Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

AI-Driven Strategies to Forecast and Combat Antibiotic Resistance

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Abstract

Antimicrobial resistance (AMR) is a pressing global health emergency fuelled by the overuse and misuse of antibiotics and threatens human and animal health. Conventional diagnostic and therapeutic approaches tend to be slow, resource-consuming, and of limited predictive ability. Artificial intelligence (AI) and machine learning (ML) advancements provide disruptive potential to predict, prevent, and regulate AMR. Artificial intelligence -driven models can handle and analyse complex, advanced clinical, genomic, and epidemiologic information to predict patterns of resistance, guide antibiotic selection, and maximize stewardship programs. Applications range from rapid diagnostic testing, decision support systems, and drug discovery platforms to novel approaches like AI-assisted antimicrobial peptide design and nanoparticle therapeutics. Promising as these are, there are barriers to their uptake in the form of data quality, model bias, explain ability, infrastructure requirements, and regulatory adoption. This review integrates state-of-the-art, technology innovation, and prospective AI-based AMR management and emphasizes the need for multidisciplinary team effort in facilitating innovation and harvesting AI potential into clinical and public health applications.

Keywords: Antibiotics, Resistance, Machine – learning, Therapeutics, Nanoparticles, Public health, Therapeutics

1. Introduction

Emergence of antibiotic resistance in bacteria is certainly the most important problem of modern medicine. Such fast and easy spread of multidrug resistance in bacteria is a global problem for humans as well as animals and raises an obligation not only in the field of integral diagnosis of drug resistance, but also in the use of means of bacterial control supplementary to antibiotics. (1) Antimicrobial resistance (AMR) is a sophisticated global health emergency that demands adaptive, locally responsive, and evidence-based response, not a straightforward clinical or microbiological challenge.(2)

Early detection of infectious diseases, infectious and non-infectious pathology differentiation, and proper treatment of consequences are all important factors for combating antibiotic resistance. For this worldwide issue, AI can be a highly important factor. Antibiogram preparation and later customized machine learning

(ML)-based AMR prediction models could be highly useful AI techniques for high-peak risk infectious bugs and their trends in the susceptibility patterns.(3)

Antibiotic resistance can be of following types.

Intrinsic mechanisms of antibiotic resistance are primarily borne by the chromosome.(4) Intrinsic resistance is associated with a change in the structural characteristics of bacterium. These are intrinsic characteristics and do not have anything to do with antibiotic selective pressure. For example, alteration of Gram-negative bacteria outer membrane permeability makes them resistant to glycopeptides.(5)

Acquired resistance mechanisms are usually acquired through horizontal gene transfer (HGT) and encoded by plasmids and transposon-mediated antibiotic resistance.(4) Antibiotic resistance in K. pneumoniae is largely mediated by horizontal gene transfer (HGT), which supports the rapid spread of antimicrobial resistance genes (ARGs) among bacterial populations.(6) Resistance genes can be transferred between bacterial species via horizontal can be transferred by gene transfer or may happen spontaneously through mutations, which are practices worsened by inappropriately prescribing and under-dosing.(7)

Adaptive resistance is discovered to be caused by epigenetics.changes caused by some environmental stimulus, e.g., pH, stress, growth rate, antibiotic concentration, and ion concentration (5)

