African Journal of Pharmaceutical Research & Development

Available online at **https://ajopred.com**

Vol. 15 No.1; pp. 32-48 (2023)

VACCINE TARGET OPTIMISATION AND DEVELOPMENT: THE ROLE OF MACHINE LEARNING ALGORITHMS AND EMERGING AI TECHNOLOGIES

CHUKWUEMEKA SYLVESTER NWORU[1,3,*], RUPHIN KUSINZA BYAMUNGU[2], THIERRY MUGENZI[4]

1. Department of Pharmacology & Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria
2. Department of Cybersecurity, Faculty of Computing & Sciences, Olivia University, Bujumbura, Burundi
3. Faculty of Pharmaceutical Sciences, Olivia University, Bujumbura, Burundi
4. Department of Artificial Intelligence, Faculty of Computing & Sciences, Olivia University, Bujumbura, Burundi

ABSTRACT

Vaccines are significant advancements in modern medicine, preventing numerous life-threatening diseases. Their development is a complex, multidisciplinary process involving antigen identification, production, preclinical testing, human clinical trials, regulatory approval, large-scale manufacturing, and distribution to target populations. However, vaccine development is expensive and has a high failure rate. This situation is further complicated by pathogen mutations, which can reduce vaccine effectiveness. This review examines the application of machine learning algorithms (MLA) and artificial intelligence (AI) in vaccine development, with a focus on identifying optimal vaccine targets and the significance of employing advanced technologies for the rapid production of effective vaccines against existing and emerging infectious diseases. The review process involved searching various academic databases such as PubMed, ScienceDirect, and Google Scholar, using a combination of keywords and Boolean operators to find relevant articles related to vaccine target optimization and development that utilized machine learning algorithms and emerging AI technologies and appraising relevant studies to provide a comprehensive summary of the available evidence. It was discovered that incorporating machine learning algorithms and artificial intelligence has the potential to expedite and enhance vaccine development and rollout. AI facilitates the proficient analysis of extensive data sets, identifying patterns that might be missed by conventional methods. By scrutinizing the genomic data of pathogens, AI assists in pinpointing potential antigen targets for vaccine development. This results in creating more effective vaccines against specific strains or variants, accelerating the process. Targeted and efficient vaccine development is crucial during pandemics or when new infectious diseases emerge. Moreover, AI technologies can predict the potential effectiveness of vaccine candidates, detect side effects and adverse events, guarantee safety, and optimize dosage regimens. The application of AI in vaccine design and development offers several benefits but also presents several ethical considerations and challenges. In summary, MLA and other AI technologies can substantially improve vaccine target optimization, expedite development, and enhance the accuracy and speed of target selection, antigen design, and clinical trial optimization.

ARTICLE INFO

Received:
14 March 2023
Revised:
30 April 2023
Accepted:
04 May 2023

KEYWORDS:

Antigen selection, Artificial intelligence, Epitope optimization, Machine learning algorithms, Vaccines development

Corresponding author:
chukwuemeka.nworu@oliviauniversity.com; chukwuemeka.nworu@unn.edu.ng;+25767500003

1.0 INTRODUCTION

The importance of vaccines is immense, as they protect not only the individuals who receive them but also contribute to herd immunity, reducing the spread of infectious diseases in the general population. Vaccines have eradicated deadly diseases such as smallpox and significantly reduced the incidence of illnesses like polio, measles, and rubella. They are among the most effective methods for preventing infectious diseases and have saved millions of lives worldwide. Vaccines function by activating the body's immune system to identify and combat specific viruses or bacteria, thereby offering protection against future infections.

Machine learning and AI technologies have revolutionized vaccine development. By using these advanced technologies, the discovery and development of new vaccines, optimize their efficacy, and enhance safety can be expedited. Machine learning algorithms can analyze vast genomic datasets, identifying potential targets for vaccine development. These algorithms also help predict virus or pathogen mutations over time, enabling the design of more effective vaccines that keep up with rapidly evolving pathogens. AI technologies can optimize vaccine formulations, ensuring safety and effectiveness for all populations. Machine learning algorithms analyze clinical trial data, identifying patterns indicating adverse reactions or safety concerns [1]. The use of machine learning and AI in vaccine development has the potential to significantly improve public health outcomes by accelerating new vaccines' development and enhancing existing vaccines' safety and efficacy [2].

