typhus—were some of the deadliest threats to humankind (Kohli, 2024). In 1928, Alexander Fleming invented penicillin, which revolutionized medicine. Many scholars and journalists proclaimed that the Golden Age of Medicine had come (Logan, Prescott, Katz, 2019; Richardson, Underwood, 2024). Indeed, other critical medical discoveries followed, such as antidepressants, vaccinations, and breakthroughs in surgery, biochemistry, and psychology. Scientists' understanding of medicine and the human body has dramatically expanded (Richardson & Underwood, 2024).

However, this medical progress had its downfalls with inhumane human experimentation, wrongful or misleading conduct of surgery, medicine administration, and psychoanalysis

(Richardson & Underwood, 2024). Indeed, that list would also be the brushed-aside consequences of antibiotic use. At the time, doctors believed that bacterial infections would soon become a non-issue and that humans would soon invent a cure for malicious bacteria (Richardson & Underwood, 2024). Nearly an entire century later, the World Health Organization (WHO) has warned of antibiotic resistance, under the umbrella of antimicrobial resistance, to be one of the top ten threats to humanity ("Antibiotic resistance: a global threat," 2024).

In the United States, there are more than 2.8 million annual antibacterial infections ("Antimicrobial facts," 2024). Antibiotics are crucial to infection treatment, from strep throat and asthma to bacterial infections (Dhakad, et al., 2022). However, there are negative consequences related to the frequent use of antibiotics. The most critical problem is antibiotic resistance (Tamma et al., 2017). Harmful bacteria are prone to becoming resistant or immune to the drugs designed to decimate their population (Frieri et al., 2017). Due to the nature of bacteria, antibiotics are often highly programmed to target key traits against select bacteria, such as penicillin, which is used to inhibit peptidoglycan production (Yip, 2024). However, mutated bacteria have evolved to counter or negate the effectiveness of antibiotics. For example, antibiotic-resistant Salmonella variants have been plaguing the United States, causing many food items to be recalled from grocery stores ("Investigation details," 2024). As such, the fight between antibiotics and bacteria is a race with no end goal.

Background

To understand how antibiotics work, one must first examine their intended target. Bacteria are single-celled organisms averaging two micrometers in length and 0.5 micrometers in width (Kadner & Rogers, 2024; Kaiser, 2023). While they are often depicted as oblong, they are most commonly found shaped like spirals, cones, or rods. All but a few exceptions are not visible to the naked eye (Kaiser, 2023; Bailey, 2019). Some are autotrophs, producing sugar molecules through photosynthesis or chemosynthesis or the decomposition of organic matter or chemical compounds. Some bacteria form a symbiotic relationship with other organisms, helping them break down and digest materials they cannot. (Harwood, Wilkin, 2020). Bacteria reproduce asexually through binary fission. They exist almost everywhere, both in the environment and within host organisms (Werth, 2024). Bacteria are highly adaptable and hardy and are some of the most prolific organisms on this planet, with some thriving in outer space (Love, 2024). While bacteria's average lifespan is around 12 hours, some have even been known to survive for millions of years (Kadner, Rogers, 2024).

Antibiotics embody many diverse medicines with very little in common. They share the objective of aiding in eliminating harmful bacteria from a patient's system (Dhakad et al., 2022). Bactericidal antibiotics exterminate hostile microorganisms by attacking their cell walls, membranes, or other functionality. Bacteriostatic antibiotics inhibit bacterial growth by disrupting their reproductive functions, allowing the patient's immune system to eliminate the weakened threat (Dhakad et al., 2022; Anggita et al., 2022). However, these medicines have risks due to their invasive nature. Studies have shown many patients are averse to accepting treatment that could harm them (Brown et al., 2016). Moreover, while most side effects are manageable, in a few instances, they can be life-threatening (Wade & Williams, 2019).

Understanding an antibiotic's function and taking preventive measures to minimize its potential side effects to maximize its effectiveness and safety (Brown et al., 2016). Scientists are exploring options other than antibiotics in combating bacteria and other similar microorganisms. Two possibilities are programming and injecting bacteriophages into a patient's body to reinforce the immune system and using artificial intelligence (AI) to generate formulas to counteract antibiotic-resistant bacteria (Qadri et al., 2023). Antibiotics, crucial to modern medicine and bacterial infection treatment, can lead to various side effects.

