Syncytia
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Review

Antibiotic resistance and a dire need for novel and innovative therapies: The impending crisis

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Abstract

Antibiotic resistance poses an escalating global crisis as pathogens like the ESKAPE organisms – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species—are evolving to evade our antibacterial arsenal. We desperately need innovative strategies to fill the pipeline with effective treatments. BioSAXS, which maps antibiotic targets using X-ray scattering and biophysics, and artificial intelligence, which expedites drug creation and screening, are two promising approaches. In addition to conventional antibiotics, scientists are investigating immunotherapies, phage treatment, antimicrobial peptides, and synergistic combinations. Major challenges still exist, though, in turning these insights into licensed medical interventions. Enhanced public-private partnerships, improved data sharing, and incentives like milestone prizes could help spur the development of new antimicrobials. Regulators should consider pathways to accelerate approval for therapies that address urgent needs against resistant infections. The COVID-19 pandemic spotlighted concerning gaps in infectious disease preparedness that must be addressed. With global coordination and increased funding, we can reignite antimicrobial discovery and development to combat superbugs before routine injuries and illnesses become untreatable again. Overcoming the scientific and economic challenges will require commitment from all stakeholders. We urgently need imagination and resolve to build a robust pipeline of novel therapies to meet the threat of modern "superbugs" before the antibacterial era comes to an end.

Received: 19 September 2023
Accepted: 14 November 2023
Published: 31 December 2023

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Keywords
Antibiotic resistance;
Antimicrobial drug development;
BioSAXS;
ESKAPE pathogens

Introduction

The discovery of penicillin by Alexander Fleming in 1928 marked the dawn of the antibiotic age, providing doctors with the first effective treatment against previously untreatable bacterial infections. But the miracle drugs that saved countless lives in the 20th century are now under threat. Through rapid evolution and adaptation, many disease-causing bacteria have developed resistance to our most potent antibiotics. Antimicrobial resistance (AMR) has emerged as one of the most serious threats to global public health in the 21st century. Common illnesses are becoming harder to treat, leading to longer and more severe illnesses, greater risk of spreading infection, and more deaths. The human costs are staggering - the World Health Organization (WHO) estimates AMR already causes at least 700,000 deaths annually and by 2050, the mortality toll might reach 10 million annually if answers are not discovered swiftly (World Health Organization, 2019). Our never-ending battle with infectious diseases has progressed into a new phase. New classes of antimicrobial medicines are badly needed because many of the antibiotics already in use are losing their effectiveness. To turn promising discoveries into practical therapies, however, considerable obstacles in the fields of science, regulation, and the economy must first be addressed. Due to the high costs and risks associated with research and

Citation
Bhaskar, P. (2023). Antibiotic resistance and a dire need for novel and innovative therapies: The impending crisis. Syncytia, 1(2), 27-35. DOI: 10.52679/syncytia.2023.0w8yx9

development, pharmaceutical companies are not financially motivated to invest in the pipeline for new antibiotics, which has caused it to stall to a trickle. The COVID-19 pandemic exposed weaknesses in our preparedness that need to be rectified and served as a crucial reminder of the ongoing threat that infectious illnesses offer. Before it's too late, we can rekindle innovation in the fight against superbugs by coordinating efforts across industries and nations. To create novel antibiotic medicines, scientists are investigating strategies like bacteriophage therapy, artificial intelligence, antimicrobial peptides, and synergistic combinations. However, more funding and more solid public-private partnerships are vital to moving promising discoveries along the pipeline and providing patients with new, effective therapies. Acting now will prevent minor infections from becoming incurable.

One of the biggest risks to public health worldwide is antibiotic resistance (Laxminarayan et al., 2013). Antimicrobial resistance (AMR) has been spreading like a sneaky epidemic throughout the world, driven by the very medications designed to combat it. When disease-causing bacteria adapt to the effects of drugs that formerly could eradicate them, antimicrobial resistance (AMR) takes place. Selective evolutionary pressure is applied by the overuse and misuse of antibiotics and other antimicrobials, allowing resistant bacteria to flourish while their vulnerable counterparts perish (Davies & Davies, 2010). These hardy bacteria then proliferate rapidly via international travel, animal husbandry, inadequate sanitation, and poor infection control. AMR already causes an estimated 700,000 deaths annually, but the crisis is worsening as common pathogens become increasingly untreatable. If the same death rate seen in current resistant infections is applied worldwide, AMR could claim 10 million lives per year by 2050 (World Health Organization, 2019). This potential mass mortality would dwarf the havoc wreaked by any pandemic illness. Like the Black Death of medieval times, antimicrobial resistance threatens to become a scourge on human civilization. But this time, the pathogen is of our own making. A concerted effort is urgently needed to change course before the antibacterial era comes to an end and we face a world where a scraped knee could be fatal.

