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Antimicrobial Resistance and Artificial Intelligence Applications

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Abstract

The computational comprehension of intelligent behavior is the main goal of the scientific and engineering field of artificial intelligence (AI). Many human professions, particularly clinical diagnosis and prognosis, greatly benefit from artificial intelligence. The authorities need to take action to stop the excessive and improper the application of antibiotics to battle the increasing percentages of resistance to antibiotics since the occurrence of AMR is becoming a serious problem. In addition to causing drug resistance, the extensive using antibiotics in medical settings has raised the risk of super-resistant microorganisms. As antimicrobial resistance (AMR) increases, physicians face challenges in rapidly treating bacterial infections, and the expense of medicine may become unaffordable for patients' healthcare needs. Potential benefits include a potentially infinite speed up in the development of novel antimicrobial medications, increased precision in diagnosis and treatment, and decreased costs all at the same time, the WHO, has released a ranking of the most important dangerous infections that require the development of novel antibiotics due to the threat posed by antimicrobial resistance to global public health. The search and introduction of novel antibiotics is an expensive and time-consuming procedure. Just eighteen new antibiotics have been authorized since 2014, In line with the WHO study on clinically developed antibacterial medications. Thus, new antibiotics are desperately needed. Since its latest technological advancement, artificial intelligence (AI) has been quickly used in medication research, significantly increasing the effectiveness of discovering new antibiotics. Most AI solutions for AMR that have been proposed are designed to be useful tools to assist doctors in their work, not to take the place of a doctor's prescription or advice.

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1. Introduction

A natural phenomenon when bacteria, viruses, fungi, and parasites develop what is known as antimicrobial resistance (AMR) learn to withstand the medications meant to destroy them. The antibiotic the origin and spread have been expedited by misuse and overuse in human medicine, animal husbandry, and the environment. antimicrobial resistance (AMR). This syndrome makes treatments that were once successful useless, resulting in longer illnesses, greater death rates, and more expensive medical care. Thus, AMR presents a significant and immediate worldwide risk to human well-being, necessitating immediate action. The system for monitoring antibiotic resistance and use was

developed according to the World Health Organization (WHO), showing that AMR is becoming more common and a major cause of death [1]. It was projected that 1.27 million fatalities worldwide were directly due to AMR caused by bacteria in 2019 alone, out of an anticipated 4.95 million deaths worldwide. Western With 27.3 deaths from resistance per 100,000 persons, sub-Saharan Africa had the worst death rate overall (20.9–35.3)[2]. The study published by according to data from the Centers for Disease Control and Prevention, at least 23,000 deaths and over two million illnesses occur annually in the US alone as a result antibiotic resistance to at least first-line therapy [3]. Antibiotic-resistant bacteria accounted for almost in 2019 there were 2.8 million diseases in the US [4]. By 2050, AMR is anticipated to be the reason for 10 million fatalities annually [5] .The *Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp. are among the six pathogens that the Infectious Disease Society of America has identified as "ESKAPE" organisms, meaning that they present the biggest risk to human health because their rapidly developing resistance to antibiotics [6]. The WHO has produced a list of "priority pathogens" resistant to antibiotics to assist drug development in identifying the infections that require innovative antibiotics immediately. In China, AMR is become a public health concern.

Information gleaned from the Chinese Antimicrobial Monitoring System indicate a notable rise in Gram-negative bacteria's rate of resistance, resistant to carbapenem. Notably, between 2005 and 2022, the percentage of 39.0 to 71.9% more *A. baumannii* were found to be carbapenem- resistant, whereas the percentage of from 2.9 to 24.2% of cases of carbapenem-resistant *K. pneumonia*. Furthermore, in recent years, *S. aureus* resistant to methicillin has been continuously found at a high rate of about 30% [7]. There are now fewer treatment choices in clinics for bacterial illnesses resistant to antibiotics as a result of the continuous decline in the number of novel medicines researched and licensed over the previous ten years, with just four approved between2010 and 2014 [8].