Findings

Antibiotics are commonly prescribed for patients suffering from debilitating illnesses caused by bacterial growth. However, their potency also has a caveat—the use of antibiotics has been documented to lead to severe health problems due to disturbances in gut microbiota, increased antibiotic resistance, and decreased immune system efficiency (Frieri et al., 2017; Dhakad et al., 2022; Sandoval-Motta & Aldana, 2016).

The invasive nature of antibiotics is also a problem. Humans require bacteria to perform many of the body's necessary functions. For example, digestion requires bacteria to function (Kadner & Rogers, 2024). There are ten times more bacterial cells than human cells in the human body. Antibiotics can potentially harm these beneficial bacteria (Allen, 2017).

One of the most essential parts of the human body is the gut, which is known to aid digestion and waste excretion (Li et al., 2020). Recent studies have shown that the gut's function is far greater than that. While not as complex as the brain-centered nervous system, two layers of a hundred million nerve cells line the gastrointestinal system, the enteric nervous system, or ENS. Moreover, the gut-brain axis is a bidirectional connection between the central nervous system (CNS) and the enteric nervous system (ENS) (John Hopkins Medicine, 2019).

This direct link between the brain and the gut is a double-edged sword. While it does help the nervous system communicate feelings of hunger, satiation, and queasiness, it also transmits stress, unhappiness, and discomfort (Johns Hopkins Medicine, 2019; "Irritable Bowel Syndrome," 2022). One of the most well-documented examples is irritable bowel syndrome (IBS) and its relationship to depression (Dalton & Drossman, 2017; "Irritable Bowel Syndrome," 2022). While IBS and depression have not been proven to be directly linked, many patients report that the symptoms of one coincide with the symptoms of the other. However, the dual nature of this exacerbation can also work the other way around (Dalton & Drossman, 2017). Antidepressants are used to treat patients with IBS who have no depression symptoms, a treatment that is sparsely researched. Also, tricyclic antidepressants and some serotonin inhibitors have reduced the visceral connection between gut pain and the central nervous system (CNS) (Dalton & Drossman, 2017; “Tricyclic Antidepressants,” 2022). Another under-researched method is cognitive behavioral therapy (CBT). While not a direct cure for IBS, CBT has helped patients regulate their emotions more effectively, especially during IBS flare-ups (Gillette, 2023).

The gradual increase of antibiotic resistance among bacterial populations is another critical consequence of antibiotic usage (Frieri et al., 2017; Sandoval-Motta, Aldana, 2016; “Antimicrobial facts,” 2024). While this increase is not necessarily due to the prescribing of antibiotics, it merely survival of the fittest, presents a noticeable deficit in alternatives. In other words, overreliance on antibiotics can lead to antibiotic-resistant populations (“Antimicrobial Facts,” 2024). If antibiotic-resistant bacteria variant outbreaks are not addressed immediately, disastrous consequences could follow such viral outbreaks (Frieri, Kumar, Boutin, 2017).

Fortunately, antibiotics are not the only solution scientists have identified to prevent bacterial outbreaks. Chief among these are stringent hygiene practices, both personal and commercial. Avoiding bacterial infection (“Antimicrobial Facts,” 2024) is more critical than dealing with an outbreak.

While antibiotics play a critical role in modern medicine, defending many against the attacks of harmful bacteria, it is also important to note that unless such bacteria are eradicated, it is a never-ending race ("Antimicrobial Facts," 2024). Bacteria are some of the most adaptable and prolific organisms on this planet. Given enough time, they can mutate traits that become immune or resistant to their most surefire counterplay, thus repeating the cycle as scientists race to create new medicines. At the same time, strains of bacteria fight to counteract these developments (Osterloh, 2022). Moreover, prolonged usage of antibiotics can also lead to detrimental effects on the human body, such as the disruption of the gut microbiota.