The growing threat of ESKAPE pathogens

Among the most notorious superbugs causing the antimicrobial resistance crisis are the ESKAPE pathogens, which includes *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. Experts in infectious diseases have identified these bacteria as the greatest hazards to human health at the moment due to their high medication resistance, high death rates, and widespread presence in hospitals. Numerous diseases, such as sepsis, pneumonia, UTIs, and wound infections, are brought on by ESKAPE bacteria. All of them are gram-negative bacteria with innate resistance to some antibiotics (Santajit & Indrawattana, 2016). Furthermore, they have improved their ability to overcome our antibacterial arsenal through genetic alterations and resistance gene transfer (De Oliveira, et al., 2020). These superbugs are now resistant to several drug groups, including carbapenems, which are last-resort antibiotics.

The few available treatments for infections caused by the ESKAPE bacteria frequently result in death. According to studies, they are responsible for a significant portion of deaths from resistant infections and are thought to be responsible for two-thirds of all hospital-acquired infections worldwide (Mulani et al., 2019). Due to its widespread use in medical settings and severe medication resistance, patients suffer from longer illnesses and experience greater rates of death. ESKAPE viruses will

put a great deal of strain on healthcare systems as they move between patients, across hospitals, and across borders.

The increasing aggressiveness and frequency of ESKAPE bacteria highlight the critical need for novel approaches to tackle superbugs. These extremely resistant microorganisms could render normal surgeries and cancer treatments unfeasible due to their resistance to current antibiotics and alternative therapies. The word ESKAPE aptly depicts how these multifaceted microorganisms persist in eluding our attempts to manage them. It is critical to find solutions to counter these concerns before the world moves into a "post-antibiotic era."

The paramount importance of innovation in antibiotics

The increasing prevalence of resistance in bacterial diseases, such as the ESKAPE species, highlights the vital necessity for innovation in restocking our supply of potent antibiotics. There has been a risky pause in the introduction of new antibiotic classes since the 1980s. Resistance has also increased as a result of the overuse of currently available antibiotics in agriculture and healthcare. The supply of new antibiotics is currently running low, and resistant superbugs are still proliferating.

Increasing the global priority of antibiotic discovery and development is imperative. However, there are important scientific and financial challenges that must be solved first. There are drawbacks to the conventional techniques for identifying antibiotics from soil microorganisms. Even if cutting-edge techniques like synthetic biology, machine learning, and genomics show promise, it is still difficult to turn these discoveries into legally prescribed medications. Simultaneously, the majority of significant pharmaceutical corporations have given up on researching antibiotics because of exorbitant R&D expenses, protracted development periods, and low return on investment.

Innovation can be encouraged by improved data sharing, stronger public-private partnerships, and new financial incentives. Regulators ought to think about quickening the approval process for treatments that address urgent requirements against infections with resistance. To maintain the efficacy of novel medications, better infection control and antibiotic stewardship practices are also required.

To keep abreast of the rise in antibiotic resistance, we can rekindle antibiotic research and development with swift, coordinated efforts across industries (Bhaskar & Sahu, 2023). However, to advance potential novel antibiotic candidates through the pipeline, more funding and changes to policy are imperative. The COVID-19 pandemic provided a sobering reminder that infectious diseases remain a constant threat. We need imagination and resolve to develop novel therapies before routine infections again become untreatable.

Antibiotics in clinical development with the potential to treat infections caused by ESKAPE pathogens

While the antibiotic pipeline has slowed dramatically, there are still some promising new agents in development that offer hope against ESKAPE pathogens. Novel tetracyclines like omadacycline and eravacycline can overcome common resistance mechanisms and have shown efficacy against drug-resistant *Acinetobacter* and *Klebsiella* species (Deolankar et al., 2022). Dalbavancin and oritavancin are long-acting lipoglycopeptides active against Vancomycin-resistant *Enterococcus* isolates (Tran et al., 2022). Cefiderocol, a unique siderophore cephalosporin, appears

effective for difficult-to-treat Gram-negative pathogens including carbapenem-resistant strains of *Pseudomonas* and *Acinetobacter* (Soriano et al., 2022).

Additionally, there are new examples of existing antibiotic classes that remain potent against resistant superbugs. Lefamulin is the first pleuromutilin antibiotic approved for human use and is active against MRSA and drug-resistant *Streptococcus pneumoniae* (Wu et al., 2020). Meropenem-vaborbactam combines a carbapenem with a novel beta-lactamase inhibitor for treating carbapenem-resistant *Enterobacteriaceae* (Bhowmick & Weinstein, 2020). Cefepime-zidebactam takes a similar approach pairing a cephalosporin antibiotic with a beta-lactamase inhibitor (Karlowsky et al., 2020).