Historically, most antibiotics have been found by screening secondary metabolites from soil microbes that have antibacterial properties [9].

Regrettably, the rediscovery problem—in which the same compounds are discovered repeatedly—is making it harder and harder to identify new antibiotics [10]. Therefore, the need for clinical treatment cannot be met by the discovery of new drugs alone, particularly for those pathogens that are high on the WHO priority list. The

purpose of (AI) research in computer science is to construct intelligent computers that can perform activities that normally require human intelligence [11]. AI technologies have been incorporated into various disciplines to expedite scientific discoveries. In the field of medicine, AI has made it easier to find new medications and sped up the process of developing new drugs and conducting clinical research in its entirety [12]–[13][14]. AI has consistently played a key role in coordinated multidisciplinary efforts to address the AMR crisis [15].

1.1. Structure clinical development of antibacterial agents

It is time-consuming and resources to produce new medications since thousands of molecules that are taken from already-approved medications or mechanisms must be synthesized. After that, toxicity and preliminary activity screening are conducted to find one or two possible candidates. As per the WHO's yearly assessment of the pipeline of pharmaceuticals, the current advancement in novel antibacterial therapies is insufficient to tackle the swift rise in antibiotic resistance. Eighteen antibiotics have been licensed and made available between 2014 and the end of 2021, one of which is for the management of TB that is extremely drug-resistant (Table 1).

Table 1: Antibiotics approved between 2014 and 2021

1.	Drug	2.	Target pathogen	3.	Class	4.	Approval year	5.	Approved by
6.	Dalbavancin	7.	Gram-positive pathogens	8.	Glycopeptide	9.	2014	10.	US FDA; EMA
11.	Tedizolid	12.	Gram-positive pathogens	13.	Oxazolidinone	14.	2014	15.	US FDA; EMA
16.	Oritavancin	17.	Gram-positive pathogens	18.	Glycopeptide	19.	2014	20.	US FDA
21.	Ceftolozane/tazobactam	22.	β-lactamase enzyme producing bacteria	23.	β-lactam/β-lactamase inhibitor	24.	2014	25.	US FDA; EMA
26.	Cefazidime/avibactam	27.	CRE	28.	β-lactam/β-lactamase inhibitor	29.	2015	30.	US FDA; EMA
31.	Isavuconazonium	32.	Antifungal	33.	Triazole	34.	2015	35.	US FDA
36.	Delafloxacin	37.	Gram-positive pathogens	38.	Fluoroquinolone	39.	2017	40.	US FDA; EMA
41.	Vaborbactam/meropenem	42.	CRE	43.	β-lactam/β-lactamase inhibitor	44.	2017	45.	US FDA; EMA
46.	Plazomicin	47.	CRE	48.	Aminoglycoside	49.	2018	50.	US FDA
51.	Eravacycline	52.	CRE	53.	Tetracycline	54.	2018	55.	US FDA; EMA
56.	Omadacycline	57.	MRSA and CRE	58.	Tetracycline	59.	2018	60.	US FDA
61.	Relebactam + imipenem/Cilastatinilastatin	62.	CRE, and potential activity for CRPA	63.	β-lactam/β-lactamase inhibitor	64.	2019	65.	US FDA; EMA
66.	Lefamulin	67.	MSSA	68.	Pleuromutilin	69.	2019	70.	US FDA; EMA
71.	Pretomanid	72.	XDR-TB	73.	Nitroimidazole	74.	2019	75.	US FDA; EMA
76.	Lascufloxacin	77.	Gram-positive	78.	Fluoroquinolone	79.	2019	80.	PMDA

		ve pathogens						
81.	Cefiderocol	82. CRAB, CRPA, CRE	83.	Siderophore β-lactam (cephalosporin)	84.	2019	85.	US FDA; EMA
86.	Levonadifloxacin	87. Gram-positive pathogens	88.	Fluoroquinolone	89.	2020	90.	CDSCO
91.	Contezolid	92. MRSA	93.	Oxazolidinone	94.	2021	95.	US FDA; EMA; China