This can lead to severe long-term consequences or even death (Allen, 2017). However, the importance of antibiotic drugs should be considered; they deserve their well-earned title among the best of modern medicine. However, given their unintended consequences, there are antibiotic options (Adhikari, Saha, Tiwary, 2022).

Perhaps the most common and well-studied antibiotic alternative is *phage therapy*, artificially modifying and inducing bacteriophages—a virus that hunts down bacteria—into a patient's body (Aswani, Shukla, 2021; Benisek, 2023). While this method was first recorded in 1922 and demonstrated results in that decade, the treatment died out around the late 1950s, primarily due to the efforts of Gunther Stent, an understudy of Max Delbrück, founder of the infamous "phage group" at the California Institute of Technology. Stent claimed that "ever since antibiotics have shown themselves to be far more efficacious in the control of bacterial diseases than [bacteriophages], the strange bacteriophage therapy chapter of the history of medicine may now be fairly considered as closed" (Hibstu, Belew, Akelew & Mengist, 2022). Stent-related phage therapy is similar to the work of the Germans and the Japanese, the World War II U.S. enemies. Moreover, Stent wasn't alone in his stance on the effectiveness of bacteriophages (Hibstu, Belew, Akelew & Mengist, 2022). In retrospect, it can be determined that a sizable portion of failed cases was due to improper storage, purification, preparation, and conduct of therapeutic phages. Many doubted whether phages could perform up to standard, especially as antibiotics became more common and well-known. Phage therapy soon fell out of favor in much of the Western world (Mylenikov, 2018; "Phage therapy," 2022). Today, phage therapy has been relegated to "compassionate use" in the United States, a treatment method only employed when all else fails. It is to be said, however, that bacteriophage therapy is still a standard treatment method in Eastern European countries like Russia, Poland, and Georgia (Mylenikov, 2018; "Phage therapy", 2022).

That is not to say that bacteriophage therapy is infallible, it has been affected by post-war propaganda and the rising anti-Communist sentiment. However, it has several shortcomings that must be addressed before it can be widely commercialized (Mylenikov, 2018; McCallin, 2013). One of the most pressing issues is the potential for bacteriophages to trigger a negative reaction from the patient's immune system. Given that patients requiring phage therapy area likely in a compromised state due to the severity of their illness, such a reaction could further weaken or exacerbate their condition (Mylenikov, 2018; Hibstu, Belew, Akelew & Mengist; 2022). While no serious side effects of phage therapy have been reported in the U.S., the data is not entirely reliable due to the limited number of trials conducted (Benisek, 2017).

In Russia, where phage therapy has been a staple and is commonly available in pharmacies, the scope of the study is much broader. In George Eliava Institute, named after its founder, Giorgio Eliava, a close research partner of French-Canadian microbiologist Félix d'Herelle, who coined the term 'bacteriophage' in 1917, presents itself as a veteran of phage therapy study (Gordillo & Barr, 2019; Aswani & Shukla, 2021). Although few works survived the post-Soviet Union transformation—especially since Eliava himself was executed during the Great Terror - some have proven invaluable to the bacteriophage field (Gordillo & Barr, 2019;

Aswani & Shukla, 2021). For example, an issue of "Young Scientist" by A. K. Popova and M. K. Kozhevnikov details the early struggles and adaptations of Soviet scientists. Despite some ambitious projects failing, numerous success stories emerged, including the use of phages to purify water and detect signs of HIV-1 (Chikaev, et al., 2021).

Given its impressive background, it is important to highlight the benefits of phage therapy that warrant such extensive study. The most significant advantage is its ability to combat antibiotic resistance, especially as the World Health Organization (WHO) has declared an antibiotic crisis ("Antimicrobial resistance", 2024). Efforts like the World Antibiotic Awareness Week which began in 2015 have been invaluable in raising awareness of this issue. This attention has also highlighted phage therapy as a leading solution to growing antibiotic resistance (Gordillo & Barr, 2019). A notable cause from the same year involved Dr. Tom Patterson, whose infection was resistant to all antibiotics administered ("Phage therapy", 2022). Forthunately, his wife, Dr. Steffanie Strathdee suggested phage therapy to his doctors. With the FDA's approval, a phage cocktail was administered, and within a couple of weeks, Patterson made a full recovery. ("Phage therapy", 2022). This case occurring in the same year as the WHO's 2015 campaign, further propelled therapeutic phages to the spotlight ("Phage therapy", 2022).

