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## Review Article

# Artificial intelligence in combating antimicrobial resistance

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## ABSTRACT

Antimicrobial resistance (AMR) occurs when microorganisms, acquire genetic changes resistant to antimicrobial drugs, including antibiotics. Conventional techniques for combating AMR are expensive and time consuming, but Artificial intelligence (AI) is currently being developed that can rapidly scan through extensive chemical libraries and forecast possible antibacterial substances. The use of AI in medical research has significant promise, particularly in addressing multidrug-resistant (MDR) infections to battle AMR. Algorithms of AI monitors antibiotic usage, occurrences of diseases, and trends of resistance, thus influencing the development of novel drugs. Through AI, researchers can rapidly identify potential new drugs that could be effective against antibiotic-resistant bacteria, saving valuable time in the development process. By analyzing vast amounts of data, AI algorithms can also help to predict future trends in antibiotic resistance, allowing for proactive measures to be taken. With the ability to analyze data at a rapid pace, AI is revolutionizing the way researchers approach drug development, health risks and disease prevention. As technology continues to advance, the impact of AI in combating antimicrobial resistance becomes more significant. Overall, the integration of AI in medical research shows great potential in the ongoing battle against antimicrobial resistance. This review describes the application of AI to identify AMR markers, diagnosis in AMR, small molecule antibiotic development and also emphasizes emerging research domains, such as AMR detection and novel drug development, that contribute to the management of AMR.

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## 1. Introduction

AMR has emerged as a critical global public health issue in the twenty-first century. AMR develops when microorganisms such as bacteria, fungi, parasites, and viruses undergo evolutionary changes that render them resistant to antimicrobial agents, including antibiotics, which are commonly used to treat various infections

which is due to the inappropriate or excessive use of antibiotics across multiple sectors, including food industry, animal healthcare, clinical settings, agriculture, and military operations.<sup>1</sup> Often referred to as the "Silent Pandemic," AMR demands immediate and decisive action rather than delay. If preventive measures are not implemented, AMR is projected to become the leading cause of death globally by 2050.<sup>2</sup> In 2019 alone, AMR was directly responsible for over 1.2 million deaths worldwide. If unaddressed, this figure is predicted to rise more than 10 million

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deaths annually by 2050.<sup>3</sup> These projections stress the urgency of adopting 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.<sup>4</sup> Once antibiotics can no longer 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 drive the development of AMR. Misuse and improper use of antibiotics, such as selecting the wrong drugs, administering too low doses, or failing to follow treatment guidelines, are significant contributors to antibiotic resistance.

Three primary mechanisms by which AMR develops are the ability of antibiotics to penetrate bacterial membranes, alterations in bacterial proteins targeted by antimicrobial agents, and the enzymatic breakdown of antibacterial compounds.<sup>5</sup> The preservation of genetic material can occur through plasmid or chromosomal maintenance. Applications of AI are extending to various aspects of medical management from cancer to antimicrobial research.<sup>6</sup> AI is a field of information technology focused on developing intelligent systems that can learn from data and make good decisions.<sup>7</sup> 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. The AI algorithms help ensure that treatments are effective and specific to certain bacterial species. The way pathogenic bacteria and their antibiotic resistance are identified is entirely changing due to AI, hence prompt and accurate diagnosis is improved to prevent antibiotic overuse and provide effective treatments. AI-driven diagnostic tools can rapidly analyze biological samples and provide important guidance on the best course of action.<sup>8</sup>

Traditional drug development methods are expensive and time-consuming, but 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 expedite the development of new antibiotics and complementary therapies.<sup>9</sup> AI algorithms also continuously monitor antibiotic usage, disease outbreaks, and resistance patterns. By analyzing current data, AI can identify areas or populations more susceptible to AMR, 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.<sup>10</sup> AI's rapid data collection and analysis capabilities offer a hopeful outlook in the fight against AMR and the pursuit 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. Discussion

### 2.1. Global threat of AMR

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.<sup>11</sup> 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. The inability to effectively manage infections, particularly without potent antibiotics, significantly raises the risks associated with standard medical procedures such as surgery, organ transplants, chemotherapy, and neonatal care.<sup>12</sup> 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.<sup>13</sup> In future, where antibiotic efficacy declines, common infections from minor injuries 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.<sup>14</sup> Antibiotic-resistant bacteria can rapidly spread across different species. Environmental exposures also play a role in the spread of AMR, as fertilizers made from animal manure can disseminate resistant bacteria throughout the environment, contaminating water sources and eventually the food supply. These bacteria can also transfer AMR genes to human and environmental microbiotas. The scarcity of effective treatments for animal diseases linked to resistance further accelerates the spread of outbreaks among livestock such as sheep, cattle, and poultry.<sup>15</sup> This results in significant economic losses when infected animals must be culled, thereby jeopardizing the food supply.