Sixteen antibiotics were authorized by the Chinese National Medical Products Administration (contezolid), the European Medicines Agency, the US Food and Drug Administration (FDA), the Central Drugs Standard Control Organization of the Government of India, and the Pharmaceuticals and Medical Devices Agency (Japan) approved one. Furthermore, only lefamulin and vaborbactam have updated MOA. The remaining antibiotics are classified into recognized classes, such as aminoglycosides (1/16), oxazolidinones (2/16), glycopeptides (2/16), and tetracyclines (2/16), β-lactam/β-lactamase inhibitors (3/16), nitroimidazoles, and fluoroquinolones (3/16) [16].

The following are examples of resistant to carbapenem: extensively drug-resistant tuberculosis (XDR-TB), the methicillin- resistant strain of Staphylococcus aureus known as MRSA, the methicillin-susceptible strain known as MSSA, and carbapenem- resistant crab Acinetobacter baumannii, Pharmacy and Medical Devices Agency, or PMDA, EMA European Medicines Agency, the FDA Food and Drug Administration and CDSCO Central Drugs Standard Control Organization.

β-lactam siderophore (1/16), and triazoles (1/16) (Figure. 1). WHO reports show that there were 42 new therapeutic agents in total in 2017 (of which 33 were medicines that target biological agents and bacterial priority pathogens, and 59 in 2021 (of which 27 were antibiotics and 32 were biologicals) . This suggests that the development of biologicals—such as monoclonal antibodies, phage endolysin, polyclonal antibodies, etc. Has accelerated recently relative to the development of traditional antibiotics. The increasing need for innovative antibacterial agents with fresh targets and mechanisms of action led to the development of these biologicals. These biologicals have helped to advance.

a change in emphasis among developers from focusing on broad-spectrum treatments to concentrating on a single pathogen. WHO guidelines, however, only consider six includes I-III Phase clinical trials and novel medication applications studies, there are 27 antibiotics to be novel medications [17]. *When treating ailments brought on by Gram-negative bacteria, they were noticeably safer and more promising combinations even though Almost half remained. combinatorial β-lactam/β-lactamase inhibitors* [18]. *Only three drugs are now accessible therapeutically to cure Gram-negative bacterial infections that are extremely resistant to drugs: ceftazidime/avibactam (2019), 2017 saw the return of polymyxins to the Chinese market, and tigecycline (FDA-approved in 2005 and available in China since 2010).*

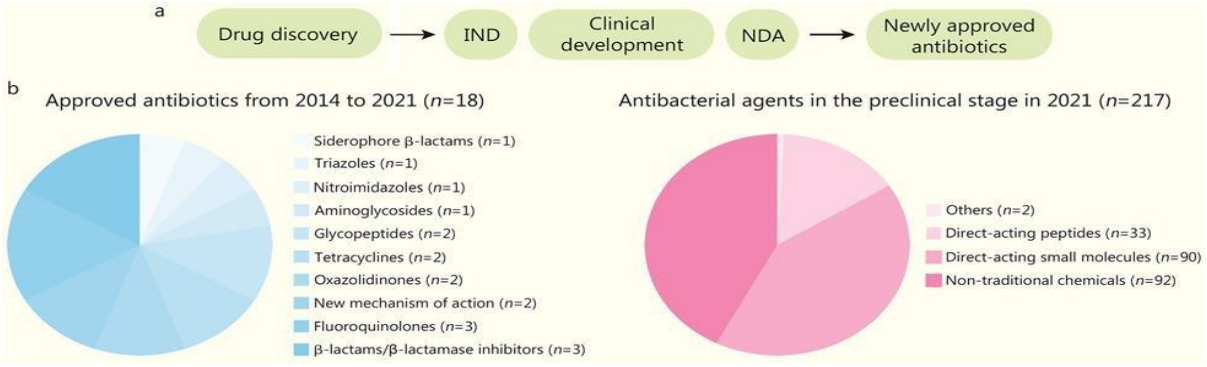

Figure 1

The state of developing novel antibiotics (b) and the pipeline (a). Before being approved, novel medications found in laboratories must pass numerous stages of development, including investigations into new drugs (INDs), clinical trials, and new drug applications (NDAs) processes. Non-traditional chemicals include Products based on nucleic acids (n = 4), peptides with indirect action (n = 2), biologics (antibodies or other), immunomodulators (n = 7), small molecules with indirect action (n = 23), and huge molecules (n = 19), and microbiome-modifying compounds (n = 1).