While phage therapy is the most popular antibiotic alternative, it is not the only one. Phytochemical vaccines have also proven effective, sometimes in combination with surgery, to combat severe bacterial infections (Osterloh, 2022). Reverse vaccination methods are used to identify specific genes coding for the targeted bacteria, making it easier to tailor vaccine doses to specific strains or patients. Another promising area is DNA vaccinations, which involves injecting sequences that trigger hormonal responses, allowing the foreign DNA to integrate into the patient's pre-existing DNA (Osterloh, 2022; Mba, 2023). However, this treatment has limitations, such as the risk of genome rearrangement, tumor development, or inactivation of the body’s natural suppressor genes. Despite these challenges, phytochemical vaccinations remain crucial in the ongoing fight against antibiotic resistance (Sandoval-Motta & Aldana, 2016). Despite these drawbacks, phytochemical vaccinations are still crucial in the ongoing war against rising antibiotic resistance (Sandoval-Motta & Aldana, 2016).

Prevention may be more effective than readministration in combating bacterial infections. Both immunotherapeutic and probiotics are based on this principle, though they operate differently (Qadri, et al., 2023). Immunotherapeutics involve drugs that harness the body’s natural immune response and are effective only when the bacteria specifically target the immune system and the patient’s immune system is equipped to respond (Allen, 2017; Qadri et al., 2023). On the other hand, probiotics rely on beneficial bacteria in the human microbiome. By cultivating these microorganisms or introducing new ones, the risk of infection can be reduced, or at least its severity minimized (“At a Glance”, 2020). While both methods are innovative and efficient, it is essential to note that prevention alone may not adequately address the underlying issue (Qadri, Shah, Alkhanani, Almilaibary, Mir, 2023).

The latest advancement in this ongoing challenge is the application of artificial intelligence (AI). The rise of AI has sparked significant progress across many fields, including its use in antimicrobial resistance (Tompa, 2024). In the past year alone, researchers at the Massachusetts Institute of Technology (MIT) have developed an improved method for treating the drug-resistant Staphylococcus aureus (MRSA) (Trafton, 2023). Meanwhile, at Stanford Medicine lab, scientists created a generative model algorithm called SyntheMol, designed to target six antibiotic resistant strains of *Acinetobacter baumannii*, a leading cause of antibiotic-resistant-related deaths (Tompa, 2024). With appropriate guidelines, this algorithm could discover treatments for antibiotic-resistant bacteria that have yet to emerge. Similar research is being conducted globally, opening new avenues for success in the fight against antibiotic resistance, and it is with cautious optimism that we anticipate the potential of artificial intelligence in this field (Tompa, 2024).

In summary, as the ongoing battle between scientists and bacteria continues, experts are exploring new avenues where humans might ultimately prevail over these microorganisms. Some of these approaches include phage therapy—by far the most well-researched and documented method -, phytochemical vaccines, and advancements in immunotherapeutic and probiotics that aim to enhance human resistance (Benisek, 2023; Allen, 2017; Aswani, Shukla, 2021; Gordillo & Barr, 2019; "At a Glance", 2020). More recently, AI has emerged as a pivotal tool, with scientists leveraging its generative models to identify potential cures for antibiotic-resistant bacteria. If further developed AI could predict future bacterial mutations, it could potentially position humans to finally overcome this persistent challenge (Lancaster, 2024; Tompa, 2024).

Discussion

Since the 1950s, antibiotics have become a cornerstone of modern medicine. Widely recognized antibiotics such as penicillin led many to believe that the golden age of medicine had arrived and that humans had once and for all triumphed over the microorganisms that once plagued them (Richardson &Underwood, 2024). Unfortunately, scientists were soon disappointed by the bacteria's adaptability in combating these new drugs. This adaptability led to a global antibiotic resistance crisis, as proclaimed by the World Health Organization ("Antimicrobial Resistance," 2024). However, antibiotics remain the most convenient and widely accessible treatment for many common bacterial infections.

