Addressing Antibiotic Resistance: Strategies For Developing New Antibacterial Agents

Majed Manea Doman Al Yami,[1] Nasser Saleh Mohammed Al Aqeel,[2] Majed Qasem Ibrahim Masoud,[3] Abdulrhman Barakh Almutairy,[4] Mohammed Atig Banihumayyim,[5] Sauod Hussain Hamed Al Sagoor,[6] Dowas Saleh Salem Almotared,[7] Aboud Meshal Aboud Alshareef,[8] Mohammed Nasser Alzmanan,[9] Rashed Hadi Rashed Alkhumsan,[10] Nasser Manea S Aldaghreer,[11] Mohammed Abdullah H Alyami,[12] Naif Ali Hussin Al Rakh,[13] Mana Abdullah Mahdi Al Hutilah,[14] Saleh Abdullah Mahdi Al Hutilah[15]

[1-]Nahogah Primary Health Care Center Najran Moh Kingdom Of Saudi Arabia.
[2]-Al Hadan Primary Health Care Center Najran Moh Kingdom Of Saudi Arabia.
[3]-Baish General Hospital Moh Kingdom Of Saudi Arabia.
[4]-Prince Mohammed Ibn Abdulaziz Hospital Ryiadh Moh Kingdom Of Saudi Arabia.
[5,6-]Thar General Hospital Moh Kingdom Of Saudi Arabia.
[7-]King Khalid Hospital Najran Moh Kingdom Of Saudi Arabia.
[8]-Al Hamar Primary Health Care Center Moh Kingdom Of Saudi Arabia.
[9]-Maternity And Children Hospital Moh Kingdom Of Saudi Arabia.
[10]-Primary Health Care Center In Al-Qabil Moh Kingdom Of Saudi Arabia.
[11,12]-Najran New General Hospital Moh Kingdom Of Saudi Arabia.
[13-]Yadama General Hospital Moh Kingdom Of Saudi Arabia.
[14,15-]Najran General Hospital Moh Kingdom Of Saudi Arabia.

Abstract:

The development of new antibiotics is paramount in combating the escalating threat of antibiotic resistance, which poses significant challenges to global public health. However, this endeavor is hampered by regulatory and economic obstacles that impede the translation of scientific innovations into clinically effective therapies. Regulatory requirements, market dynamics, and reimbursement policies create barriers to antibiotic research and development, leading to a limited pipeline of novel antimicrobial agents. Addressing these challenges requires collaborative efforts from policymakers, regulators, pharmaceutical companies, and the healthcare community. Regulatory reforms, market-based incentives, and sustainable antibiotic use strategies are essential for expediting antibiotic development, stimulating investment, and preserving the effectiveness of existing antibiotics. This review examines the regulatory and economic challenges in antibiotic development and proposes strategies to overcome them, emphasizing the importance of innovation, stewardship, and global cooperation in safeguarding the efficacy of antibiotic therapies.

Keywords: antibiotic resistance, antibiotic development, regulatory challenges, economic challenges, antimicrobial stewardship, innovation, global health, public health, drug approval, market incentives.

Introduction:

Antibiotic resistance poses a significant global health threat, rendering many conventional treatments ineffective against bacterial infections. As existing antibiotics lose their efficacy, the urgent need for novel antibacterial agents becomes paramount. This article explores various strategies employed by researchers and pharmaceutical companies to develop new antibacterial agents capable of combating antibiotic-resistant bacteria.

Antibiotic resistance stands as one of the most pressing challenges in modern medicine, jeopardizing decades of progress in treating bacterial infections. The emergence and spread of antibiotic-resistant bacteria have rendered many conventional treatments ineffective, leading to prolonged illnesses, increased healthcare costs, and heightened mortality rates. This escalating threat necessitates urgent action to develop new antibacterial agents capable of combating resistant pathogens.

Over the years, the misuse and overuse of antibiotics in healthcare, agriculture, and animal husbandry have accelerated the evolution of resistance mechanisms in bacteria. As a result, once-effective antibiotics are losing their potency, leaving healthcare providers with limited treatment options for infections that were once easily manageable. This crisis underscores the critical need for innovative approaches to develop novel antibacterial agents that can effectively address antibiotic resistance.