### 2.2. Impact of AMR on the environment, animals, and humans

The complex challenge of AMR is escalating, affecting the well-being of both humans and animals. Lengthy hospitalizations resulting from illnesses strain both patients

and healthcare systems, depleting vital resources.<sup>16</sup> Extended recovery periods also lead to reduced economic output and increased absenteeism from work. Moreover, addressing AMR necessitates the adoption of enhanced isolation protocols, increased laboratory testing, and more frequent outpatient visits. It's estimated that annually, diseases linked to AMR claim the lives of one million individuals. The scarcity of effective antibiotics significantly amplifies the risks associated with commonplace treatments such as surgery, organ transplants, chemotherapy, and neonatal care.<sup>17</sup> In scenarios where conventional medications lose their effectiveness, routine infections stemming from minor injuries could prove life-threatening. AMR might facilitate the transmission of drug-resistant diseases from animals to humans, imperiling both human health and food security. The excessive use of antibiotics in treating diseases and stimulating growth in livestock contributes to antibiotic resistance. Consequently, MDR bacteria like Salmonella and Campylobacter are more prone to spreading through the food chain or via contact with animal handlers.<sup>18</sup> 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 animal diseases associated with resistance exacerbates the proliferation of epidemics among livestock such as sheep, cattle, and poultry.<sup>19</sup> The necessity to cull sick animals, resulting from the lack of treatments, imposes significant financial and food supply risks.

### 2.3. AI to identify AMR markers

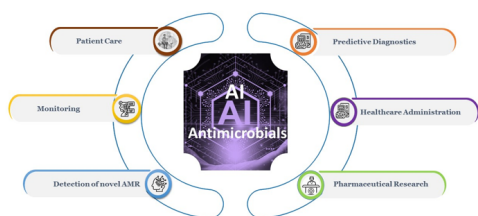
AI plays a pivotal role in transforming the healthcare sector, particularly in the realms of patient data aggregation, early detection and prevention of diseases, and the utilization of cutting-edge imaging technologies such as X-rays, Computerized Tomography and Magnetic Resonance Imaging.<sup>20</sup> AI contributes significantly to reducing costs and improving the precision of drug prescriptions. The advancements in AI technology 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 a substantial improvement in patient care, all while mitigating healthcare expenses.<sup>21</sup> AMR indicators encompass specific traits or genetic components associated with bacteria or other microorganisms' ability to withstand antibiotics. These markers serve as invaluable

diagnostic tools for detecting and identifying AMR in infections. The identification of AMR indicators is paramount for guiding appropriate treatment decisions. In cases where a patient develops antibiotic resistance, it is imperative to pinpoint the resistance markers within the infection. Armed with this crucial information, healthcare professionals can swiftly select the most effective medications to address the issue, thereby minimizing the risk of exacerbating AMR and maximizing the likelihood of a positive outcome.<sup>22</sup> Persistent efforts by scientists are directed towards developing novel methods for identifying pertinent genes linked to AMR. While current methodologies predominantly rely on culturing bacteria under specific conditions, ongoing research aims to refine these techniques. Nonetheless, challenges persist, 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 propelled by AI. Clinical decision support systems developed through the amalgamation of clinical data collection and sequencing-based artificial intelligence have demonstrated promising outcomes. The application of AI has yielded significant advantages in discerning normal organ function and anomalies across diverse organs, encompassing the gastrointestinal system, thyroid, lungs, kidneys, liver, and heart.<sup>23</sup> As technology continues to evolve, AI holds immense potential to further revolutionize healthcare practices and enhance patient outcomes.