The number of publications discussing vaccine development and mentioning "Artificial Intelligence (AI)," "Machine Learning (ML)," "Reverse Vaccinology (RV)," and "in silico vaccine" has increased over the past five years [3]. This indicates a growing integration of these technologies into vaccine development programs. Reverse vaccinology (RV) is an in-silico approach that offers detailed preliminary predictions about vaccine candidates using genome sequences, which can be employed during the design of new recombinant vaccines [4]. Over the years, various vaccine designs targeting infectious pathogens and cancer neoantigens have been based on in silico predictions of potential HLA class I-restricted epitopes.

However, despite progress, many longstanding vaccine-specific challenges persist, and new unforeseen obstacles emerge, threatening global health and the worldwide economy. Some infectious diseases, such as human immunodeficiency virus, remain unpreventable by vaccination [5]. Many chronic infections require the development of new vaccines, including HIV, hepatitis B and C, tuberculosis, malaria, dengue fever, and chikungunya. HIV, tuberculosis, and malaria vaccines have not been successful due to antigenic variability and the requirement for T-cell immunity to ensure protection [6, 7]. Researchers are also working on developing therapeutic vaccines for chronic diseases such as hypertension, potentially replacing daily medication with a few annual administrations.

Vaccines play important role in combating infectious diseases. Incorporating machine learning algorithms and emerging AI technologies in vaccine candidate selection and optimization can address numerous challenges, resulting in faster development and implementation of safe and effective vaccines. The COVID-19 pandemic has highlighted the significance of AI in expediting vaccine development. In 2022, Sharma et al. [14], reported on "Artificial Intelligence-Based Data-Driven Strategy to Accelerate Research, Development, and Clinical Trials of COVID Vaccine". However, there is still a lack of current, comprehensive, and dependable review studies exploring the potential of machine learning algorithms and emerging AI technologies for vaccine target optimization. Moreover, additional research is required to thoroughly understand the advantages and limitations of employing these technologies in vaccine development. The study involved searching various academic databases such as PubMed, ScienceDirect, and Google Scholar. Relevant articles on vaccine target optimization and development using machine learning algorithms and emerging AI technologies were identified through a combination of keywords and Boolean operators. This review examines the application of machine learning algorithms (MLA) and artificial intelligence (AI) in vaccine development, focusing on identifying optimal vaccine targets and the significance of employing advanced technologies for the rapid development of effective vaccines against widespread and emerging infectious diseases.