In this article, we delve into the strategies and initiatives aimed at developing new antibacterial agents to tackle antibiotic resistance. From exploring alternative bacterial targets to harnessing the potential of natural products and advancing drug delivery systems, researchers and pharmaceutical companies are actively seeking solutions to combat resistant pathogens. By understanding the mechanisms of antibiotic resistance and employing innovative approaches, we can strive to mitigate the impact of this global health threat and ensure effective treatments for bacterial infections in the future.[1]

Understanding Antibiotic Resistance:

Antibiotic resistance refers to the ability of bacteria to survive and multiply in the presence of antibiotics, rendering these medications ineffective in treating infections caused by resistant strains. This phenomenon arises from the natural evolutionary processes of bacteria, which adapt to the selective pressure exerted by antibiotics. Several mechanisms contribute to antibiotic resistance, including:

Genetic Mutation: Bacteria can acquire mutations in their DNA that confer resistance to antibiotics. These mutations may affect the target site of the antibiotic, preventing it from binding effectively and inhibiting bacterial growth. Examples include mutations in genes encoding antibiotic targets such as bacterial ribosomes or enzymes involved in cell wall synthesis.

Horizontal Gene Transfer: Bacteria can acquire resistance genes from other bacteria through processes such as conjugation, transformation, and transduction. This allows for the rapid spread of resistance genes within bacterial populations, even across different species. Mobile genetic elements, such as plasmids and integrons, play a crucial role in facilitating horizontal gene transfer.

Efflux Pumps: Some bacteria possess efflux pump systems that actively remove antibiotics from the bacterial cell, reducing their intracellular concentration and rendering them less effective. Efflux pumps can confer resistance to multiple classes of antibiotics and are often encoded by genes located on plasmids or the bacterial chromosome.

Biofilm Formation: Bacteria can form biofilms, complex communities of cells encased in a matrix of extracellular polymeric substances. Biofilms provide protection against antibiotics and host immune responses, making infections difficult to eradicate. Bacteria within biofilms exhibit increased resistance to antibiotics compared to planktonic (free-floating) bacteria.

The widespread use and misuse of antibiotics in human medicine, agriculture, and animal husbandry have contributed to the proliferation of antibiotic-resistant bacteria. Factors such as incomplete courses of antibiotic treatment, inappropriate antibiotic prescribing practices, and the use of antibiotics as growth promoters in livestock have fueled the development of resistance. Additionally, the lack of investment in the development of new antibiotics has exacerbated the problem, leading to a dwindling arsenal of effective antimicrobial agents.

Addressing antibiotic resistance requires a multifaceted approach that encompasses improved antibiotic stewardship, infection prevention and control measures, and the development of new antibacterial agents. By understanding the mechanisms of antibiotic resistance and implementing strategies to mitigate its spread, we can safeguard the effectiveness of antibiotics and ensure their continued efficacy in treating bacterial infections.

Targeting Novel Bacterial Pathways:

In the battle against antibiotic resistance, researchers are exploring innovative strategies to develop new antibacterial agents that target novel bacterial pathways. Traditional antibiotics often focus on well-established targets such as bacterial cell wall synthesis or protein synthesis machinery. However, the emergence of resistance has necessitated the exploration of alternative pathways essential for bacterial survival. Here are some approaches to targeting novel bacterial pathways:

Cell Wall Biosynthesis Inhibitors: While antibiotics like penicillin and vancomycin target cell wall synthesis by inhibiting peptidoglycan formation, researchers are investigating new inhibitors that target different stages of cell wall biosynthesis. These may include enzymes involved in lipid II precursor synthesis or enzymes responsible for cross-linking peptidoglycan strands.

Membrane Disruption Agents: Disrupting bacterial cell membranes represents a promising avenue for antibacterial drug development. Compounds that target essential membrane proteins or disrupt lipid bilayer integrity can destabilize bacterial membranes, leading to cell death. Lipopeptide antibiotics and antimicrobial peptides are examples of membrane-targeting agents.

Essential Metabolic Pathways: Bacteria rely on specific metabolic pathways for energy production, biosynthesis, and cellular processes. Inhibiting key enzymes or metabolic intermediates in these pathways can impair bacterial growth and survival. For example, inhibitors of enzymes involved in folate metabolism, such as dihydropteroate synthase and dihydrofolate reductase, are used as antibacterial agents.

Quorum Sensing Inhibitors: Quorum sensing is a communication system used by bacteria to coordinate gene expression in response to cell density. Inhibition of quorum sensing pathways can disrupt bacterial virulence and biofilm formation, making bacteria more susceptible to antibiotics and immune clearance. Quorum sensing inhibitors are being explored as adjuvants to traditional antibiotics.

