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Review Article

Artificial intelligence in Combating Antimicrobial Resistance

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ABSTRACT

Antibiotic resistance (AR) has become a significant worldwide public health concern in the twenty-first century. Antimicrobial resistance (AMR) occurs when microorganisms, such as bacteria, fungi, parasites, and viruses acquire genetic changes that make them resistant to antimicrobial drugs, including antibiotics. AMR, often known as the "Silent Pandemic," requires prompt and persistent intervention rather than postponement. Failure to take preventative measures will result in AMR becoming the primary cause of mortality worldwide. In the fight against multidrug-resistant bacteria to halt antibiotic resistance, conventional techniques for developing drugs are expensive and time-consuming. However, AI systems can rapidly scan extensive chemical libraries and forecast possible antibacterial agents. Considering the slow progress of ongoing antibiotic research, it is essential to accelerate the development of novel antibiotics and supplementary treatments. The acceleration is essential to effectively address the increasing health risk posed by antibiotic-resistant bacteria and to ensure that we maintain an advantage in combating these emerging threats. The use of AI in medical research holds significant promise, particularly in addressing multidrug-resistant (MDR) infections to battle AMR. This study focuses on the effective applications of AI in addressing AMR and its potential benefits for humanity. It covers fundamental concepts of AI, current available resources for AI, its uses and scope, as well as its benefits and limitations.AI algorithms consistently observe antibiotic usage, diseases occurrences, and resistance trends. This review explores how AI is used to identify AMR markers, diagnose AMR, develop small-molecule antibiotic and also emphasizes emerging research domains, such as AMR detection and novel medication development, which contribute to managing AMR.

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1. Context

AMR has emerged as a critical global public health issue in the twenty-first century. It develops when microorganisms such as bacteria, fungi, parasites, and viruses undergo evolutionary changes that render them resistant to antimicrobial agents, including antibiotics, commonly used to treat various infections. This resistence is largely driven by the inappropriate or excessive use of antibiotics across multiple sectors, including food industry, animal healthcare, clinical settings, agriculture, and military operations (1). Often called the "Silent Pandemic," AMR demands immediate and decisive action rather than delay. If preventive measures are not taken, AMR is projected to become the leading cause of death globally by 2050 (2). In 2019 alone, AMR was directly responsible for over 1.2 million deaths worldwide. If unaddressed, this number is predicted to rise more than 10 million deaths annually by 2050 (3). These projections highlight the urgent need for effective strategies to combat AMR. Mutations, or changes in genetic material such as DNA or RNA sequences, play a crucial role in the emergence and evolution of AMR. These mutations can occur due to natural selection pressures or unexpected circumstances and can alter the amino acid sequences of proteins, including receptors and enzymes targeted by various antibiotics (4). Once antibiotics can no longer effectively bind to or interact with these altered target proteins, resistance develops. Selective pressure, which promotes the survival and propagation of organisms with specific traits or mutations, can further accelerate AMR development. Misuse and improper use of antibiotics, such as selecting the wrong drugs, administering too low doses, or failing to follow treatment guidelines, significantly contribute to antibiotic resistance.

Three primary mechanisms, by which AMR develops, include the ability of antibiotics to penetrate bacterial membranes, alterations in bacterial proteins targeted by antimicrobial agents, and the enzymatic breakdown of antibacterial compounds (5). The preservation of genetic material can occur through plasmid or chromosomal maintenance. AI applications are extending to various aspects of medical management, from cancer to antimicrobial research (6). AI is a branch of information technology focused on developing intelligent systems capable of learning from data and making good decisions (7). Through the analysis of large datasets containing medical records, drug interactions, and genetic data of microorganisms, AI or machine learning can identify trends and predict the emergence of AMR strains. These algorithms help ensure treatments are effective and tailored to certain bacterial species. The way pathogenic bacteria and their antibiotic resistance are identified is entirely changing due to AI, leading to prompt and accurate diagnosis, which helps prevent antibiotic overuse and provide effective treatments. AI-driven diagnostic tools can rapidly analyze biological samples and provide critical guidance on the best course of action (8).