### 2.4. Diagnosis in AMR via AI

Two primary methodologies are commonly utilized to detect AMR, involving the analysis of antibiotic susceptibility through Antibiotic Susceptibility Testing (AST) and Whole Genome Sequencing (WGS) for Antimicrobial Susceptibility Testing.<sup>24</sup> While AST adopts the conventional approach to evaluate levels of antibiotic resistance, it often lacks in providing 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, propelling 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 progression of AI systems closely correlates with the accessibility of health records data and ongoing advancements in processing speed, pivotal in enabling intricate mathematical methodologies like neural networks (NN) and machine/deep learning.<sup>25</sup> The proliferation of deep neural network topologies,

characterized by escalating complexity over the past decade, underscores AI's significant contribution to enhancing traditional methodologies. Timely diagnosis of infectious diseases, differentiation between infectious and noninfectious conditions, and the subsequent administration of appropriate treatments are crucial in combating antibiotic resistance. AI emerges as a fundamental tool in addressing this global challenge, with the potential to substantially aid in its resolution. Antibiograms serve as indispensable instruments for scrutinizing susceptibility patterns and identifying high-risk infectious agents.<sup>26</sup> Consequently, the development of tailored ML models holds promise for forecasting and mitigating AMR. AI for antimicrobials revolutionizes clinical care through predictive diagnostics, enabling early detection and precise treatment of infections. It enhances surveillance systems for tracking AMR patterns, identifies emerging AMR strains, and optimizes 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.



**Figure 1:** AI can be applied on antimicrobials to obtain different objectives such as patient care, Pharmaceutical research, monitoring, detection of novel AMR etc.

### 2.5. AI for AMR significance to ICU

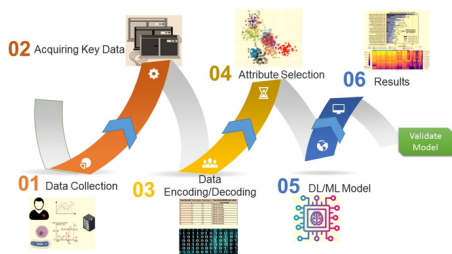
The condition of patients in intensive care units (ICUs) demands swift and accurate assessment of diverse, multidimensional inputs, comprising images, numerical data, textual information, and other relevant data types.<sup>27</sup> It is vital to discern intricate and nonlinear connections within this data. Traditional statistical methods have typically represented data patterns through mathematical equations. Deep learning, with its capacity to process and analyze large volumes of inputs simultaneously, facilitates the development of predictive models based on anticipated outcomes. Within the realm of healthcare, three primary deep learning (DL) techniques namely, recurrent neural networks convolutional neural networks and deep belief networks find extensive use in critical care unit setting.<sup>28</sup> The temporal computational model was crafted 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,<sup>29</sup> their deep learning methodology demonstrated appreciable prowess, particularly in scenarios marked by uncertainty regarding the temporal gap between an anticipated event and diagnosis. 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 performance. Moreover, the findings suggested the model's capability to predict occurrences several hours in advance with minimal compromise in prediction accuracy.<sup>30</sup> The advantages of AI in analyzing a diverse array of images, encompass 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, it is expected that more refined and dependable AI software assessments will emerge, facilitating the seamless integration of AI into clinical microbiology laboratory workflows.

### 2.6. 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 non-linear correlation between the input characteristics and outputs, which would otherwise be challenging.<sup>31</sup> 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 has to 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 is employed to enhance the robustness of the model.<sup>32</sup> A DL model comprises 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 often have greater variance, whereas comparatively 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 speedy and accurate prediction of TB drug resistance based on genomic sequences.<sup>33</sup> For example, a CNN identifies mutations in *Mycobacterium tuberculosis* that are 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 that are influencing the goal.<sup>34</sup> Decision tree-based models are hierarchical classifiers that assess characteristics based on their variance at internal nodes. These models utilize a clear decision criterion 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 the applications of these approaches in antibacterial research.