HISTORY OF AMR

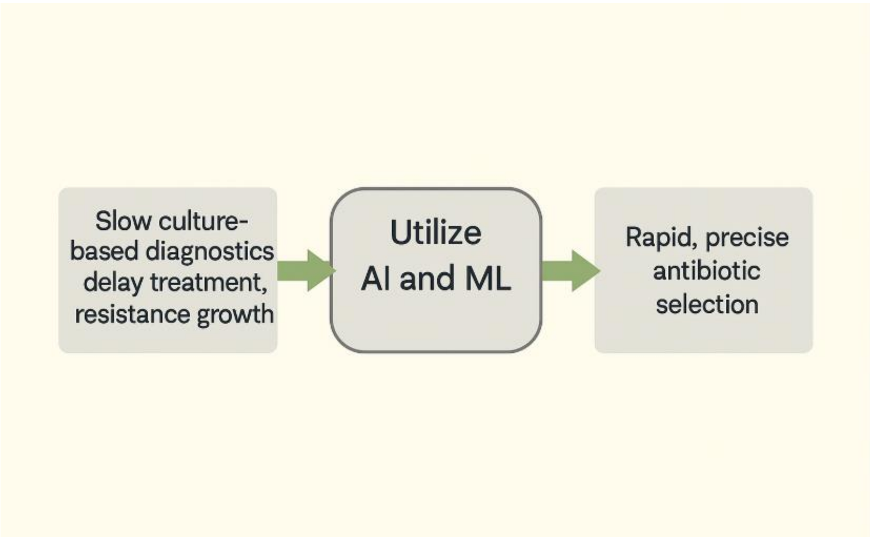
The World Health Organization categorizes antibiotic resistance one of the global top 10 health risks(7) Antibiotic stewardship programs have been identified worldwide to be at the center of the worldwide fight against antimicrobial resistance (AMR) by maximizing antibiotic use to achieve the best for patients, minimizing microbial resistance, and minimizing transmission of infection by multidrug-resistant organisms.(8) The first-ever mention of antibiotic resistance was in 1930 when sulfonamides were first launched. Then, it predicted the eventual appearance of antibiotic resistance, even if there are deadly pathogens. Bacterial strains gain resistance genes from a foreign bacterium via transgenes, phages, or plasmids, or because of chromatin instability and mutation, all resulting in cross resistance.(9) According to the World Health Organization (WHO), Nigeria boasts one of the highest rates of antimicrobial resistance (AMR) in Africa (10). In 2019, it was reported that more than 88% of Nigerians used anti-biotics without prescription, resulting in the development of resistant bacterial diseases.(11)

USE OF AI FOR AMR MANAGEMENT

We foresee that an effect of trickle-down from related ML research will drive substantial AI-enabled innovation in antibiotic discovery in the next ten years. We predict that this process of innovation will demand greater data quality and quantity, probing novel areas of chemical space, revisiting familiar areas by drug repurposing, interaction between computational and experimental researchers, and greater explain ability via IML.(12)

The introduction of AI also poses the challenge of coping with the complexity of technology infrastructure and investment. As appealing as AI potential in reshaping healthcare is, the initial cost of technology acquisition, software creation, and integration is an exorbitant hurdle, particularly to financially constrained healthcare centres. In addition, the trust and explain ability in AI systems are contentious issues. Rendering AI-driven decisions as transparent, verifiable, and trustworthy to the healthcare practitioners is of critical importance.(13) AI can help patients overcome practical problems, i.e., missing doses or shortages of supplies, by reminding them or facilitating refilling. AI can also help patients access high-quality, low-cost antibiotics by guiding them to reliable sources or offering discounts or coupons. Gives an overview of how chatbots support the control of antibiotic resistance. (14)

The advent of ML and AI transformed this setting. enabling real-time pathogen identification and patient-specific antibiograms, radically enhancing diagnostic pace and therapeutic efficacy.(15) The difference between AI-based methods and conventional methods in antimicrobial resistance (AMR) management has colossal differences in cost-effectiveness, precision, and issues of practice problems in the real world. The conventional diagnostic methods to AMR, including phenotypic and biochemical testing, are typically time-consuming, resource-intensive, and labour-intensive, leading to delay in the provision of results and the initiation of the right treatment.(16)



Protein structures improve the design of antimicrobial drugs significantly. With its accurate structural prediction of disease proteins, Alpha Fold enables the design of targeted antimicrobial drugs that are not only more effective but also less susceptible to resistance. It also offers novel concepts of mechanisms of AR through its prediction of structural adaptations due to protein mutations, which can be applied to the design of new drugs against resistance. The fast and highly accurate predictions of Alpha Fold enable rapid research and development cycles required to counteract rapidly evolving microbial pathogens.(17)

Prediction of AMR by AI

Machine learning models of antibiotic resistance prediction and the use of AI-based decision support systems for antibiotic prescribing are only two means through which artificial intelligence (AI) is revolutionizing antibiotic stewardship that are addressed in this section. Machine learning models, through the examination of intricate datasets including clinical, genetic, and epidemiological data, have been highly promising in predicting antibiotic resistance(18) These models use machine learning algorithms to identify patterns and correlations between various parameters and thus accurately predict whether or not a bacterial strain will be resistant to a given antibiotic. Healthcare professionals can provide valuable insights into the most likely to be useful antibiotics for a particular infection by using machine learning algorithms to analyze parameters like the genetics of the bacteria, patient history, and regional resistance patterns. Healthcare professionals can make better decisions regarding antibiotic administration based on this information, improving patient care and minimizing the development of antibiotic resistance. AI-powered decision support systems are under development to help healthcare professionals make decisions about the best treatment for a particular patient in terms of antibiotic drugs, as well as predicting antibiotic resistance.(10) AMR prediction tools developed through genotype-phenotype learning can become biased since the data archives are constructed on nonrandomized sampling. This sample provenience and time of collection may influence species representation and bias the association of genetic traits with AMR.(19)