Unlike traditional drug development methods, which are expensive and time-consuming, AI systems can rapidly search large chemical databases and predict potential antibacterial compounds. Given the slow pace of current antibiotic research, it is crucial to accelerate the development of new antibiotics and complementary therapies (9). AI algorithms also continuously monitor antibiotic usage, disease outbreaks, and resistance patterns. By analyzing current data, AI can identify vulnerable areas or populations, enabling targeted interventions to curb its spread. Integrating AI technology into research, diagnostics, and treatment strategies holds significant promise against the growing threat of AMR (10). AI's rapid data collection and analysis capabilities offer an optimistic outlook in the fight against AMR and support the achievement of Sustainable Development Goals (SDGs). Addressing this global health challenge requires effective collaboration that leverages AI alongside traditional methods. This review aims to present the latest advancements in AI and highlight areas where AI can be utilized to combat AMR. The subsequent sections provide a comprehensive explanation of the general approach of using machine learning and deep learning for antimicrobial resistance (AMR) prediction.

2. Evidence Acquisition

AMR is a complex problem affecting both human and animal health. Prolonged illnesses requiring extended hospital stays place a strain on both patients and healthcare systems (11). These longer recovery periods also lead to increased absenteeism and reduced economic productivity. AMR diseases necessitate additional isolation protocols, laboratory tests, and outpatient visits. Each year, AMR infections are responsible for about one million deaths worldwide. The inability to effectively manage infections, particularly in the absence of potent antibiotics, significantly increases risks associated with standard medical procedures such as surgery, organ transplants, chemotherapy, and neonatal care (12). Currently, hospitals are facing significant challenges from multidrug-resistant (MDR) bacteria, collectively known as "ESKAPE," which include *Enterococcus faecium, Klebsiella pneumoniae, Staphylococcus aureus*, and strains of *Pseudomonas aeruginosa* resistant to *Enterobacter* species (13). In future, declining antibiotic efficacycould render common infections from minor injuries that could become fatal. AMR also poses a serious threat to both human health and food production by facilitating the transmission of drug-resistant diseases from animals to humans. As a result, MDR bacteria such as *Salmonella* and *Campylobacter* are more likely to spread through the food chain or via contact with animal handlers (14). Antibiotic-resistant bacteria can rapidly spread across different species. Environmental exposures also influence the spread of AMR, as fertilizers made from animal manure can spread resistant bacteria throughout the environment, contaminating water sources and eventually entering the food supply. These bacteria can also transfer AMR genes to human and environmental microbiotas. The lack of effective treatments for animal diseases linked to resistance further accelerates outbreaks among livestock such as sheep, cattle, and poultry (15). This results in significant economic losses when infected animals must be culled, thereby threatening food supply and security.

3. Results

3.1. Impact of AMR on the Environment, Animals Humans

The escalating challenge of AMR affects the well-being of both humans and animals. Lengthy hospitalizations caused by illnesses strain both patients and healthcare systems, depleting vital resources (16). Extended recovery periods also lead to reduced economic productivity and increased work absenteeism. Moreover, addressing AMR necessitates stricter isolation protocols, increased laboratory testing, and more frequent outpatient visits. It is estimated that annually, AMR-related diseases cause one million deaths worldwide. The scarcity of effective antibiotics significantly amplifies the risks associated with routine treatments such as surgery, organ transplants, chemotherapy, and neonatal care (17). In scenarios where conventional medications fail, routine infections stemming from minor injuries can become life-threatening. AMR might facilitate the transmission of drug-resistant diseases from animals to humans, imperiling human health and food security. The overuse of antibiotics in livestock farming, for treating diseases and stimulating growth ,contributes to antibiotic resistance. Consequently, MDR bacteria like Salmonella and *Campylobacter* are more likely to spread through the food chain or via contact with animal handlers (18). Antibiotic-resistant bacterial strains have the ability to spread rapidly across diverse species. Animals can also indirectly acquire AMR from their environment, hastening the spread of diseases. Resilient bacteria disseminated through the application of animal waste as fertilizer, contaminate water sources and eventually the human food supply, posing a threat to the ecosystem. Furthermore, they disseminate AMR genes to commensal microbiotas in both human and environmental settings. The absence of effective treatments for resistant animal diseases further exacerbates the outbreaks of epidemics among livestock such as sheep, cattle, and poultry (19). The necessity of culling infected animals, resulting from the lack of treatment, imposes significant economic losses and threatens food supply.