While these new antibiotics offer incremental advancements, the world needs truly novel classes. One exciting approach is teixobactin, the first new class of antibiotics discovered in decades (Hussein et al., 2020). Teixobactin attacks multiple targets, making resistance more difficult to develop (Shukla et al., 2020; 2022). Combination therapies are also promising to improve efficacy and prevent resistance. More creative strategies will be essential as ESKAPE pathogens continue adapting.

Of course, any new antibiotic introduced runs the risk of triggering another cycle of resistance. Thus, prudent use and stewardship programs are vital. Still, building our arsenal with diverse new therapies offers hope against these formidable superbugs. With collective commitment from the public and private sectors, the antibiotic pipeline can be replenished to meet the challenge of evolving pathogens.

Promising new approaches to antibiotic discovery

Reigniting the antibiotic pipeline will require leveraging new technologies and strategies to discover novel drug candidates. Traditional methods of isolating antimicrobials from soil microbes have largely been exhausted. However, new developments offer chances to investigate unexplored chemical varieties. Microbial genomes can be mined for novel natural compounds never before cultivated in a lab thanks to technologies like metagenomics and genomics. Machine learning and other bioinformatics methods can examine gene clusters to predict chemical structures and create novel pathways (Durrant & Amaro, 2015). Testing millions of synthetic chemicals to find antibiotics with novel modes of action is made possible by high-throughput robotic screens. Lead molecules are constructed using fragment-based methods from smaller chemical components, whereas molecular networking shows the connections between molecules through visual mapping (Bon et al., 2022). Structure-based drug design combines methods such as cryoelectron microscopy, X-ray crystallography, and NMR to create medicines that specifically target proteins found in bacteria (Maveyraud & Mourey, 2020).

Researchers are looking into alternative therapeutics such as phage viruses, immune system boosters, microbiome modulators, and antimicrobial peptides in addition to traditional antibiotics (Murugaiyan et al., 2022; Mdarhri, 2022). Uncountable antibacterial chemicals can also be found in natural products derived from unexpected sources, such as the venom of snakes, frogs, and cone snails. Collaboration between the public and private sectors, as well as between disciplines, is necessary to fully utilize these technology advancements. Computational tools and open-source data sharing enable a larger group to engage in research. We can fully utilize potent new techniques to create novel medicines against resistant germs if funding and incentives are enhanced.

Artificial Intelligence-enabled drug screening

The use of machine learning and artificial intelligence has become a viable method to speed up the development of antibacterial drugs. High-throughput virtual screening of millions of chemical compounds to find potential lead antibiotics is made possible by these computer tools. AI enables researchers to concentrate costly laboratory testing on those candidates most likely to provide positive results by forecasting activity and selectivity (Vora et al., 2023). Multiple strategies are being used. To screen huge libraries, neural networks can identify patterns that connect compound properties to antibacterial potency. By creating molecules from scratch, deep learning algorithms may even recognize entirely new scaffolds. Using molecular docking simulations, one can anticipate the affinity and toxicity of a chemical by observing its interactions with bacterial protein targets (Agu et al., 2023). Experiment validation is guided by the hidden correlations found through big data analytics.

AI-powered platforms use massive datasets from previous studies—both successful and unsuccessful—to guide their future research. Machine learning increases research efficiency by foreseeing possible problems before they arise. In comparison to manual methods, the discovery process is substantially sped up by the automation of screening, design, and data analysis. There are certain restrictions, though. Large, excellent training datasets are necessary for AI models, but they are not always available, particularly for recently discovered topics. Lab validation and cautious interpretation of the results are still required. However, AI helps scientists to concentrate their experimental efforts on the most promising leads.

Startups and large tech companies are working hard to create new AI technologies specifically tailored for drug research. Barriers for researchers are lowered by the democratization of these technologies through cloud computing services. When used carefully, AI has enormous potential to increase the number of antibiotics we have. Through extraordinary chemical space exploration, machine learning can reveal novel therapeutics that would have remained undiscovered through conventional methods alone.

BioSAXS – a method to accelerate antimicrobial drug development

A new method called biological small-angle X-ray scattering, or bioSAXS, has the potential to accelerate the creation of antibiotics (Rumancev et al., 2022; Baranova et al., 2023). This technique uses complex biophysical modeling in conjunction with X-ray scattering to examine proteins. BioSAXS facilitates quick screening and compound creation that produces compounds that can bind and inhibit certain proteins by shedding light on the forms and movements of therapeutic targets.