Despite their effectiveness, doctors should exercise caution when prescribing antibiotics (Dhakad et al., 2022). Beyond the concern of antibiotic resistance, these drugs can cause a variety of side effects that, while rare, can prove to be fatal (Tamma et al., 2017). Because antibiotics must be highly specialized to target different bacterial species and their related diseases, the varied nature of microorganisms limits the potential alternatives to antibiotics. Nevertheless, scientists continue to explore alternative solutions (Adhikari et al., 2022). A range of treatments and prevention methods is already in development. Among these is phage therapy, which involves engineering a lysed bacteriophage to be injected into a human's body to target and destroy harmful bacteria (Benisek, 2023). Although phage therapy fell out of favor in the Western world due to post-war propaganda and inadequate technology, it has recently seen a resurgence and now stands as a promising approach against the rapid spread of antibiotic-resistant microbes (Gordillo & Barr, 2019; Aswani & Shukla, 2021). Another significant innovation is phytochemical vaccinations, which break down the bacteria's chemical composition through reverse vaccinology. In addition, AI has emerged as a powerful tool, capable of generating countless potential values and compounds to combat future bacteria mutations (Lancaster, 2024; Tompa, 2024).

Conclusion

Antibiotics are crucial in treating many common diseases. However, their reliability and ease of use also present significant downsides, such as increasing antibiotic resistance among bacterial populations and side effects that range from mild to potentially life-threatening. To address these issues, scientists have begun exploring alternative treatments, including programming bacteriophages to target harmful bacteria and developing therapeutic practices to enhance the body's resistance to infection. Despite these challenges, the effectiveness of antibiotics has secured them a well-deserved place in modern medicine.

References

Adhikari, M., Saha, T., & Tiwary, B. (2022). Quest for Alternatives to Antibiotics: An Urgent Need of the Twenty-First Century. Alternatives to Antibiotics, 3–32. https://doi.org/10.1007/978-981-19-1854-4_1

Allen, H. K. (2017). Alternatives to Antibiotics: Why and How. *NAM Perspectives*, *7*(7). https://doi.org/10.31478/201707g

Anggita, D., Nurisyah, S., & Wiriansya, E. P. (2022). Mekanisme Kerja Antibiotik: Review Article. *UMI Medical Journal*, *7*(1), 46–58. https://doi.org/10.33096/umj.v7i1.149

Aswani, V. H., & Shukla, S. K. (2021). An Early History of Phage Therapy in the United States: Is it Time to Reconsider? *Clinical Medicine & Research*, *19*(2), 82–89. https://doi.org/10.3121/cmr.2021.1605

AT A GLANCE Scientific Foresight: What if? (2020). https://www.europarl.europa.eu/RegData/etudes/ATAG/2020/641545/EPRS_ATA(2020)641545_EN.pdf

Bailey, R. (2019, August 20). 3 common shapes of bacteria. ThoughtCo. https://www.thoughtco.com/bacteria-shapes-373278

Benisek, A. (2023, January 11). What Is Phage Therapy? WebMD. https://www.webmd.com/a-to-z-guides/what-is-phage-therapy

Brown, M. T., Bussell, J., Dutta, S., Davis, K., Strong, S., & Mathew, S. (2016). Medication Adherence: Truth and Consequences. *The American Journal of the Medical Sciences*, *351*(4), 387–399. https://doi.org/10.1016/j.amjms.2016.01.010

CDC. (2024, April 22). *Antimicrobial Resistance Facts and Stats*. Antimicrobial Resistance. https://www.cdc.gov/antimicrobial-resistance/data-research/facts-stats/index.html

CDC. (2024, June 27). Investigation details. Centers for Disease Control and Prevention. https://www.cdc.gov/salmonella/backyardpoultry-05-24/details.html