1.2. Commonly employed AI algorithms for antimicrobial resistance

In Table 1 for AMR, we examined the most popular AI methods, such as artificial neural networks (ANN), support vector machines (SVM), random forests (RF), decision trees (DT), and naïve Bayes (NB).

Table 2: AMR algorithm comparison using popular AI algorithms.

Benefits and drawbacks of the method	Learning speed	Interpretation
NB: Quick and simple to use; appropriate for datasets containing missing values. Every aspect must, nevertheless, stand-alone.	1	4
DT: Although decision tree results are easily interpreted, their applicability to datasetswith missing values varies with tree complexity.	2	1
RF: This approach can handle a wide range of features and works well with huge datasets. It is not particularly sensitive to anomalous data, though.	4	3
SUM: Despite being extremely sluggish and requiring the user to provide numerous parameters, SVM may handle complex issues by utilizing kernel functions.	5	5
ANN: Multiple layers of a perceptron can be used by an ANN to learn a wide range of complicated issues. Accuracy will rise with increased model depth, although learning maygo extremely slowly.	5	5

These approaches' from 1 to 6, speed and interpretability are graded, with 1 being the best.[19].

1-Naïve Bayes

The Bayes theorem forms the basis of the Naïve Bayes classification method, which makes separate assumptions for every feature[20]. The input/output joint probability distribution for a training dataset is computed. Using the Bayes theorem, we may ascertain which output, y, has the highest posterior probability given a particular input x:

$$y = f(x) = arg\ \underset{ck}{max} P(y = c_k) \prod_{i=}^{n} \rho(X^{(i)} = X^{(i)} | Y = C_k)$$

The input space defines the random vector, and the output space defines the random variable. indicated by X by Y, and the class label is represented by c.

To track AMR, recent research has generally used the Naïve Bayes model [21, 22]. Rezaei- Hachesu and his colleagues for instance, employed a priori and naïve Bayes methods to identify the resistance factor and extract resistant patterns [22]. Furthermore, Choisy and his colleaguesestimated the likelihood that AMR-related unsuccessful therapy using Naïve Bayes [23].

2-Decision tree

Typically, the decision tree [24] is employed in classification. A straightforward decision tree is used in Figure 1A to separate a dataset into three classes. Three steps are often included in a decision tree's learning process: (1) feature selection, (2) formation of decision trees, followed by their trimming (3) [19]. ID3, C4.5, and CART [25,26]]. provide the majority of the fundamental basis for these phases [27].