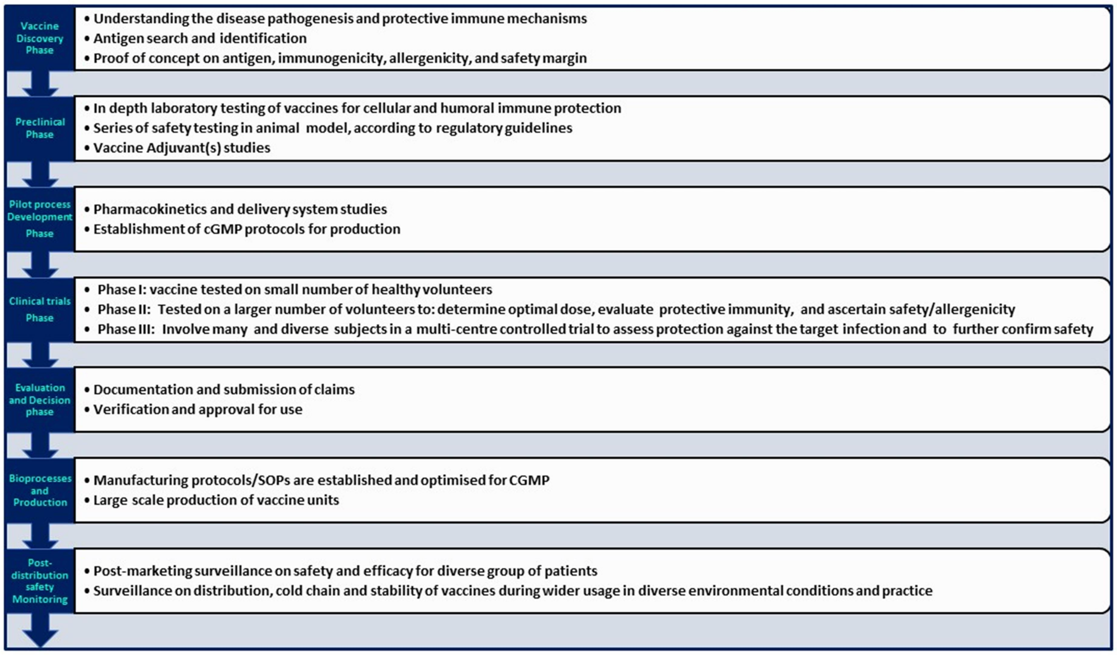

Figure 1: The traditional phases and processes of vaccine development, testing and, approval

1.1 Phases in Vaccine Development

The traditional vaccine design, testing, and development are complex processes that involve multiple phases that require extensive research and testing before a vaccine can be approved for public use (Figures 1 and 3). The following are the major phases of vaccine design, testing, and development:

1. Exploratory stage: In this stage, emphasis is to identify and select suitable antigen for the vaccine, which triggers specific and protective immune responses. Common methods used to identify antigens include genomics, proteomics, and bioinformatics.
2. Pre-clinical stage: In this stage, the vaccine candidate is tested in the laboratory and on animals to determine its safety and efficacy. The vaccine is optimized and formulated to ensure stability and effectiveness.
3. Clinical development: This stage involves testing the vaccine in humans in three phases: Phase 1, Phase 2, and Phase 3 (Figure 1 and 3).
4. Regulatory approval: Once the clinical trials are complete, the data is submitted to regulatory agencies such as the Food and Drug Administration (FDA) for approval.
5. Manufacturing: Once the vaccine is approved, it will be manufactured on a large scale and distributed to healthcare providers and facilities.
6. Post-marketing surveillance: After the vaccine is released to the public, investigators continue to monitor its safety and efficacy through post-marketing surveillance.

1.2 Definition of Machine Learning and AI Technologies

Artificial Intelligence (AI) is the simulation of human intelligence in machines programmed to execute tasks typically requiring human capabilities, such as visual perception, speech recognition, decision-making, and language translation. AI encompasses several subfields, including machine learning, natural language processing, robotics, expert systems, and computer vision (Figure 2). These subfields employ techniques like neural networks, deep learning, and reinforcement learning to create intelligent systems capable of learning from experience and enhancing performance over time.

Machine learning (ML) is a subset of artificial intelligence (AI) that involves training computer algorithms to learn from data and make predictions or decisions without being explicitly programmed to do so [8, 9]. This is done by feeding large amounts of data into a model, which then uses statistical techniques to identify patterns and relationships in the data. These patterns can then be used to make predictions about new data [10]. Deep learning is a subset of machine learning that uses artificial neural networks with multiple layers to analyze and extract patterns from complex datasets (Figure 2).

Artificial intelligence (AI) technologies, on the other hand, refer to a broader range of technologies that enable machines to perform tasks that would normally require human intelligence [11]. This includes natural language processing, computer vision, robotics, and more. The goal of AI is to create machines that can think, reason, and learn like humans.

Together, machine learning and AI technologies are revolutionizing industries ranging from healthcare to finance to transportation. By enabling machines to analyze vast amounts of data and make intelligent decisions based on that data, these technologies are helping organizations become more efficient, effective, and innovative. One example of AI being used in vaccine design is the development of a COVID-19 vaccine [12]. The Pfizer-BioNTech vaccine was developed using machine learning algorithms to predict which parts of the virus would generate the strongest immune response [13, 14]. This enabled the research team to quickly identify a promising vaccine candidate and move it into clinical trials [12, 15].