Toxin Neutralization: Some bacteria produce toxins that contribute to pathogenesis and immune evasion. Targeting bacterial toxins or their delivery mechanisms can attenuate virulence and enhance bacterial clearance by the host immune system. Neutralizing antibodies and small molecule inhibitors are potential strategies for blocking bacterial toxins.

Essential Gene Expression Regulators: Bacteria rely on precise regulation of gene expression for adaptation and survival in different environments. Inhibiting essential gene expression regulators, such as transcription factors or riboswitches, can disrupt bacterial physiology and render bacteria more susceptible to antibiotics.

Bacterial Cell Division Machinery: Inhibitors of bacterial cell division proteins, such as FtsZ inhibitors, disrupt the formation of the cytokinetic ring and block cell division. These agents represent a novel approach to targeting bacterial growth and proliferation.

By targeting novel bacterial pathways, researchers aim to develop antibacterial agents with unique mechanisms of action that are less prone to resistance development. These innovative approaches hold promise for addressing the challenge of antibiotic resistance and ensuring effective treatment of bacterial infections in the future.

Harnessing Natural Products:

Amidst the escalating threat of antibiotic resistance, researchers are turning to nature's vast repertoire of compounds as potential sources for new antibacterial agents. Natural products, derived from plants, fungi, marine organisms, and microorganisms, have historically served as a rich source of bioactive compounds with diverse chemical structures and mechanisms of action. Here's how researchers are harnessing natural products for antibacterial development:

Plant-Derived Compounds: Plants produce a wide array of secondary metabolites with antimicrobial properties, including alkaloids, flavonoids, terpenoids, and phenolic compounds. These compounds often serve as defense mechanisms against microbial pathogens. Examples include berberine from barberry plants, curcumin from turmeric, and resveratrol from grapes. Researchers are screening plant extracts and isolating bioactive compounds to identify potential antibacterial agents.

Microbial Products: Microorganisms such as bacteria and fungi produce a plethora of bioactive compounds with antibacterial activity. Streptomycin, tetracycline, and erythromycin are examples of antibiotics derived from soil bacteria. Fungi like Penicillium and Streptomyces produce secondary metabolites such as penicillin and cephalosporins. Researchers are exploring microbial biodiversity and employing innovative screening techniques to discover novel antibacterial compounds from microorganisms.

Marine Natural Products: The marine environment harbors a diverse range of organisms that produce bioactive compounds with pharmaceutical potential. Marine sponges, algae, and bacteria are prolific sources of antibacterial agents. Compounds like peptides, polyketides, and alkaloids isolated from marine organisms exhibit promising antibacterial activity against resistant pathogens. Researchers are conducting expeditions to unexplored marine habitats and employing advanced analytical techniques to discover novel antibacterial compounds.

Natural Product Libraries: Natural product libraries, consisting of extracts or purified compounds from diverse sources, serve as valuable resources for antibacterial drug discovery. High-throughput screening of natural product libraries against bacterial pathogens allows researchers to identify lead compounds with potent antibacterial activity. Additionally, computational approaches, such as molecular docking and virtual screening, aid in predicting the antibacterial potential of natural products and optimizing their structures for enhanced efficacy.

Synergistic Combinations: Combining natural products with conventional antibiotics can enhance antibacterial efficacy and mitigate the development of resistance. Synergistic interactions between natural products and antibiotics can potentiate their antibacterial effects, allowing for lower doses of antibiotics and reducing the risk of resistance emergence. Researchers are investigating synergistic combinations of natural products with antibiotics to combat multidrug-resistant bacteria effectively.
Harnessing natural products for antibacterial development offers a promising avenue for discovering novel antibacterial agents with diverse chemical scaffolds and mechanisms of action. By tapping into nature's chemical diversity, researchers aim to replenish the antibiotic pipeline and address the growing threat of antibiotic resistance effectively. However, challenges such as compound purification, structural elucidation, and optimization remain hurdles in the development of natural product-based antibacterial therapies.

Antibiotic Combination Therapy:
In the face of increasing antibiotic resistance, combination therapy has emerged as a strategic approach to enhance bacterial eradication, prevent the emergence of resistance, and broaden the spectrum of activity against multidrug-resistant pathogens. Here, we explore the rationale behind antibiotic combination therapy, examples of synergistic combinations, and challenges associated with its implementation.