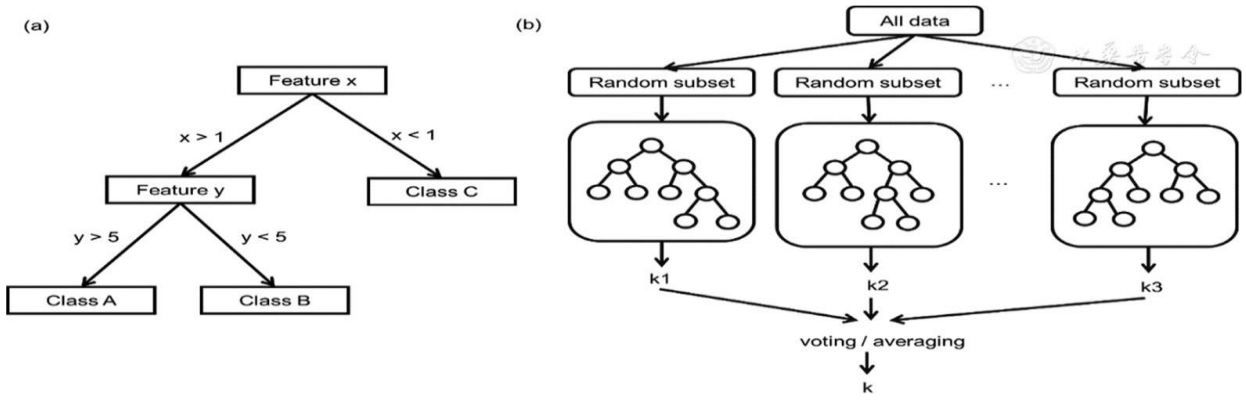

Figure 2: (A) A straightforward decision tree model that uses two features to separate a dataset into three classes. (B) The random forest algorithm's schematic representation.

A common method for allocating medical resources and estimating the burden of antimicrobial resistance resources correctly [28], [29]. When estimating healthcare consumption and costs for

antimicrobial resistance (AMR), Reynolds and his colleagues for instance, used a DT model [30]. This shows that lowering AMR or improving antibiotic selection can result in significant cost savings.

Shorter treatment durations and lower overall dosages were achieved by Voermans and his colleagues used a DT model based on procalcitonin (PCT) [31] to direct the administration of antibiotics [11].

3-Random forest

To increase accuracy and reliability, the ensemble method of Random Forest uses numerous decision trees [32]. As Fig. 2B illustrates, it makes use of two important ideas rather than just averaging the forecast outcomes of all trees, which would lead us to refer to it as "forest". First, certain samples will be utilized more than once in a tree since they are selected at random from the training dataset. The random forest often converges to a decreasing generalization error as the number of trees rises; yet, the effectiveness of a single tree inside it may be diminished because the other subset of features is random [33]. Antibiotic combination prediction has long been a focus of random forest models. Using chemogenomic data and orthology, for instance, Chandrasekaran and his colleagues utilized a RF model [34] to forecast a powerful mix of antibiotics treatment. This model performs well in generalization (AUC for synergy = 0.79),It has a low computational complexity and a straightforward, regular structure (n2/2). Using the chemical fingerprint, Mason and his colleagues increased the ability to forecast previously stated models. as a feature because chemogenomic data are insufficient [35, 36].

4-Support vector machine

An algorithm known as the Support Vector Machine (SVM) for binary classification [37] divides samples into distinct classes by locating a dividing hyperplane in the sample space (Figure 3).

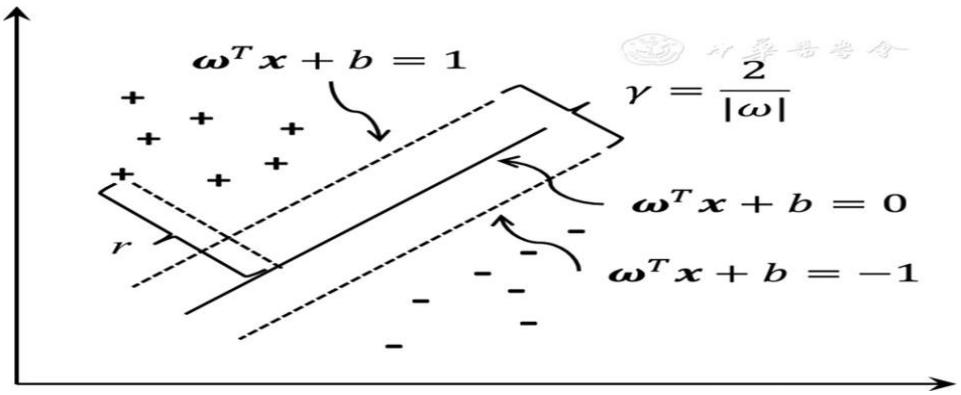

Figure 3: A dataset is divided into two classes using a basic support vector machine [37].