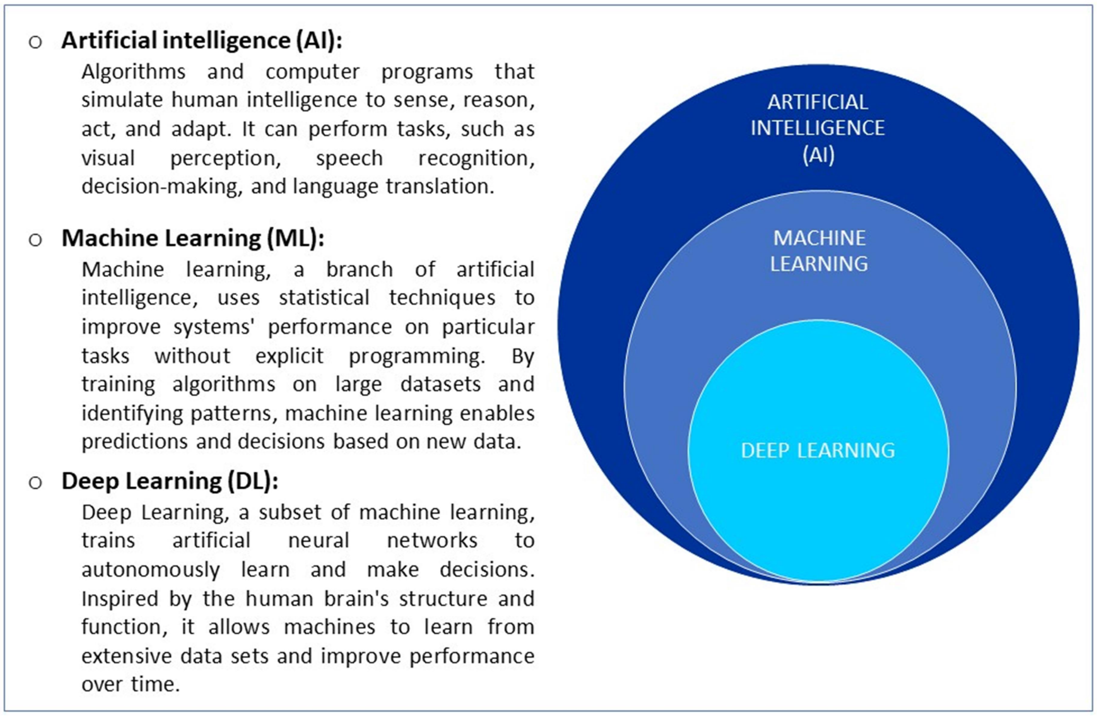

Figure 2: Artificial intelligence Machine Learning, and Deep Learning

1.3 Overview of the Applications of Machine Learning and AI Technologies in Vaccine Development

Machine learning and AI technologies have been increasingly applied in vaccine development to expedite the process of vaccine discovery, design, and optimization [16]. Machine learning and AI technologies have transformed the field of vaccine development in recent years. These technologies have been applied to various stages of vaccine development, including antigen selection, adjuvant identification, formulation optimization, and clinical trial design (Figure 3).

There are several advanced vaccine design software that have been created using AI and ML. These software use algorithms and machine learning techniques to predict the efficacy of different vaccine candidates and help researchers in designing new vaccines. Some of the popular vaccine design software created by ML/AI and their applications are presented in Table 1.

One of the key applications of machine learning and AI in vaccine development is in antigen selection [2]. Machine learning algorithms can analyse large datasets of viral sequences and identify conserved regions that could serve as potential vaccine targets. This approach has been used successfully in the development of vaccines for influenza, HIV, and other infectious diseases [9, 17].

Another important application of machine learning and AI in vaccine development is in adjuvant identification [18-21]. Adjuvants are compounds that are added to vaccines to enhance their efficacy by stimulating the immune system. Machine learning algorithms can analyze large datasets of adjuvant structures and predict which ones are most likely to be effective. This approach has been used to develop novel adjuvants for vaccines against cancer and infectious diseases [18, 21].

Machine learning and AI technologies can also be applied to formulation optimization, which involves identifying the optimal combination of antigens, adjuvants, and other components in a vaccine [22]. By analyzing large datasets of formulation data, machine learning algorithms can predict which combinations are most likely to be effective and safe.

Machine learning and AI can be used to design clinical trials for vaccines. By analyzing data from previous trials and other sources, these technologies can help in designing trials that are more efficient and effective [23].

Generally, the applications of machine learning and AI technologies in vaccine development hold great promise for accelerating the pace of vaccine discovery and improving global health outcomes. AI have the potential to fundamentally change the field of vaccine development by accelerating the discovery and optimization of new vaccines. As these technologies continue to evolve, we can expect to see even more innovative applications in this field.