**Figure 2:** The basic process for using ML and DL models in the investigation of AMR

### 2.7. AI in small molecule antibiotic development

Especially during the zenith of antibiotic exploration in the 1950s and 1960s, the primary strategy for discovering new antibiotics entailed screening secondary metabolites produced by soil bacteria for their antibacterial properties.<sup>35</sup> However, this method encountered challenges, particularly the issue of rediscovery. Consequently, many newly identified antibiotics utilized in clinical settings were derivatives of known antibiotic classes. The sustained efficacy of these derivatives was hampered 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 shown notable success, AI-driven methodologies are gaining traction. For example, the DeepBGC DL approach has accurately predicted the chemical activity of products and revealed novel BGC classes.<sup>36</sup> 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, often failing to elucidate the mechanism of action (MOA) of identified compounds.<sup>37</sup> To address these constraints, Johnson and collaborators devised a groundbreaking method known as Primary Screening of Strains to Uncover Expanded Chemistry and Targets. This innovative approach entails initially screening hypomorphs—mutant strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) devoid of essential targets.<sup>38</sup> Through these advancements, AI-assisted methodologies are positioned to transform antibiotic discovery by surmounting conventional limitations and expediting the identification of effective antimicrobial agents.

### 2.8. 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 humanity'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. Similarly, contemporary farming practices involve regular administering antimicrobials to cattle for both infection prevention and growth promotion. Antimicrobial stewardship programs in healthcare and revised animal husbandry rules are not being implemented promptly, despite recognizing of the hazards of antibiotic resistance caused by excessive antibiotic usage. In addition to these problems, the process of developing antibiotic drugs is unable to match the ongoing changes in multi-drug resistant microorganisms.<sup>39</sup> Pharmaceutical firms are progressively discontinuing expensive research on antimicrobial drugs due to inadequate financial incentives. AMR surpasses regional limits and has a worldwide influence on communities. Recently, illnesses that were formerly easy to control have transformed into noteworthy health issues. The lack of effective antimicrobial drugs makes ordinary medical treatments, such as surgery, chemotherapy, and organ transplants, riskier. AMR not only has a negative effect on human health, but also poses significant economic difficulties for healthcare systems, governments, and societies in general.<sup>40</sup> 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.

### 2.9. Current AI tool for AMR

MetaSUB AMR is a collaborative initiative AI tool of an International Consortium of Weill Cornell Medicine Mason Lab and employs metagenomic data and algorithms to monitor and track AMR in urban environments.

It analyzes environmental DNA samples from public transportation systems and other urban settings to identify and map AMR genes. This tool can be accessed from MetaSUB consortium.<sup>41</sup> DeepAMR AI tool employs deep learning and analyzes DNA sequences to identify resistance genes and mutations, enabling accurate and rapid identification of resistant pathogens and are useful in clinical settings. Researchers can access it by downloading the associated repositories.<sup>42</sup> DeepARG is an advanced AI tool applies deep learning algorithms to analyze genetic sequences and identify potential resistance genes in complex microbial communities for rapid identification of AMR profiles is crucial for treatment decisions and public health interventions. DeepARG can be accessed through their website or academic institutions involved in AMR research.<sup>43</sup> Mykrobe Predictor AI identifies specific genetic mutations associated with resistance, helping clinicians to tailor antibiotic treatment plans more effectively and is crucial for patient management and infection control. It can be obtained through the official website.<sup>44</sup> AMR FinderPlus is an AI bioinformatics tool developed by the National Center for Biotechnology Information (NCBI) for identifying antimicrobial resistance (AMR) genes and mutations in bacterial genomes which rapidly detect and characterize AMR profiles from genomic data, aiding in the surveillance and management of antibiotic-resistant bacteria. AMRFinderPlus is freely accessible through the NCBI website.<sup>45</sup>

### 3. Conclusion

Prompt and precise identification of AMR in infections is essential for prescribing appropriate medications for therapeutic use. This study aims to examine the current utilization of AI and other methodologies in the detection of AMR. Antimicrobial resistance is a global health concern for which artificial intelligence has demonstrated to be highly helpful. Medical professionals can decide on patient treatment and containment measures rapid and precise since AI technologies dramatically increase the accuracy of recognizing AMR infections. Effective use of AI in AMR detection reduces AMR risk, safeguards 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. Using this ability, new AMR strains can be precisely and promptly identified and their spread controlled. Furthermore, AI-driven diagnostic tools reduce the wasteful use of antibiotics, raise the precision of testing for antibiotic susceptibility, and reduce the decision of a course of therapy.

### 4. Conflict of Interest

Conflict of interest declared none.

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