We may whether or not the training set can be divided linearly or almost linearly, use either soft margin maximization or hard margin maximization to generate a linear SVM.:

$f(x) = sign(wT\omega + b)$

where the distance between the origin and the hyperplane is given by the displacement term, b, and the normal vector, ω. In the event that the training set cannot be divided linearly, the kernel function and soft margin maximization can be employed. to produce a nonlinear SVM.

$f(x) = Sign(\omega T\phi(x) + b)$

ϕ is a kernel function.

To forecast AMR phenotypes, such as "resistant" or "susceptible," recent research has frequently used SVM models [[38], [39]. Using SVM models, for instance, Her and his colleagues predicted if E. coli is resistant to drugs [38]. The model's average accuracy of predictions was up to 0.95 (based on the AUC), according to the results. Furthermore, Liu and colleagues utilized Support Vector Machines Tetracycline, ampicillin, sulfisoxazole, trimethoprim, and enrofloxacin are the five drugs whose resistance was examined using support vector machines (SVM). [39]. The findings indicated that the model's accuracy was 90% or higher. Regarding AMR monitoring and medical diagnosis. we therefore view SVM models as promising instruments.

5-Artificial neural network

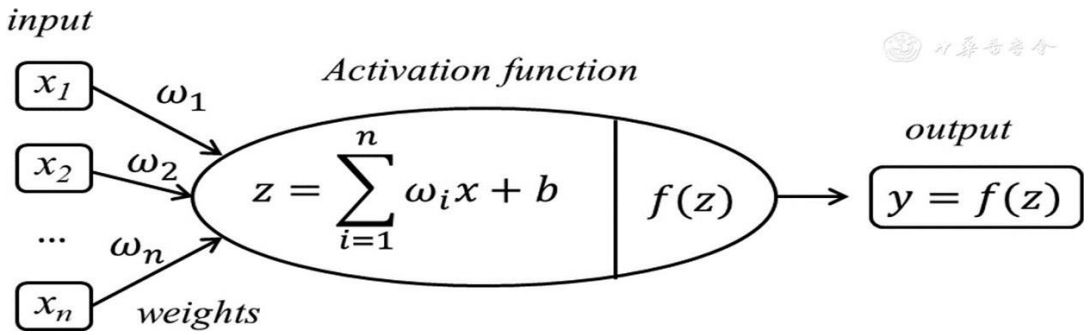

Figure 4: An artificial neural network neuron [40].

Artificial neural networks use layers of interconnected, weighted computer units, or "neurons" (Figure 4)—mathematical abstractions to transfer information [40]. These networks are based on loosely modeled human brain neurons. Equation 4 provides a mathematical description of the neuron's output.

$$y = f \sum_{i=1}^{n} \omega_i x_i + b)$$

Neural network training algorithms reduce weights ωi and biases b's activation function. Gradient descent is typically used to achieve this.

$$w_k \rightarrow \omega_k' = \omega_k - \eta \frac{\partial f}{\partial \omega k}$$

Of them, the activation function is denoted by f, the learning rate by η, and the weight by ω.

Among the ANN was recently deployed by Stokes and his colleagues deep learning, to identify new medicines without making any presumptions beforehand [41]. In animal tests, these compounds have been shown should possess antimicrobial qualities against a variety of infections. Next, we will enhance current compounds and create new antibiotics using a deep-learning approach, which may represent a paradigm shift in the field of antibiotic development.

2. AI Assistance Techniques for AMR

Fighting antibiotic resistance involves several critical components, including early infectious disease detection, identifying infectious from non-infectious pathologies, and appropriate treatment of any effects. AI is crucial to this global challenge. AI approaches should possess antimicrobial qualities against a variety of and associated trends in susceptibility patterns, such as the creation of antibiograms and the subsequent individualized, AMR prediction models based on machine learning (ML) may prove highly beneficial[42]. Through the use of this method, Yelin and his colleagues examined more than 0.7 million UTIs were found in the community throughout 10- year longitudinal dataset, and discovered a strong association between AMR and patient demographics, urine culture history, and antibiotic use in the past. Following examinations, they created an AMR prediction model based on machine learning and detailed the high-risk UTI bugs along with their AMR patterns [43]. Figure 5 describes the application of deep sequencing AI models.