1.4 Advantages of Using Machine Learning and AI Technologies in Vaccine Development

Machine learning and AI technologies have significantly enhanced vaccine development by accelerating the process, increasing accuracy, reducing costs, creating personalized vaccines, and identifying new targets [24, 25]. Here, some of the advantages of using these technologies are considered:

Speeding up the process: Vaccine development is a time-consuming process that can take years, if not decades, to complete. However, machine learning and AI technologies can help speed up the process by identifying potential vaccine candidates and predicting their efficacy. For example, machine learning algorithms can be used to analyze vast amounts of genomic data to identify potential targets for vaccines. This can significantly reduce the time it takes to develop a vaccine.

Improving accuracy: Machine learning algorithms can accurately predict which vaccine candidates are most likely to be effective based on large datasets of clinical trial results. This can help investigators avoid costly and time-consuming clinical trials for vaccines that are unlikely to be effective.

Reducing costs: Developing a new vaccine is an expensive process that requires significant investment in research and development. By using machine learning and AI technologies, potential vaccine candidates could be identified quickly and accurately, which can help reduce the overall cost of vaccine development.

Personalized vaccines: Machine learning algorithms can be used to analyze an individual's genetic makeup and immune system response to identify personalized vaccine candidates. This could lead to more effective vaccines with fewer side effects.

Identifying new targets: Machine learning algorithms can analyze vast amounts of genomic data to identify new targets for vaccines. This could lead to the development of vaccines for diseases that were previously thought to be untreatable.

1.5 Recent Successes of AI Technologies in Vaccine Development

Vaccines have been a crucial aspect of modern medicine and have helped to eradicate or control many infectious diseases. The development of vaccines has been a long and complex process that requires extensive research, testing, and clinical trials. With the advent of artificial intelligence (AI), the process of vaccine development has been revolutionized. AI has enabled the analysis of large amounts of data quickly and accurately, identify potential targets for vaccines, and design new vaccine candidates.

One example of a vaccine target that has been identified with the help of AI is the human papillomavirus (HPV). HPV is a common sexually transmitted infection that can cause cervical cancer, among other health problems. Genetic data from HPV and identified specific proteins that could be targeted by a vaccine was analyzed using AI [26]. This led to the development of the HPV vaccine, which has been highly effective in preventing cervical cancer.

Another example is the flu vaccine. Every year, strains of the flu virus that will be most prevalent in the upcoming flu season are analyzed using AI and appropriate vaccine(s) developed accordingly. This process can be time-consuming and imprecise. However, AI has been used to analyze data on previous flu seasons, as well as information on how the virus mutates over time [27, 28]. This has led to more accurate predictions and more effective flu vaccines. AI has also been used in the development of COVID-19 vaccines [12, 16, 29]. It was possible to use AI to analyze the genetic sequence of the virus and identify potential targets for vaccines. This enabled them to develop multiple vaccine candidates in record time, with some vaccines being approved for emergency use within a year of the start of the pandemic.

In recent years, robotics, a branch of AI, has significantly contributed to vaccine development by accelerating the process and enhancing accuracy. The influenza vaccine, one of the most prevalent worldwide, protects against the flu virus. Robotics has aided its deve lopment in various ways, such as employing robots to identify new flu virus strains for creating novel vaccines. Robots assist in testing the efficacy of various vaccine formulations and this facilitates the identification of the most effective options [30-32].

In addition to these examples, AI has been used in many other aspects of vaccine development (Figure 2), including clinical trial design, manufacturing optimization, and post-market surveillance.

2.0 MACHINE LEARNING AND AI TECHNOLOGIES FOR VACCINE DESIGN

AI tools can improve the speed, accuracy, and efficiency of vaccine development by enabling faster and more accurate identification of potential vaccine targets and increasing our understanding of vaccine interactions with the immune system [14, 33]. Various AI technologies have been employed in vaccine design and these include:

(a). **Machine Learning Algorithms (MLA)** - These can be trained on extensive datasets of genomic and proteomic data to identify patterns and predict potential vaccine targets. For instance, machine learning algorithms have been employed to identify potential epitopes for a COVID-19 vaccine based on the virus's genome sequence [12, 29].