3.2. AI to Identify AMR Markers

AI plays a pivotal role in transforming the healthcare sector, particularly in patient data aggregation, early detection and prevention of diseases, and the utilization of cutting-edge imaging technologies such as X-rays, Computerized Tomography and Magnetic Resonance Imaging (20). AI significantlycontributes to reducing costs and improving the precision of drug prescriptions. The advancements in AI have showcased exceptional accuracy in tasks such as medical imaging and signal recognition. This sophisticated technology not only boosts productivity and ensures safety but also streamlines labor processes, ultimately leading to enhanced human well-being and substantial improvement in patient care, all while reducing healthcare expenses (21).

AMR indicators include specific traits or genetic components associated with bacteria or other microorganisms' ability to withstand antibiotics. These markers are invaluable diagnostic tools for detecting and identifying AMR in infections. The identification of AMR indicators is critical for guiding appropriate treatment decisions. When a patient develops antibiotic resistance, it is imperative to pinpoint the resistance markers within the infection. Equipped with this crucial information, healthcare professionals can swiftly select the most effective medications, minimizing the risk of exacerbating AMR and maximizing the likelihood of a positive outcome (22). Persistent efforts by scientists are directed towards developing novel methods for identifying pertinent genes linked to AMR. While current methodologies mainly rely on culturing bacteria under specific conditions, ongoing research aims to refine these techniques. Challenges remain, particularly concerning certain species with prolonged reproduction cycles in their natural habitats or live microorganisms that are challenging to culture. Recent achievements in AMR management have harnessed the power of deep learning and machine learning driven by AI. Clinical decision support systems, which combine clinical data collection with sequencing-based AI, have shown promising outcomes. The application of AI has provided significant advantages in discerning normal organ function and detecting anomalies across diverse organs, incliding the gastrointestinal system, thyroid, lungs, kidneys, liver, and heart (23). As technology continues to evolve, AI holds immense potential to further revolutionize healthcare practices and enhance patient outcomes.

3.3. Diagnosis in AMR via AI

Two primary methodologies are commonly utilized to detect AMR, including the analysis of antibiotic susceptibility through Antibiotic Susceptibility Testing (AST) and Whole Genome Sequencing (WGS) for Antimicrobial Susceptibility Testing (24). While AST employs conventional approach to evaluate levels of antibiotic resistance, it often lacks insights into the underlying resistance mechanisms. Conversely, WGS-AST facilitates reliable and highly accurate AMR detection, albeit demanding extensive multidimensional databases for precise information retrieval. AI technology plays a pivotal role in refining these established techniques, advancing research endeavors, and nurturing the evolution of human intelligence systems. AI-enabled tasks encompass speech recognition, visual perception, natural language processing, and decision-making based on comprehensive data analysis. The progress of AI systems strongly correlates with the accessibility of health records data and ongoing advancements in processing speed, which is pivotal in enabling intricate mathematical methodologies like neural networks (NN) and machine/deep learning (25). The proliferation of deep neural network topologies, characterized by ingincreas complexity over the past decade, underscores AI's significant contribution to enhancing traditional methodologies. Timely and accurate diagnosis of infectious diseases, differentiation between infectious and noninfectious conditions, and the subsequent administration of appropriate treatments are crucial in combating antibiotic resistance. AI has become a fundamental tool in addressing this global challenge, with the potential to substantially aid in its resolution. Antibiogram is indispensable instrument for scrutinizing susceptibility patterns and identifying high-risk infectious agents (26). Consequently, the development of tailored ML models holds promise for forecasting and mitigating AMR. AI-driven antimicrobial tools revolutionize clinical care through predictive diagnostics, enabling early detection and precise treatment of infections. They enhance surveillance systems for tracking AMR patterns, identify emerging AMR strains, and optimize health system management. Furthermore, AI accelerates drug development by predicting potential drug candidates, ensuring effective and targeted antimicrobial therapies, which are shown in Figure 1, and summarizes prospective AI application in the AMR sector.