Presently, AMR is mainly diagnosed through two methods in clinical microbiology. One is traditional culture-based antimicrobial susceptibility testing (AST), and the other is whole-genome sequencing for antimicrobial susceptibility testing (WGS-AST).(20) WGS-AST is fast, reproducible, and precise in diagnosing AMR but needs large and high-dimensional data to effectively extract information. Hence, artificial intelligence techniques are utilized to enhance existing approaches as below.(21)

To understand the mechanism of AMR, antimicrobial susceptibility testing (AST) is carried out based on phenotypic testing. Phenotypes include information about the physical characteristics of micro-organisms, such as its shape, size and colour(22) Even though th**is** method is easier to apply and use, it will take at least a day or longer to yield the results, which drastically increases the empirical antibiotic course and creates the risk of failure of treatment as a consequence of inadequate therapy or the risk of antibiotic resistance due to the use of broad-spectrum antibiotics(20)

To enhance AST approaches, Inglis et al. employed a hybrid technique of flow cytometer antimicrobial susceptibility testing (FAST) and supervised machine learning to conduct antimicrobial susceptibility testing. This kind of AI technique produces a valid result within 3 h (21)
An offline smartphone application (the App) capable of interpreting disk diffusion antibiotic susceptibility tests (ASTs) and delivering interpreted results, functioning solely on a smartphone, strongly convinced that the App could have a major contribution to make in the regions where Médecins Sans Frontières (MSF) operates and the worldwide battle against AMR. The application combines new algorithms, using machine learning (ML) and image analysis, and a rule-based expert system to automate AST interpretation. The App could therefore fill the digital divide, increase patients' access to AST worldwide, and potentially enable epidemiological data collection on antimicrobial resistances.(23)

1937 E. coli genome sequences were downloaded from the European Nucleotide Archive. Six classes and 12 categories of antimicrobial resistance phenotype profiles were gathered: aminoglycosides (tobramycin TBM, gentamicin GEN), quinolone (ciprofloxacin CIP), beta-lactams (amoxicillin AMC, thiazolopyrimidine TZP), cephalosporins (cefuroxime CXM, cetirizine CET, ceftazidime CTX, ceftazidime CTZ), sulfonamide (trimethoprim TMP), and penicillin (ampicillin AMP, amoxicillin AMX). Specifically, not all isolates carry a full antimicrobial resistance phenotype profile; the most detailed information is available for those antimicrobials frequently utilized in therapy (GEN, CIP, CXM, CTX, and CTZ). The respective antimicrobial resistance phenotype profiles were formerly divided into three groups depending on the level of antimicrobial resistance: resistant (R), susceptible (S), and intermediate.

We designated the neutral intermediate strains as "S" in this study and split the overall database into three sections, of which 80% was utilized for training, and 10% for testing purposes, respectively.(24)