Chikaev, A. N., Rudometov, A. P., Merkulyeva, Y. A., & Karpenko, L. I. (2021). Phage display as a tool for identifying HIV-1 broadly neutralizing antibodies. *Vavilov Journal of Genetics and Breeding*, *25*(5), 562–572. https://doi.org/10.18699/vj21.063

Dalton, C., & Drossman, D. (2017). *The Use of Antidepressants in the Treatment of Irritable Bowel Syndrome and Other Functional GI Disorders*. https://www.med.unc.edu/ibs/wp-content/uploads/sites/450/2017/10/IBS-and-Antidepressants.pdf

Dhakad, G. G., Patil, R., Girase, D. S., Amrutkar, S. P., & Jain, R. S. (2022). Review on Antibiotics. *International Research Journal of Pharmacy*, 91–96. https://doi.org/10.52711/0974-4150.2022.00015

Duboust, O. (2023, December 31). *Scientists discover first new antibiotics in over 60 years using AI*. Euronews. https://www.euronews.com/health/2023/12/31/scientists-discover-the-first-new-antibiotics-in-over-60-years-using-ai

Friedman, N. D., Temkin, E., & Carmeli, Y. (2016). The negative impact of antibiotic resistance. *Clinical Microbiology and Infection*, *22*(5), 416–422. https://doi.org/10.1016/j.cmi.2015.12.002

Frieri, M., Kumar, K., & Boutin, A. (2017). Antibiotic resistance. *Journal of Infection and Public Health*, *10*(4), 369–378. ScienceDirect. https://doi.org/10.1016/j.jiph.2016.08.007

Gillette, H. (2023, October 3). *Can CBT Help Treat IBS?* Healthline; Healthline Media. https://www.healthline.com/health/ibs/cbt-for-ibs#:~:text=CBT%20for%20IBS%20may%20be

Gordillo Altamirano, F. L., & Barr, J. J. (2019). Phage Therapy in the Postantibiotic Era. *Clinical*

Microbiology Reviews, *32*(2). https://doi.org/10.1128/cmr.00066-18

Hibstu, Z., Belew, H., Akelew, Y., & Mengist, H. M. (2022). Phage Therapy: A Different Approach to Fight Bacterial Infections. *Biologics: Targets and Therapy*, *16*, 173–186. https://doi.org/10.2147/btt.s381237

Johns Hopkins Medicine. (2019). *The Brain-Gut Connection*. John Hopkins Medicine. https://www.hopkinsmedicine.org/health/wellness-and-prevention/the-brain-gut-connection

Kadner, R. J., & Rogers, K. (2024, August 19). Bacteria. Encyclopaedia Britannica. https://www.britannica.com/science/bacteria

Kaiser, G. (2023, August 31). 2.1: Sizes, shapes, and arrangements of bacteria. Biology LibreTexts. https://bio.libretexts.org/Bookshelves/Microbiology/Microbiology_(Kaiser)/Unit_1%3A_Introduction_to_Microbiology_and_Prokaryotic_Cell_Anatomy/2%3A_The_Prokaryotic_Cell_-_Bacteria/2.1%3A_Sizes_Shapes_and_Arrangements_of_Bacteria

Kohli, A. (2024, April 30). 7 world's deadliest diseases that impacted human history. Acko General Insurance. https://www.acko.com/health-insurance/diseases/worlds-deadliest-diseases/

Lancaster, C. (2024, June 27). *Harnessing the Power of AI to Design Novel Antibiotics*. The Scientist Magazine®. https://www.the-scientist.com/harnessing-the-power-of-ai-to-design-novel-antibiotics-71974

Li, S., Zhuo, M., Huang, X., Huang, Y., Zhou, J., Xiong, D., Li, J., Liu, Y., Pan, Z., Li, H., Chen, J., Li, X., Xiang, Z., Wu, F., & Wu, K. (2020). Altered gut microbiota associated with symptom severity in schizophrenia. *PeerJ*, *8*. https://doi.org/10.7717/peerj.9574

Logan, A. C., Prescott, S. L., & Katz, D. L. (2019, July 31). Golden age of medicine 2.0: Lifestyle Medicine and Planetary Health prioritized. Journal of lifestyle medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6894443/#:~:text=The%20'golden%20age%20of%20medicine,disease%20shifted%20to%20lifestyle%2Ddriven%2C