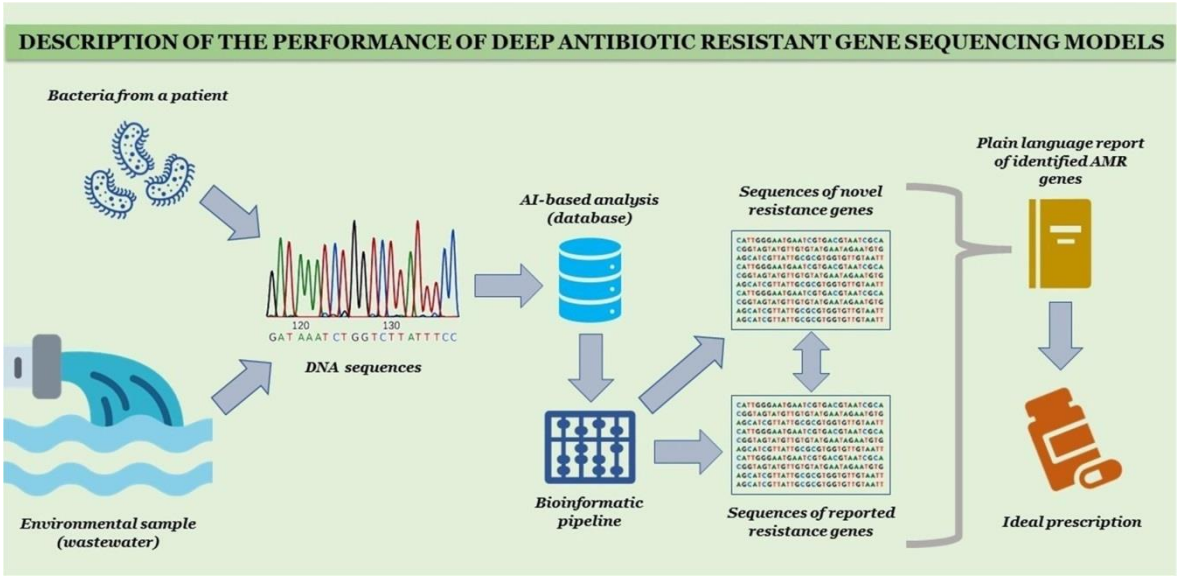

Figure 5: Gene-sequencing model with deep antibiotic resistance

2.1 Artificial Intelligence Providing Intensive Care Unit (ICU) Patient Treatment

ICUs are critical environments for the use of artificial intelligence, and numerous avenues for doing so have been investigated. Using no administrative AI techniques, a vast amount of data included in electronic patient records has been examined. Numerous AI algorithms have been developed to identify important patient outcomes [44] and extract important data from an individual's outline [45]. Algorithms related to administered AI have proven useful in radiography, pathology, and histology due to their proficiency in automated example recognition [46]. Artificial intelligence, in line with mechanical technology, is widely used in many medical fields [47], particularly in cardiology and surgery [48], oncology to classify cancer types and stages of development[49], and identification of heart failure or arrest [50].

Even yet, research has successfully assessed AI's application in the care of critically ill patients [51], even though its usage in ICUs is still in its infancy. Numerous artificial intelligence the length of hospital stays and readmission rates have been examined using (AI) systems rates in intensive care units (ICUs), death rates, and the predictors of unforeseen illnesses like sepsis. In prior work [52], an AI-based technique to predict hospital admission days and patient survival was built using data from 14,480 patients. Given a longer stay, the region beneath the Curve of the Model (AUC) was 0.82. In comparison, the findings of clinical research showed that physicians' prognostication of the duration of hospitalization in the critical care unit was only about 55% accurate [53]. The duration of stay in the ICU was accurately predicted by a hidden Markov framework applied to physiological values obtained within the first 48 hours after ICUadmission [54].