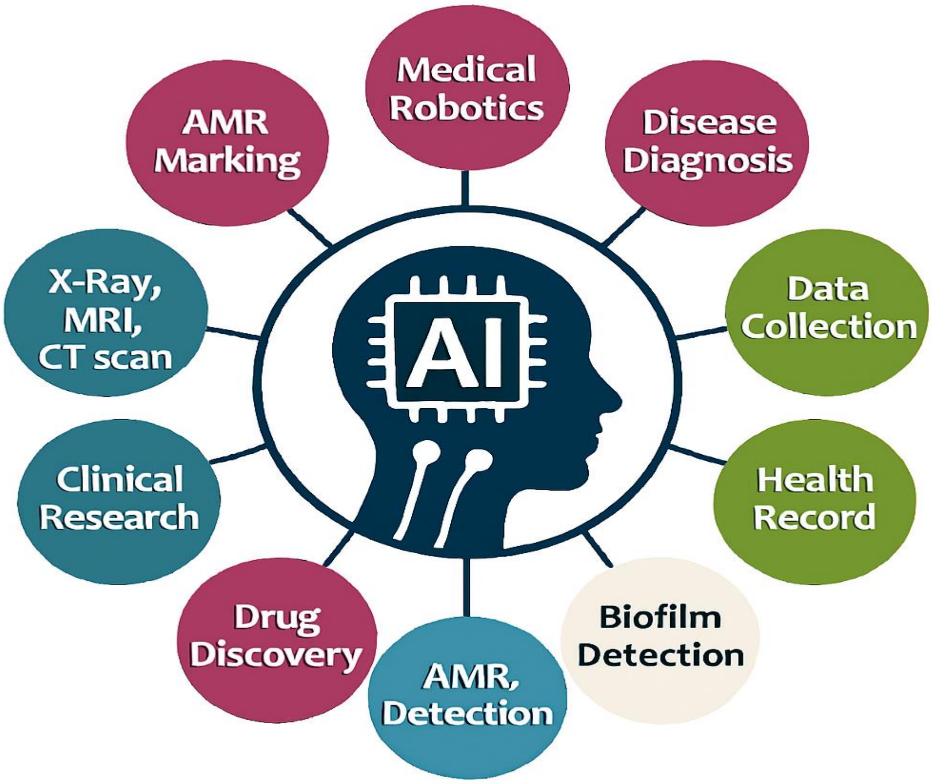
KOVER, a publicly available supervised machine learning model, was created and implemented by Drouin et al. to generate two rule-based models for WGS-AST phenotype prediction: KOVER-AMR-Set Covering Machines (SCM) and KOVER-AMR-Classification and Regression Trees (CART), from a publicly available genotype-phenotype database, based on the absence or presence of specific k-mers (a sequence of DNA with length k). Models exist for 12 bacterial species, for 56 antimicrobial treatment options. As of now, there is no tool or package of KOVER-AMR (25)

Spectroscopy and imaging technologies are emerging to rapidly detect and identify bacteria from minute samples, even without the need for culturing in certain instances. Spectroscopy methods yield spectral fingerprints, unique for each species, so they can be discriminated. Although imaging bacterial cells was a simple methodology within microbiology since the beginning, the emerging imaging technologies along with applicable AI methodologies have significantly enhanced bacterial identification performance.(26)

The WHO made available priority lists of bacterial and fungal pathogens in order to facilitate global response to their infections and AMR. Predictive modelling against AMR must prioritize pathogens of global concern.(27)

Pathogen/Topic	**Application**
Streptococcus pneumonia	-Predict susceptibility to antibiotics.
Staphylococcus aureus	-Distinguish methicillin-resistant strains
Escherichia coli	-Discover key genetic traits Optimize antibiotic treatment Strategies
Streptococcus pyogenes	-Prediction of virulence factors Salmonella
enterica	-Investigate simultaneous presence of metal and antibiotic resistance
Mycobacterium tuberculosis	-Predict resistance to specific antibiotics
Antibiotics	-Predict antibioflm activity
β-lactamases	-Classify resistance or wild type
Drug discovery	-Develop new antibacterial peptides
Sepsis	-Provide recommendations for antibiotic treatment

Some of the uses of machine learning against antimicrobial resistance**(28)**



The usage of AI in various health sectors to speed up proper and accurate diagnosis and treatment procedures.(29)

Prevention of antibiotic resistance by AI

There has been much advancement brought about by AI since it can accommodate massive amounts of electronic patient information. AI has already provided diagnostic accuracy equal or even higher than that of human doctors in some illnesses. There have also been claims that doctors can have higher diagnostic accuracy with the help of AI.(30)

HCPs, especially in hospitals and primary care, need to be trained to adhere to evidence-based antibiotic prescribing guidelines.(31) AI-enabled platforms have the ability to inform antibiotic resistance to healthcare professionals, patients, and the public.(32)

ML and DL are both forms of AI. While ML refers to AI that can adapt automatically with little human expert interference, DL is a branch of ML that applies ANNs in imitating the learning process of the human brain.(33)

Metal nanoparticles have been developed into several antibacterial medical devices, implants, and wound dressings. From the very first in vitro experiments to confirmation in animal models and eventually reaching clinical trial phases, these materials have exhibited effective therapeutic properties in the treatment of skin infections, wound healing, implant infections, and beyond. For example, aside from showing photothermal activity used against bacterial infections.(34)