Rationale for Combination Therapy:
Synergy: Combining antibiotics with different mechanisms of action can produce synergistic effects, where the combined

activity exceeds the sum of individual effects. Synergy enhances bacterial killing and reduces the likelihood of resistance development.

Broader Spectrum: Combinations can broaden the spectrum of activity, allowing for coverage of a wider range of bacterial species or strains.

Reduction of Resistance: By targeting multiple bacterial pathways simultaneously, combination therapy can inhibit the emergence of resistance or delay its onset.

Examples of Synergistic Combinations:

β-Lactam and β-Lactamase Inhibitor: Pairing a β-lactam antibiotic (e.g., amoxicillin) with a β-lactamase inhibitor (e.g., clavulanic acid) enhances the activity against β-lactamase-producing bacteria, such as certain strains of Escherichia coli and Haemophilus influenzae.

Aminoglycoside and β-Lactam: Combining an aminoglycoside (e.g., gentamicin) with a β-lactam antibiotic (e.g., penicillin) can synergistically enhance bacterial killing by disrupting cell wall synthesis and protein synthesis simultaneously.

Trimethoprim-Sulfamethoxazole (TMP-SMX) and Fluoroquinolone: The combination of TMP-SMX with a fluoroquinolone (e.g., ciprofloxacin) has been used to treat severe infections such as Pneumocystis jirovecii pneumonia and complicated urinary tract infections, exploiting synergistic effects on bacterial folate synthesis and DNA replication.

Challenges and Considerations:

Drug Interactions: Some antibiotic combinations may exhibit antagonistic interactions or increase the risk of adverse effects, requiring careful consideration of dosing regimens and pharmacokinetic properties.

Resistance Emergence: Despite the benefits of combination therapy, bacteria can still develop resistance to one or both components, particularly if they share similar resistance mechanisms.

Clinical Evidence: Robust clinical evidence supporting the superiority of combination therapy over monotherapy is limited in many cases, necessitating further research to define optimal treatment regimens.

Cost and Accessibility: Combination therapies may be more expensive and less accessible in resource-limited settings, posing challenges to widespread implementation.

In conclusion, antibiotic combination therapy represents a valuable strategy for maximizing efficacy and combating antibiotic resistance. By leveraging synergistic interactions between antibiotics with distinct mechanisms of action, combination therapy offers the potential to overcome resistance, broaden spectrum coverage, and enhance bacterial eradication. However, challenges such as drug interactions, resistance emergence, and clinical evidence gaps underscore the need for careful consideration and further research to optimize combination therapy regimens.[2,3]

Development of Narrow-Spectrum Antibiotics:

In response to the growing threat of antibiotic resistance, researchers and pharmaceutical companies are exploring the development of narrow-spectrum antibiotics as a promising strategy to combat multidrug-resistant pathogens. Unlike broad-spectrum antibiotics, which indiscriminately target a wide range of bacteria, narrow-spectrum antibiotics are designed to selectively target specific bacterial species or strains. Here, we delve into the rationale behind narrow-spectrum antibiotics, their advantages, and challenges in their development.

Rationale for Narrow-Spectrum Antibiotics:

Precision Targeting: Narrow-spectrum antibiotics selectively target pathogens responsible for specific infections while sparing beneficial commensal bacteria. By focusing on the causative agents of infections, narrow-spectrum antibiotics minimize disruptions to the normal microbiota, reducing the risk of dysbiosis and secondary infections.

Reduced Selection Pressure: Unlike broad-spectrum antibiotics, which exert significant selective pressure on microbial communities and promote the emergence of resistance, narrow-spectrum antibiotics limit the exposure of non-target bacteria to antimicrobial agents. This can help slow the development and spread of antibiotic resistance.

Minimized Collateral Damage: Narrow-spectrum antibiotics are associated with fewer adverse effects and lower rates of antibiotic-associated complications, such as Clostridioides difficile infection and allergic reactions, compared to broad-spectrum counterparts.

Strategies for Developing Narrow-Spectrum Antibiotics:

Targeted Pathogen Identification: Comprehensive microbial diagnostics, including molecular techniques and rapid diagnostic tests, enable the precise identification of causative pathogens and their susceptibility profiles. This information guides the selection of narrow-spectrum antibiotics tailored to the specific microbial etiology of infections.