3.4. AI for AMR Significance to ICU

The condition of patients in intensive care units (ICUs) demands swift and accurate assessment of diverse, multidimensional inputs, including images, numerical data, textual information, and other relevant data types (27). It is vital to discern intricate and nonlinear relationships within this data. Traditional statistical methods have typically represented data patterns through mathematical equations. Deep learning, with its ability to process and analyze large volumes of inputs simultaneously, facilitates the development of predictive models based on anticipated outcomes.

In healthcare, three primary deep learning (DL) techniques, namely, recurrent neural networks, convolutional neural networks, deep belief networks are extensively used in critical care unit settings (28). The temporal computational model was developed to forecast blood culture outcomes utilizing nine clinical parameters and employing a bidirectional long short-term memory (LSTM) approach. Utilizing a robust database containing data from 2177 ICU patients (29). This deep learning methodology demonstrated appreciable performance, particularly in scenarios with uncertainty regarding the temporal gap between an anticipated event and diagnosis.

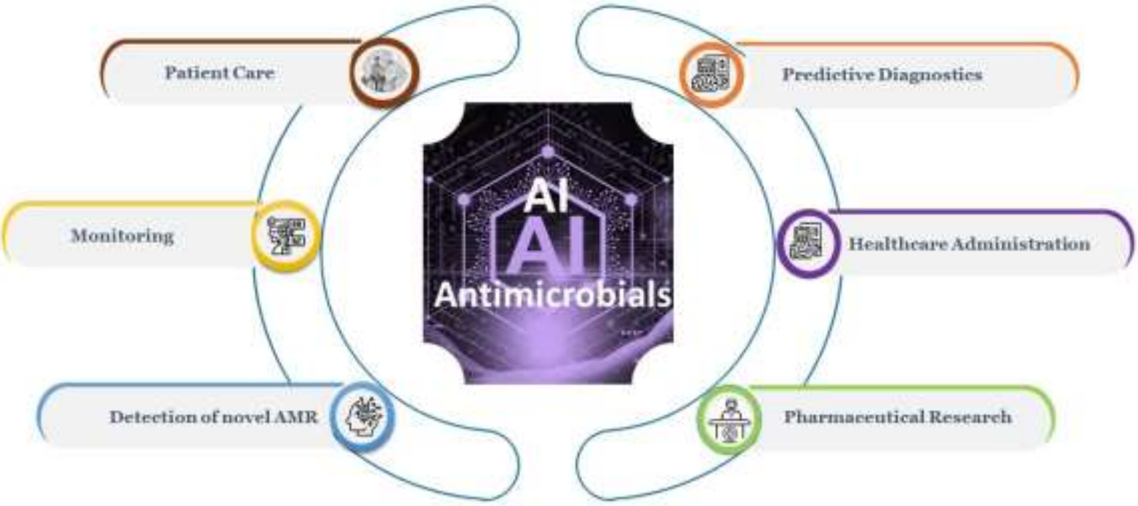

Figure 1. AI can be applied on antimicrobials to obtain different objectives such as Patient care, Pharmaceutical Research, monitoring, Detection of novel AMR etc. (Image Credit: Corresponding author).

The model yields impressive mean area under the curve (AUC) values of 0.99 and 0.82 for receiver operating characteristic curves, underscoring its robust predictive capability. Moreover, the results suggested the model could predict occurrences several hours in advance with minimal loss of accuracy (30). The advantages of AI in analyzing a wide range of images, include whole-genome sequences (WGS) of bacteria, macroscopic or microscopic images, and MALDI-TOF mass spectra. AI is progressively finding utility in clinical microbiology, enhancing the diagnostic capabilities of laboratory personnel. As AI technology continues to progress, more refined and reliable AI software assessments are expected to emerge, facilitating the seamless integration of AI into clinical microbiology laboratory workflows.