Pharmaceutical research using AI provides the potential to enhance the prediction of the efficacy and toxicity of lead drug compounds. This can aid in the creation of more effective and safer drugs and speed up the drug discovery process. (35) Another important application of AI in drug discovery is the creation of new compounds with particular properties and actions. The conventional approaches tend to depend on the detection and alteration of known compounds, which may be time and labour-consuming. AI-enabled strategies, however, have the ability to facilitate quick and effective development of new compounds with favourable properties and activities.(36)

AI could very substantially minimize inefficiency in healthcare, optimize patient flow and experience, and optimize caregiver experience and patient safety along the care pathway; for instance, AI can be used for the remote monitoring of patients (e.g., smart telehealth through wearables/sensors) to detect and provide timely treatment of patients at risk of deterioration.(37)

One. of the main reasons for AMR is the abuse of broad-spectrum antibiotics, which have the ability to kill several types of bacteria. It is important that the appropriate antibiotic be administered at the appropriate time in order to maintain the effectiveness of the antibiotics that can cure drug-resistant infections. It is, however, essential for frontline providers to initiate antibiotic therapy immediately if a patient poses a threat of life-threatening infection like bacteraemia (bloodstream infection), which can progress to sepsis. The choice of the first antibiotic is important and occurs with a restricted ability to predict AMR, leading to overuse of broad-spectrum antibiotics.(38)

An ML-based clinical decision support system can utilize a patient's electronic health record to estimate the patient's personal risk of a resistant infection and suggest the narrowest spectrum antibiotic that is most likely to cure the infection(39)

Certain ML-based systems have demonstrated unequivocal potential to decrease broad-spectrum antibiotic over-prescribing in promising trials(40)

In 2020, 222 AI-based medical devices were registered in the USA(41), and 64 of them were FDA-approved (42); in the EU, where medical device approval is more de-centralized, 240 AI-based medical devices were approved. The majority of these technologies are employed for diagnostic use, yet only 4 of them aim at microbiology—2 that have been approved in both the USA and Europe (one for sepsis and one for plate read automation) and 2 solely in the USA (one for sepsis and one for syphilis)(41). The majority of the AI algorithms employed for diagnosis are pattern recognition(42). Such algorithms can process large data volumes within a short time, identify subtle patterns within such data, and support the detection of disease, including infectious disease.(38)

the effects of various antibiotic regimens for the prevention and treatment of TD on the gut microbiome, resistome, inflammatory state, and strain dynamics using well-characterized samples from two large clinical trials. We observed that microbiome diversity was stable over the period of the study for all but most treatment groups. Twice-daily rifaximin, however, reduced microbiome richness substantially over time. Likewise, antibiotic resistance gene diversity and abundance were generally stable but significantly greater for the twice-daily rifaximin prophylaxis arm of the PREVENT TD trial.(43)

AI for clinical decision support systems: antimicrobial stewardship (ASP)

There were some studies that proved huge potential of AI in antimicrobial stewardship augmentation.(44,45) It was seen in one study that ML models detected 60% of antibiotic discontinuation cases, while 19% were detected in normal care, with a 98% success rate for switching to oral antibiotics.(45)Another research pointed out that AI systems reduced antibiotic de-escalation by 24 hours.(46)

A third study found CDSS with active ASP optimized antibiotics more effectively for community-acquired pneumonia (CAP) than without ASP.(44) Moreover, two INSPIRE (Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotics Section) randomized controlled trials compared the effect of a CPOE (computerized provider order entry) bundle with usual ASP on empiric antibiotic ordering for pneumonia and urinary tract infection (UTI) in non-critically ill adults. The CPOE decreased days of extended-spectrum antibiotic use by 28.4% for pneumonia and 17.4% for UTI with comparable decreases for vancomycin and antipseudomonal use. Safety outcomes and ICU transfers did not differ significantly in the two trials.(46)

Appropriateness of antibiotic prescribing Three studies assessed AI-augmented CDSS systems that aim to enhance antibiotic prescribing. One study showed that a CDSS coupled with national guidelines enhanced diagnostic performance and minimized inappropriate antibiotic use in UTIs, enhancing prescriber confidence.(47)