Rational Drug Design: Structure-based drug design and computational modeling facilitate the development of narrow-spectrum antibiotics with high specificity for essential bacterial targets. By optimizing drug-target interactions and minimizing off-target effects, researchers can design antibiotics with enhanced efficacy against target pathogens.

Combination Therapies: Combinations of narrow-spectrum antibiotics with synergistic mechanisms of action or adjuvants targeting bacterial virulence factors can enhance antibacterial efficacy while minimizing the risk of resistance development. Strategic antibiotic combinations can overcome bacterial resistance mechanisms and improve treatment outcomes.

Challenges and Considerations:

Diagnostic Limitations: Limited access to accurate and timely microbial diagnostics in clinical settings can hinder the implementation of narrow-spectrum antibiotic therapy. Improved diagnostic technologies and point-of-care tests are needed to facilitate targeted antibiotic prescribing.

Narrow Market Potential: Narrow-spectrum antibiotics may have a narrower spectrum of activity and limited indications compared to broad-spectrum counterparts, potentially limiting their commercial viability and investment incentives for drug development.

Resistance Mitigation: Despite their precision targeting, narrow-spectrum antibiotics are not immune to resistance development. Continued surveillance of antibiotic resistance patterns, stewardship efforts, and the development of combination therapies are essential for mitigating resistance emergence.

In conclusion, the development of narrow-spectrum antibiotics represents a promising strategy for combating antibiotic resistance while minimizing collateral damage to the microbiota and reducing the risk of resistance. By leveraging precision targeting, rational drug design, and strategic combination therapies, narrow-spectrum antibiotics offer the potential to improve treatment outcomes and preserve the efficacy of antimicrobial agents for future generations. However, addressing challenges related to diagnostics, market incentives, and resistance mitigation is crucial for realizing the full potential of narrow-spectrum antibiotics in clinical practice.

Novel Drug Delivery Systems:

Innovations in drug delivery technologies for improving the efficacy and specificity of antibacterial agents. Examples of nanoparticle-based delivery systems, liposomal formulations, and targeted drug delivery approaches. Potential for reducing systemic side effects and enhancing bacterial killing within infection sites.

Overcoming Regulatory and Economic Challenges:

The development of new antibiotics faces significant regulatory and economic hurdles, which contribute to the limited pipeline of novel antimicrobial agents and the growing threat of antibiotic resistance. Addressing these challenges is crucial for incentivizing antibiotic research and development (R&D) and ensuring the availability of effective treatments for bacterial infections. Here, we explore the regulatory and economic challenges in antibiotic development and potential strategies to overcome them.[4]

Regulatory Challenges:

Stringent Regulatory Requirements: Antibiotic development is subject to rigorous regulatory standards set by health authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These requirements include extensive preclinical and clinical testing to demonstrate safety, efficacy, and quality, resulting in lengthy and costly development timelines.

Limited Regulatory Pathways: The traditional regulatory pathways for antibiotic approval may not adequately address the unique challenges of antimicrobial drug development, such as small patient populations for certain infections and the emergence of resistance during clinical trials. Alternative regulatory pathways, such as limited population approval and adaptive licensing, are needed to facilitate the approval of urgently needed antibiotics.

Market Incentives: The market incentives for antibiotic development are limited due to factors such as low prices, short treatment durations, and the need for stewardship to preserve antibiotic efficacy. Without adequate returns on investment, pharmaceutical companies may prioritize other therapeutic areas with greater profit potential, leading to a lack of investment in antibiotic R&D.

Economic Challenges:

Market Failure: Antibiotic development is characterized by market failures, where the societal benefits of new antibiotics, such as reducing morbidity, mortality, and healthcare costs associated with resistant infections, are not fully captured by the market. This disconnect between the private returns on investment and the broader societal benefits creates disincentives for antibiotic R&D.

Antibiotic Pricing: The pricing of antibiotics is often low compared to other therapeutic classes, reflecting the need for affordable access to essential medicines and concerns about antibiotic overuse and resistance. However, low prices may not adequately incentivize pharmaceutical companies to invest in antibiotic development, particularly for narrow-spectrum or reserved antibiotics with limited market potential.

Reimbursement Challenges: Reimbursement policies and mechanisms for antibiotics may not fully account for the value of new antimicrobial agents or the complexities of antibiotic stewardship. Innovative reimbursement models, such as subscription-based payments, delinkage of revenue from sales volume, and value-based pricing, are needed to incentivize sustainable investment in antibiotic development.