2.2 AI Models Previously Used in ICUs about Infections and Antimicrobial Resistance

In ICU, patients' critical conditions necessitate a prompt and accurate evaluation of textual inputs that are high-dimensional but raw, statistics, photographs, and other data. Furthermore, it is necessary to ascertain complex, nonlinear relationships between the data. Patterns in data have been represented as mathematical equations using a variety of statistical approaches [54]. A "best-fit line" is suggested by linear regression. Deep learning (DL) tackles complex medical data like a physician would, painstakingly evaluating the available data to reach a logical conclusion rather than reducing the connection to an equation in mathematics. Unlike a single physician, DL can capture and assess multiple inputs at once, enabling the creation of prediction models based on the intended outcome. DL approaches, namely Utilized are the convolution the use of recurrent neural networks (RNN), deep belief networks (DBN), and neural networks (CNN) intensive care units (ICUs) with other AI techniques linked to healthcare.

To anticipate the results Based on a high-quality database containing 2177 ICU patients, Steenkiste and his colleagues (2019) used a temporal computational model of blood culture tests that included a bidirectional long short-term memory (LSTM) and nine clinical factors monitored over time. When it's uncertain how long has passed between an expected event and the diagnosis, this kind of deep learning method works effectively. The network exhibited a typical area behind the curve (AUC) of 0.82. with 0.99 as the region beneath the operating

characteristic curve of the receiver.

Moreover, the outcomes demonstrated that forecasting several hours before the occasion may only be accomplished with a slight decrease in predictive strength [55].Using a dataset an RNN with LSTM was developed by Kaji and his colleagues (2019) to forecast daily sepsis, myocardial infarction (MI), and the availability of the antimicrobial vancomycin (VA) for two weeks. patient's condition progressed. These models attained the expected AUCs for sepsis, MI, and VA treatment were 0.823, 0.876, and 0.833, respectively. The systems' attention maps illustrated the instances during which input elements had the biggest impact on the predictions, giving doctors some interpretability. Additionally, they displayed factors that served as stand-ins for clinical judgment, highlighting the challenge of developing clinical decision support systems with adaptable deep learning methods that are educated based on information from electronic medical documents (EHRs) [56].

In a study on the potential uses of AI in microbiology, Smith and his colleagues (2020) found that whole-genome sequences (WGS) of bacteria, MALDI-TOF mass spectra, and images—microscopic and macroscopic—may all profit from AI. Artificial Intelligence is beginning to be used in clinical microbiology and is currently providing laboratory staff with various diagnostic testing tools. It appears the quantity of AI instruments, the caliber and dependability of evaluations using AI software, including the incorporation Incorporating AI into the operations of medical microbiology laboratories with all rise soon. In the future, when AI frees up greater time to focus on diagnosing issues, difficult technical clarifications, and quality assurance in laboratories, it will be used more and more by microbiology technicians for preliminary testing and analyzing standard test findings for infectious diseases. The alterations will enhance the quality and efficacy of diagnostic bacterial testing, which is advantageous to our patients as well as the lab. [57].

3. Conclusion

The development of antimicrobials has been sluggish, even though antimicrobial resistance, also known as AMR, seriously endangers the safety of humans has received significant attention. Between 2014 and 2021, just 18 new antibiotics were licensed; of those, only two have a unique MOA (mechanism of action). Two tendencies in the creation of novel antibiotics have been identified through analysis of antibiotics that are presently undergoing clinical development:1) from small synthetic chemicals to biologicals; 2) from wide to limited spectrum. AI has previously been used in drug repurposing, resistance mechanism prediction, and the identification of new AMPs and EOs (essential oils) to address the ever-increasing demands of the therapeutic community. This review shows that industrialized countries have effectively used AI in their healthcare infrastructures, with electronic data entry being the most prevalent example. It also sheds light on current AI practices surrounding antibiotic resistance worldwide.

4. Conflict of Interests

author does not any conflict of interest related to their research work.

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