Another study utilized a random forest model within a CDSS to facilitate antibiotic choice for paediatric infection, specifically enhancing ceftriaxone resistance predictions, with estimated AUROC of 0.80. A third study evaluated a CDSS that used patient information and previous cultures to enhance empiric treatment of gram-negative bacteraemia, allowing narrower-spectrum antibiotic therapy in 78% of cases and lowering suboptimal treatment. Its effectiveness depended on antibiotic susceptibility breakpoints, and multivariable models had excellent discrimination, with AUROCs of 0.68–0.89 for Gram-stain-guided and 0.75–0.98 for pathogen-guided models.(46) Antibiotics are endogenous and exogenous medications that can influence microbial survival by preventing their growth or destroying them. Antibiotics cure bacterial infection in humans and find application in animal health and welfare.(48)

Hopping on board with cutting-edge research tools like metagenomics and synthetic biology can be used to improve bacteriophage isolation and characterization(49). The two methods can be utilized to discover new phages with wide-spectrum activity against MDR disease-causing microorganisms. Lastly, for phage therapy to be made available in African clinical settings, conducting well-controlled, rigorous clinical trials needs to be done to determine the efficacy, safety, and economic value of this therapy. These trials should be formulated in consultation with local and global health authorities, respecting the epidemiological and clinical particularities of the regions. The outcomes of these experiments will provide a foundation for the elaboration of clinical guidelines and regulatory policies suitable for the application of phage's in the treatment of resistant infections in Africa.(50)

The researchers have developed a hollow polycarbonate microneedle array. The bottom diameter and mean height of this device were 750 μm and 995 μm, respectively, and its hollow aperture was 100 μm. The researchers have found that this device can perforate the skin completely and release BPs. Bioavailability is as high as 100% using this transdermal delivery device. The depth and width of the residual pores of the skin are 210μm and 600μm, respectively, and these can be closed quickly after treatment(51)

AMP-antibiotic combination/adjuvant treatments have been extensively tested and used in recent years to enhance the efficacy of existing drugs(52,53). Our findings are consistent because HPE at sub-MBC concentrations (1.0–12.0 μg/mL) enhanced ampicillin, ciprofloxacin, gentamicin and trimethoprim efficacy 2 to 32-fold. HPE can thus be particularly valuable for combination treatments to resuscitate the use of existing antibiotics against drug-resistant bacterial species/strains. Synergy results with S. aureus and P. aeruginosa are especially of interest, given that these species are well known for high resistance; there are instances of other combinations of AMPP and antibiotics at equivalent effective concentrations being effective against these species,(54,55) Interference with bacterial cell membrane integrity/permeability due to AMPPs is a mode in which antibiotics are able to gain easier access to targets(56). In synergistic mixtures with traditional antibiotics, the bioactive principles of HPE need to transmit independent (e.g., direct inhibition of enzymes) and complementary (e.g., compromised membrane integrity) modes of action to interfere with cell function.(57)

AI technology can make computers learn and get better automatically without direct programming and build and forecast models from data. The field of methodology that is dealt with in AI predominantly encompasses reasoning, knowledge representation, solution search and machine learning (ML)(58)

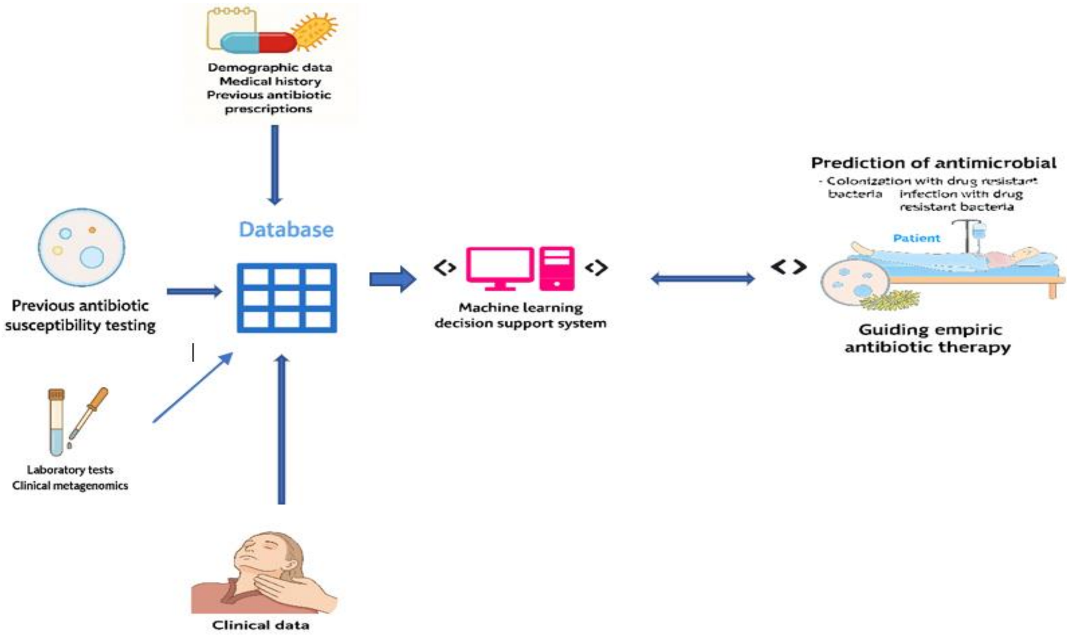
Generative DL can be used for computational antibiotic discovery through several means. In this work, we are interested in de novo design of molecules, which tends to use generative adversarial networks (GANs), variational autoencoders (VAEs), or similar architectures. Made up of competing generative and discriminative models, GANs learn the probability distribution from which training samples come to build new samples from the same distribution.(59)