Strategies for Overcoming Challenges:

Regulatory Reform: Regulatory agencies should collaborate with stakeholders to develop streamlined pathways for antibiotic approval, including flexible trial designs, surrogate endpoints, and expedited review processes for drugs targeting priority pathogens. Enhanced post-market surveillance and pharmaco-vigilance are essential for monitoring the safety and efficacy of new antibiotics after approval.

Market-Based Incentives: Governments, philanthropic organizations, and international agencies can provide financial incentives, grants, and prizes to stimulate antibiotic R&D and bridge the gap between the societal value of new antibiotics and their commercial returns. Initiatives such as the AMR Action Fund and the Global Antibiotic Research and Development Partnership (GARDP) aim to address market failures and accelerate the development of new antibiotics.

Sustainable Antibiotic Use: Antibiotic stewardship programs, public awareness campaigns, and regulatory interventions can promote responsible antibiotic use and preserve the effectiveness of existing antibiotics. By reducing the incidence of resistant infections and prolonging the lifespan of existing antibiotics, these initiatives contribute to the economic viability of antibiotic development and the sustainability of healthcare systems.
In conclusion, overcoming the regulatory and economic challenges in antibiotic development requires a multifaceted approach involving regulatory reform, market-based incentives, and sustainable antibiotic use strategies. By addressing barriers to antibiotic R&D and incentivizing investment in new antimicrobial agents, policymakers, regulators, and stakeholders can strengthen the antibiotic pipeline, mitigate the threat of antibiotic resistance, and safeguard public health.[5]

Conclusion: Efforts to develop new antibacterial agents are critical in addressing the growing threat of antibiotic resistance. By employing innovative strategies, such as targeting novel bacterial pathways, harnessing natural products, and utilizing advanced drug delivery systems, researchers and pharmaceutical companies can contribute to the fight against antibiotic-resistant infections. However, overcoming regulatory hurdles and economic barriers remains essential to ensuring the sustainable development and availability of effective antibacterial treatments.
The development of new antibiotics is critical in the fight against antibiotic resistance, a global health crisis that threatens the efficacy of existing treatments and jeopardizes patient outcomes. However, this endeavor is hindered by regulatory and economic challenges that impede the translation of scientific discoveries into clinically viable therapies. Regulatory requirements, market dynamics, and reimbursement policies create barriers to antibiotic research and development, leading to a dwindling pipeline of novel antimicrobial agents.

Addressing these challenges requires collaborative efforts from policymakers, regulators, pharmaceutical companies, and the broader healthcare community. Regulatory reforms aimed at streamlining approval pathways, enhancing post-market surveillance, and fostering innovation are essential for expediting antibiotic development while ensuring patient safety. Market-based incentives, including grants, prizes, and delinkage mechanisms, can stimulate investment in antibiotic R&D and align commercial interests with public health goals.

Furthermore, sustainable antibiotic use strategies, such as antibiotic stewardship programs and public awareness campaigns, are crucial for preserving the effectiveness of existing antibiotics and reducing the burden of resistant infections. By promoting responsible antibiotic prescribing practices and minimizing unnecessary antibiotic exposure, these initiatives contribute to the economic viability of antibiotic development and the long-term sustainability of healthcare systems.

In conclusion, overcoming regulatory and economic challenges in antibiotic development is essential for replenishing the antibiotic pipeline, combating antibiotic resistance, and safeguarding public health. By implementing evidence-based policies, fostering innovation, and promoting stewardship, we can ensure the continued availability of effective antibiotics for future generations.

References:

1-Boucher HW, Talbot GH, Benjamin DK Jr, et al. 10 x '20 Progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(12):1685-1694. doi:10.1093/cid/cit152

2-Outterson K, Powers JH, Daniel GW, McClellan MB. Repairing the broken market for antibiotic innovation. Health Aff (Millwood). 2015;34(2):277-285. doi:10.1377/hlthaff.2014.1024

3-Rex JH, Eisenstein BI, Alder J, et al. A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. Lancet Infect Dis. 2013;13(3):269-275. doi:10.1016/S1473-3099(12)70319-2

4-Theuretzbacher U, Piddock LJ. Non-traditional Antibacterial Therapeutic Options and Challenges. Cell Host Microbe. 2019;26(1):61-72. doi:10.1016/j.chom.2019.06.003

5-Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-327. doi:10.1016/S1473-3099(17)30753-3