3.5. DL/ML Models for AMR Prognosis

The fundamental concept behind the DL/ML model is to construct a model by utilizing a vast quantity of data in order to capture the inherent nonlinear correlation between the input characteristics and outputs, which would otherwise be challenging (31). Training datasets are used as the initial step in training both DL and ML models. Once the models have been trained, they may be tested with data that has not been previously seen. Initially, it is necessary to preprocess the data and extract significant and pertinent input characteristics. The data further must then be divided into separate sets for training, testing, and validation. Initially, the model undergoes training by inputting the characteristics of the training dataset. The training procedure will optimize and acquire the most favorable settings. During the training process, Specific components are utilized to confirm and enhance the optimization. Cross-validation method is employed to enhance the robustness of the model (32). A DL model involves many hyper parameters. One crucial aspect of implementing DL/ML is to carefully choose the best suitable model based on the specific application and the characteristics of the input information. Complex models tend to have greater variance, while simpler models tend to have larger bias. Less complicated models are more easily understandable, but they may exhibit better accuracy when dealing with intricate elements.The use of traditional machine learning with CNN enables the rapid and accurate prediction of TB drug resistance using genomic sequences (33). For example, a CNN identifies mutations in *Mycobacterium tuberculosis* associated with antimicrobial resistance. DL is also employed to detect antimicrobial peptides derived from the human gut microbiome. Interpretable models should include the capability to assess individual input characteristics, allow for bidirectional tracing, and enable the analysis and utilization of relationships between various factors influencing the outcome (34). Decision tree-based models are hierarchical classifiers that assess characteristics based on their variance at internal nodes. These models use clear decision criteria to categorize data into specific groups, reaching the final step. Consequently, every node in these models can be traced. Figure 2 provides a comprehensive overview of these approaches' applications in antibacterial research.

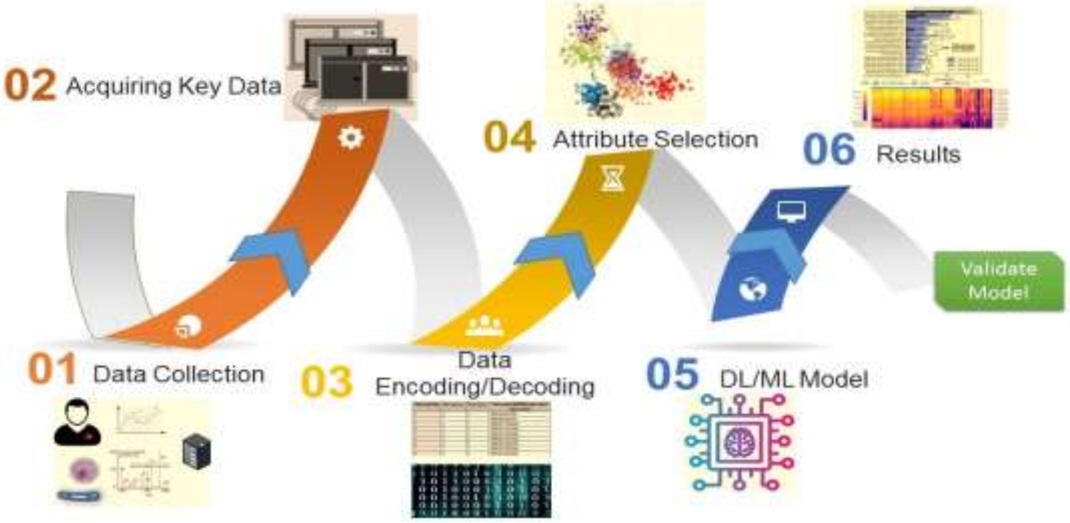

Figure 2. The basic process for using ML and DL models in the investigation of AMR (Image Credit: Corresponding author).

3.6. AI in Small-Molecule Antibiotic Development

During the peak of antibiotic discovery in the 1950s and 1960s, the primary strategy included screening secondary metabolites produced by soil bacteria for their antibacterial properties (35). However, this method faced challenges, particularly the issue of rediscovery. Consequently, many newly developed antibiotics used in clinical settings were derivatives of existing antibiotic classes, whose efficacy was limited by the prevalence of existing resistance mechanisms. Therefore, the principal aim of modern antibiotic research should focus on identifying novel chemical structures with unique modes of action, distinct from existing antibiotics. AI is increasingly pivotal in the discovery of small-molecule antibiotics, comprising four core components: identification of biosynthetic gene clusters, screening chemical libraries, rational drug design based on protein structure and function, and drug repurposing.