(b) **Structural Biology tools** - Structural biology tools, such as X-ray crystallography and cryo-electron microscopy, can be used to determine the structure of viral proteins and identify potential vaccine targets. AI technologies can be used to analyze these structures and predict how they will interact with the immune system.

(c) **Computational modelling**- Computational modelling can simulate vaccine interactions with the immune system and predict efficacy. AI technologies optimize these models and identify potential improvements in vaccine design.

(d) **Natural language processing (NLP)**- NLP can be used to analyze scientific literature and identify potential vaccine targets or drug candidates. For instance, NLP has been utilized to discover potential drugs for COVID-19 by examining relevant scientific papers [12, 29].

2.1 Overview of Vaccine Design Process

Vaccine design is a complex process involving several stages: target identification, antigen selection, formulation development, preclinical testing, clinical trials, and regulatory approval [34]. The goal is to develop safe and effective vaccines that stimulate the immune system to produce a protective response against specific pathogens.

In the target identification stage, a specific target within the pathogen is identified by studying its biology and understanding its interaction with the immune system. After identifying an appropriate target, antigens capable of stimulating an immune response against the pathogen are chosen. These selected antigens are typically proteins or other molecules on the pathogen's surface that can be recognized by the immune system.

Formulation development entails selecting adjuvants and additional components to enhance the vaccine's immune response. Adjuvants are substances that stimulate the immune system and increase vaccine effectiveness. Preclinical testing assesses the safety and efficacy of a vaccine in animal models before advancing to clinical trials in humans.

Clinical trials involve evaluating the vaccine's safety and effectiveness in human volunteers. Regulatory approval, such as from the FDA in the United States, is necessary for marketing and distributing vaccines to the public, ensuring they are safe and effective based on preclinical and clinical study data. Generally, vaccine design is a complex process necessitating collaboration among scientists, clinicians, regulatory agencies, and other stakeholders. Nonetheless, it is crucial for developing vaccines that protect against infectious diseases.

2.2 Techniques used for Designing Vaccines Using Machine Learning

The traditional approach for vaccine development is time-consuming and involves a trial-and-error process [35]. However, with the advent of machine learning, it has become possible to design vaccines more efficiently and accurately. There are several techniques used for designing vaccines using machine learning. Some of them are:

Reverse Vaccinology: This technique involves the identification of potential antigens in a pathogen's genome. Machine learning algorithms can predict which parts of the genome are most likely to produce effective antigens [36]. This approach has been successfully used to develop vaccines for diseases such as meningitis B.

Epitope-based Vaccines: Epitopes are small parts of a pathogen's antigen that are recognized by the immune system. Machine learning algorithms can predict which epitopes are most likely to be effective in triggering an immune response [37].

This approach has been used to develop vaccines for diseases such as influenza.

Table 1: Some examples of AI-driven advanced vaccine design tools and their applications

Vaccine Design Software	Application of Software in Vaccine Design and Development
EpiMatrix®	EpiMatrix® uses AI and ML algorithms to predict the immunogenicity of different peptides and proteins. The software can also identify potential T-cell epitopes, which are important for inducing a robust immune response.
DeepVacPred	DeepVacPred® is a web server that predicts potential vaccine candidates against pathogens using deep learning algorithms
Vaxign®	Vaxign® can analyze genomic data from pathogens and identify potential vaccine targets. It can also predict the likelihood of a vaccine candidate inducing an immune response.
iVAX®	iVAX® uses AI and ML algorithms to predict the immunogenicity of different peptides and proteins. The software can also identify potential T-cell epitopes and predict the likelihood of a vaccine candidate inducing an immune response.
AlfaPred®	AlfaPred® is a web server tool, based on a machine learning algorithm, that predicts the potential of protein-ligand binding sites in a given protein structure. The algorithm uses a support vector machine (SVM) to classify potential binding sites as either "ligand-binding" or "non-binding". The analysis examines features of the protein structure, including shape, electrostatics, and surface area, to predict the likelihood of a ligand binding to a specific site on the protein.
Immune Profiler®	Immune Profiler® uses advanced algorithms to analyze large datasets, providing accurate immune response data from various sources like flow cytometry, RNA sequencing, and mass cytometry. It offers a comprehensive analysis of the immune response by identifying different cell types, their functions in the immune system, and biomarkers associated with various diseases and conditions.
Vaxrank®	Vaxrank® is a computational tool for selecting neoantigen vaccine peptides from tumour mutations, tumour RNA data, and patient HLA type. It is a Python package that can be installed from the Python Package Index.
Generative Adversarial Networks (GANs)	Generative Adversarial Networks (GANs) are deep learning algorithms used to create new, unseen data from existing datasets. Comprising two neural networks- a generator that produces fake data and a discriminator that evaluates its authenticity. GANs show potential in vaccine design and development. They generate synthetic data to identify immunogenic components of pathogens, optimize adjuvant design, and predict pathogen evolution.
Vaxjo®	A database of vaccine adjuvants that provides information on the chemical properties, mechanisms of action, and safety profiles of different adjuvants, allowing researchers to select the most appropriate ones for their vaccine formulations.