In a Nature paper published in 2020, MIT and Harvard researchers employed a deep learning model to identify a novel class of antibiotics that are effective against methicillin-resistant Staphylococcus aureus (MRSA), a bacterium that produces fatal infections and is resistant to most current antibiotics. MRSA infects over 80,000 individuals in the US annually and kills over 10,000. The scientists employed a deep learning model of the graph convolutional neural network (GCNN) type, which has the capability of learning from the graph structure representation of chemical structures, in which atoms are nodes and bonds are edges.(60)

The identification of novel antibiotic classes with AI has several implications for the fight against antibiotic resistance. it has the potential to speed up the process of drug discovery and decrease the complexity and expense of development, thus incentivizing the pharmaceutical company and public sector to invest more in antibiotic research.(61)

CHALLENGES AND FUTURE PROSPECTS With the revolution brought about by AI changing the world today, there is increasingly greater scope for AI to aid in improving the design of new AMP-based antibiotics and combat antimicrobial resistance. In fact, numerous breakthroughs have been achieved in recent.(62–64)

The blending of ML and DL is essentially revolutionizing drug discovery by vastly improving data analysis capacity and predictive accuracy, hence promising quicker and more efficient therapeutic development.(65)



Data inputs to guide antimicrobial resistance prediction and treating in severe infections**(66)**

Proper prescribing of antimicrobials is a multifaceted problem, since one must choose the right treatment for the presumed pathogen, control the level of the antimicrobial drug and its frequency of dosing, and choose the correct route to achieve the desired drug concentration at the site of infection (67). In the paediatric context, it also has to be taken into account that the patterns of infection and resistance differ considerably with age, and there is great variation with age and weight in dosage.(68)

AI systems are able to forecast the probability of a compound being antimicrobial and thus narrow down the list of candidates for experimental verification(69). For instance, using deep learning algorithms to screen millions of chemical compounds for antibacterial potential has identified several new compounds having powerful antimicrobial activity.(70)

ARGs are a higher potential environmental threat than antibiotics and play a critical role in human health. According to reports, illness from antibiotic resistance sickens approximately two million individuals per year in the United States with a death rate of 1.5%. Globally, antibiotic-resistant diseases kill 700,000 individuals per year.(71)

Current research continues to explore the mechanisms of resistance and solutions to reduce or eliminate it. In conclusion, while nanomaterials can help fight drug resistance, the ability of microorganisms to acquire resistance to both ionic and Nano-metals needs to be considered.(72)

CONCLUSION

Artificial intelligence has proved to be an important weapon in the fight against rising antimicrobial resistance through supporting quick diagnosis, maximizing treatment specificity, and speeding up new drug discovery. Predictive modelling, machine learning, and AI-powered stewardship programs have demonstrated measurable benefits in limiting the use of unnecessary antibiotics and improving patient outcomes. Additionally, AI-enabled strategies in drug development and combination therapy provide novel opportunities to reverse resistance mechanisms. But effective implementation hinges on surmounting principal barriers, such as standardization of data, openness, and fair access to technology. The mainstreaming of AI in universal AMR strategies, anchored by solid infrastructure, clinician buy-in, and regulatory harmonization, can make infection control history and ensure antibiotics' efficacy for generations to come.

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