Mba, I. E., Sharndama, H. C., Anyaegbunam, Z. K. G., Anekpo, C. C., Amadi, B. C., Morumda, D., Doowuese, Y., Ihezuo, U. J., Chukwukelu, J. U., & Okeke, O. P. (2023). Vaccine development for bacterial pathogens: Advances, challenges and prospects. *Tropical Medicine & International Health*. https://doi.org/10.1111/tmi.13865

McCallin, S., Alam Sarker, S., Barretto, C., Sultana, S., Berger, B., Huq, S., Krause, L., Bibiloni, R., Schmitt, B., Reuteler, G., & Brüssow, H. (2013). Safety analysis of a Russian phage cocktail: From MetaGenomic analysis to oral application in healthy human subjects. *Virology*, *443*(2), 187–196. https://doi.org/10.1016/j.virol.2013.05.022

Myelnikov, D. (2018). An Alternative Cure: The Adoption and Survival of Bacteriophage Therapy in the USSR, 1922–1955. *Journal of the History of Medicine and Allied Sciences*, *73*(4), 385–411. https://doi.org/10.1093/jhmas/jry024

Osterloh, A. (2022, May 10). Vaccination against bacterial infections: Challenges, progress, and new approaches with a focus on intracellular bacteria. Vaccines. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9144739/

Phage therapy: Past, present and future. ASM.org. (2022). https://asm.org/articles/2022/august/phage-therapy-past,-present-and-future

Qadri, H., Shah, A., Alkhanani, M., Almilaibary, A. & Mir, M. (2023). Immunotherapies against human bacterial and fungal infectious diseases: A review. *Frontiers in Medicine*, *10*. https://doi.org/10.3389/fmed.2023.1135541

Richardson, R. G., & Underwood, E. A. (2024, May 6). Medicine in the 20th Century. Encyclopaedia Britannica. https://www.britannica.com/science/history-of-medicine/Medicine-in-the-20th-century

Sandoval-Motta, S., & Aldana, M. (2016). Adaptive resistance to antibiotics in bacteria: a systems biology perspective. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, *8*(3), 253–267. https://doi.org/10.1002/wsbm.1335

Tamma, P. D., Avdic, E., Li, D. X., Dzintars, K., & Cosgrove, S. E. (2017). Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Internal Medicine*, *177*(9), 1308. https://doi.org/10.1001/jamainternmed.2017.1938

Tompa, R. (2022, December 20). *Generative AI develops potential new drugs for antibiotic-resistant bacteria*. News Center. https://med.stanford.edu/news/all-news/2024/03/ai-drug-development.html

Tracy, L., & DeVries, K. (2015). Wounds and wound repair in medieval culture. Brill.

Trafton, A. (2023, December 23). Using AI, MIT researchers identify a new class of antibiotic candidates. MIT News. https://news.mit.edu/2023/using-ai-mit-researchers-identify-antibiotic-candidates-1220

UNEP. (2024). Antimicrobial resistance: A global threat. UNEP. https://www.unep.org/topics/chemicals-and-pollution-action/pollution-and-health/antimicrobial-resistance-global-threat

USDA ERS - Cost Estimates of Foodborne Illnesses. (2023, March 2). Www.ers.usda.gov. https://www.ers.usda.gov/data-products/cost-estimates-of-foodborne-illnesses/

Wade, S., & Williams, M. (2019). Antibiotic side-effects: from the anticipated to the bizarre. *Prescriber*, *30*(11), 16–21. https://doi.org/10.1002/psb.1801

WebMD. (2022). *Irritable Bowel Syndrome (IBS) and Depression*. WebMD. https://www.webmd.com/ibs/irritable-bowel-syndrome-ibs-depression

WebMD. (2022). *Tricyclic Antidepressants for Bipolar Disorder*. WebMD. https://www.webmd.com/bipolar-disorder/tricyclic-antidepressants

Yip, D. W. (2024, February 20). Penicillin. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK554560/