While conventional rule-based systems like Antibiotic Resistant Target Seeker (ARTS) and Antibiotics and Secondary Metabolite Analysis Shell (anti-SMASH) have demonstrated notable success, AI-driven methodologies are gaining prominence. For example, the DeepBGC DL approach has accurately predicted the chemical activity of products and identified novel BGC classes (36). Similarly, the DeepRiPP DL method, leveraging genomic and metabolomic data, has identified peptides synthesized by ribosomes and subsequently modified during translation. The traditional approach to drug screening is hindered by the scale of chemical libraries and often fails to elucidate the mechanism of action (MOA) of identified compounds (37).

To address these limitations, Johnson and colleagues developed a groundbreaking method called Primary Screening of Strains to Uncover Expanded Chemistry and Targets. This innovative approach involves initially screening hypomorphs—mutant strains of *Mycobacterium tuberculosis* lacking essential targets (38). Through these advancements, AI-assisted methodologies are positioned to transform antibiotic discovery by surmounting conventional limitations and accelerating the identification of effective antimicrobial agents.

3.7. Challenges in Addressing AMR

Addressing the rise of AMR poses many difficulties with no simple answers. The pervasive incorporation of antimicrobials into medical treatment and food animal production economics is a significant obstacle to efforts aimed at reducing human's extensive use of these substances. Due to the absence of quick point-of-care diagnostic tools, doctors frequently rely on empirical antibiotic prescribing as a precautionary measure against bacterial infections (39). Similarly, contemporary farming practices involve regular administering antimicrobials to cattle for infection prevention and growth promotion. Despite recognizing the risks associated with excessive antibiotic use, antimicrobial stewardship programs in healthcare and revised animal husbandry rules are not being implemented promptly. In addition to these problems, the process of developing antibiotic drugs is unable to keep up with the ongoing changes in multi-drug resistant microorganisms (40).

Pharmaceutical companies are progressively withdrawing expensive research on antimicrobial drugs due to inadequate financial incentives. AMR exceeds regional limits and has a worldwide influence on communities. Recently, illnesses that were formerly easy to control have transformed into noteworthy and serious health issues. The lack of effective antimicrobial drugs makes ordinary medical treatments, such as surgery, chemotherapy, and organ transplants riskier. AMR not only adversely affects human health but also poses significant economic burdens for healthcare systems, governments, and societies in general (41). The financial burden of managing resistant infections is greatly increased due to prolonged hospital stays, increased healthcare visits, and the need for expensive medications as a final resort.

4. Conclusion

Prompt and precise identification of AMR in infections is essential for prescribing appropriate medications for therapeutic use. This study aims to evaluate the current applications of AI and other methodologies in AMR detection. Given its potential to significantly enhance the recognition and containment of resistant infections, AI has proven to be a valuable tool in this global health challenge. Medical professionals can decide on patient treatment and containment measures rapidly and precisely since AI technologies dramatically increase the accuracy of recognizing AMR infections. Effective use of AI in AMR detection reduces AMR risk, protects public health, and promotes the judicious use of antibiotics. One of AI primary advantages in AMR detection is its ability to scan enormous datasets from many sources, such as genetic sequences, medical records, and real-time epidemiological data.Having used this feature, new AMR strains can be precisely and promptly identified and their spread controlled. Furthermore, AI-driven diagnostic tools reduce the unnecessary antibiotic use, raise the precision of testing for antibiotic susceptibility, and reduce the decision of a course of therapy.

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Authors' Contribution

Conceived, designed and supervised the study: D.NS, H. AN.

Contributed to data collection, interpretation and final approval of data for the work: AA. RM, ST.

Developed the first and final draft of the manuscript: R. KV, D. NS.

Developed the second draft of the manuscript: AA. RM, R. KV.

All figures and tables were designed and checked: D. NS, ST.

Ethics

Not applicable

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

This study.

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