BioSAXS can find new targets for antibiotics and confirm that lead compounds interact with those targets as anticipated. The method offers valuable information about drug localization and target vulnerability that is not possible with conventional screening techniques (Rumancev et al., 2022). One can adjust chemical structures to maximize potency and counteract resistance mutations by learning how to lead molecules link to important proteins in a bacterial pathogen.

By offering information to help identify the most suitable candidates for animal testing, BioSAXS can also expedite pre-clinical development. It helps formulation

studies in clinical development to choose the best dose forms. BioSAXS produces data all along the way that lowers the risk of investing in new candidates. BioSAXS's potential for use in biological applications has increased with its integration with AI and ML. This approach allows for the quick clarification of drug interactions and protein structures when used with high-throughput screening.

Although there are certain difficulties in putting BioSAXS into practice, it has special benefits in the creation of antibiotics that call for increased use. Shortening schedules and lowering attrition rates, BioSAXS offers unmatched insight into the structural biophysics underlying novel medicines. This novel approach can speed up the creation of new medications by optimizing the effectiveness of antimicrobial discovery and development through increased access to infrastructure and skilled researchers.

Alternative therapies

Researchers are exploring a variety of alternative medicines that may offer new treatment choices because conventional antibiotics are not as effective against resistant superbugs. Among them are:

Antimicrobial peptides (AMPs) are tiny proteins that the immune system naturally produces and which can damage the membranes of bacteria. Numerous have been recognized and combined. It is difficult to develop resistance because they target the structure of cell membranes rather than particular proteins (Lei et al., 2019).

Viruses that infect and destroy bacteria are called bacteriophages. Purified virus particles are used in phage therapy to cure illnesses. It doesn't damage the beneficial microbiome and is extremely selective to bacterial strains (Lin et al., 2017).

Bacteriophage-derived enzymes known as lysins cause bacterial lysis by dissolving cell wall components. used with phages frequently (Fischetti, 2008).

Certain pathogens can be targeted by cloning monoclonal antibodies from survivors to address multi-drug resistant bacterial infections (Otsubo & Yasui, 2022; Seixas et al., 2022).

Probiotics and prebiotics: Increasing the number of good bacteria or nourishing the ones that are already there to fend against illnesses and reduce pathogens (Iqbal et al., 2021).

Inhibitors of quorum sensing: These agents interfere with bacterial signaling to prevent pathogenicity and the production of biofilms (Roy et al., 2018).

Immunotherapies: Boost the patient's defenses against infection by their immune system. comprises immunizations (Seixas et al., 2022).

These methods offer benefits, but they also have limitations, such as short half-lives, a narrow spectrum, production challenges, and immunogenicity issues. The majority are still in their early stages of development. On the other hand, utilizing these various modalities in addition to or instead of conventional antibiotics may provide novel approaches. Against adaptive infections, a diversified approach will probably be required. While there is still much to be done to integrate alternative medicines into clinical practice, they offer exciting prospects to expand our antibacterial toolkit.

Conclusion: Addressing AMR before it's too late

The cornerstones of contemporary medicine are under existential threat from antimicrobial resistance. But we can stop its hazardous trend if we take determined steps in public health, legislation, and research.

To restock our armory, we must make full use of cutting-edge scientific approaches like genomics, AI drug discovery, and alternative medicines. Antibiotic innovation can be rekindled with greater public-private partnerships and financing for basic research. Market failures in antimicrobial investment can be addressed with the support of tax incentives, milestone rewards, and modifications to intellectual property laws. Reforms to regulations and reimbursements ought to encourage innovation while guaranteeing the responsible use of novel antibiotics.

While improved diagnostics enable focused therapy, increased infection control and vaccination distribution can avoid illnesses. New medications must be shielded from abuse by extensive antimicrobial stewardship programs for both human and animal health. Campaigns for behavior modification and public education are essential to reducing the misuse of over-the-counter antibiotics. Through tackling resistance in many One Health domains, policymakers may execute the diverse approaches required to counter this intricate menace. An integrated platform for coordinating international actions is offered by the UN Interagency Coordination Group.

When it comes to combating superbugs, we cannot afford to be lazy. The COVID-19 pandemic served as a reminder to increase biosecurity and pandemic preparedness. But before it's too late, similar caution is required because of the slow-moving threat posed by AMR. We can protect antibiotics so that modern life can continue with creativity, determination, and international cooperation. However, the window of opportunity is quickly closing, so this is the moment to act. A dire threat is posed by antibiotic resistance. In 20 years, any one of us could need minor surgery in a hospital and pass away from a common infection that is resistant to antibiotics if we don't take action now.

Declarations

Author Contribution: PB conceived and conceptualised the presented idea, performed literature search and analysis and drafted the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Funding: Not applicable.

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