Structural Vaccinology: This technique involves the use of computational methods to predict the structure of a pathogen's antigens [38]. Machine learning algorithms can analyze the structure and predict which parts are most likely to be effective in triggering an immune response. This approach has been used to develop vaccines for diseases such as HIV [39].

3.0 VACCINE TARGET IDENTIFICATION AND OPTIMIZATION USING MACHINE LEARNING

Vaccine target identification and optimization are essential steps in vaccine development, involving the recognition of specific pathogen components that stimulate immune responses and their enhancement for increased effectiveness [40]. Machine learning has become a valuable tool in this process, enabling the analysis of extensive data and accurate identification of potential vaccine targets. These algorithms can analyze vast amounts of genomic, proteomic, and other data to pinpoint potential vaccine targets. These algorithms can be utilized to predict the efficacy of various vaccine candidates and optimize their design. By integrating machine learning with tools like structural biology and immunology, more effective vaccines against a broad spectrum of pathogens can be created [41]. In summary, vaccine target identification and optimization using machine learning is an exciting area of research with enormous potential for improving global health

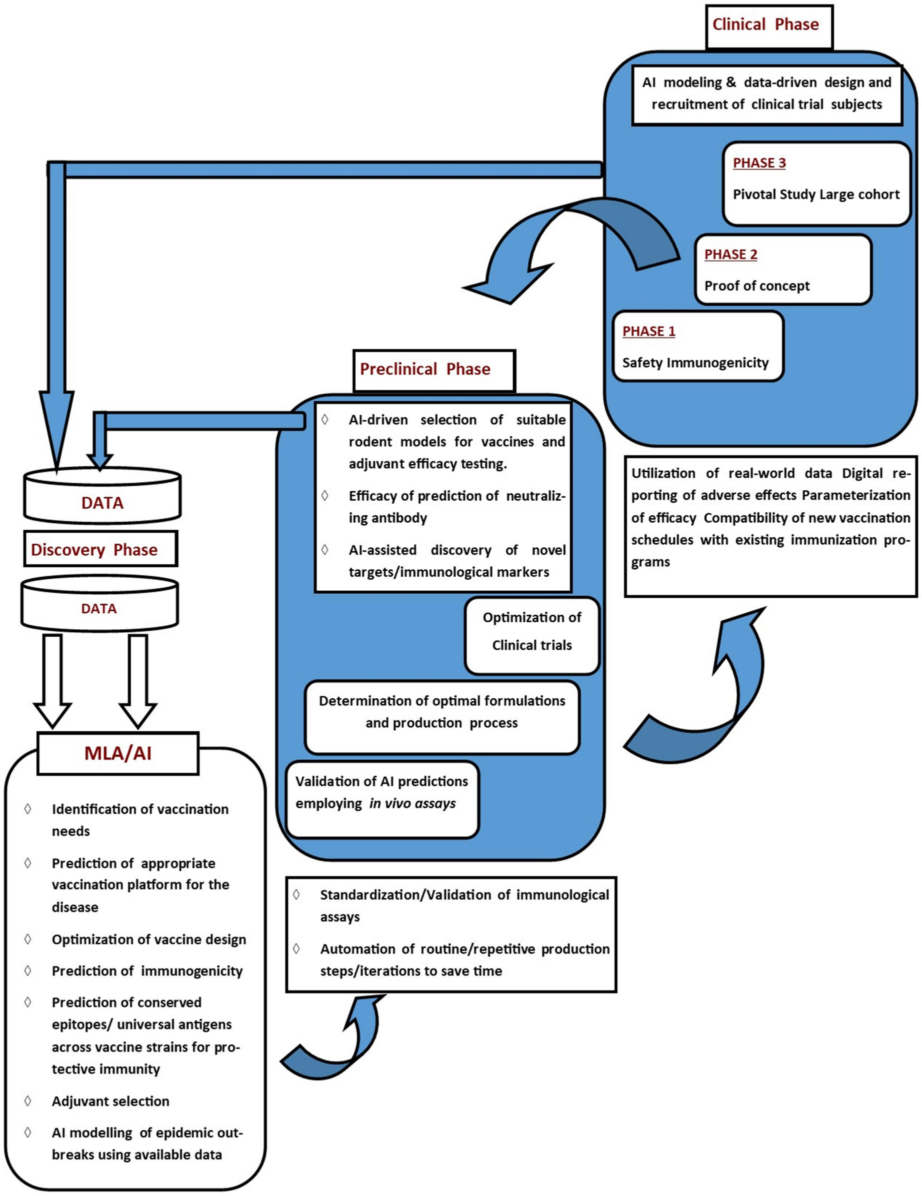

Figure 3: Schematic Representation of the role of machine learning algorithms and emerging AI technologies in vaccines target identification, design optimization and testing

3.1 Importance of Identifying the Right Antigen/Epitope Targets for Vaccine Design and Development

Identifying the right antigen/epitope targets for a vaccine is crucial in maximizing efficacy, minimizing side effects, and reducing cross-reactivity [42]. This requires a thorough understanding of the pathogen's biology, the host immune response, and the available technologies for antigen/epitope identification. An antigen is a substance that triggers an immune response, while an epitope is the specific part of the antigen that is recognized by the immune system. The immune system produces antibodies that recognize and bind to these epitopes, which then help to neutralize or eliminate the pathogen. Therefore, identifying the right antigen/epitope target(s) for a vaccine is crucial in developing an effective vaccine. In this section, we examine and discuss the importance of accurately identifying the appropriate antigen/epitope targets for a vaccine:

(a). **Maximizing vaccine efficacy:** The immune system can only respond to a limited number of epitopes at any given time. Therefore, it is important to identify the epitopes that are most likely to induce a strong and long-lasting immune response [43]. By targeting the right epitopes, vaccine developers can maximize the efficacy of their vaccines and provide better protection against the targeted pathogen.

(b). **Minimizing side effects:** Vaccines can sometimes cause side effects, such as fever, soreness at the injection site, or allergic reactions. By identifying the right epitopes, vaccine developers can minimize these side effects by avoiding non-essential parts of the antigen that may trigger unwanted immune responses [43].

(c). **Reducing cross-reactivity:** Some pathogens may share similar antigens or epitopes with other organisms or even with our own cells. If a vaccine targets an antigen or epitope that is too similar to those found in our own cells or harmless organisms, it may lead to cross-reactivity and autoimmunity. By identifying unique and specific epitopes, vaccine developers can reduce the risk of cross-reactivity and autoimmunity [44].

3.2 The Role of Machine Learning in Identifying Potential Vaccine Targets

Machine learning is employed in identifying potential vaccine targets, which are specific molecules or structures on a pathogen recognized by the immune system. This crucial step aids in developing effective vaccines. By analyzing extensive data from various sources, machine learning algorithms help identify conserved regions

within a pathogen's genome or proteome, serving as potential vaccine targets [45]. This leads to more efficient and accurate vaccine development efforts.

Machine learning algorithms can analyze vast amounts of data from various sources, such as genomic and proteomic data, to identify potential vaccine targets. For instance, these algorithms can examine the genetic sequences of different virus strains to pinpoint conserved regions that may serve as potential vaccine targets. Moreover, machine learning can predict which parts of a pathogen's proteins are most likely to be recognized by the immune system.

Several types of machine learning algorithms are utilized in identifying potential vaccine targets, including [14]:

(a). Supervised learning: Supervised learning involves training a machine learning algorithm on pre-classified data to predict the classification of new, unlabeled data. In identifying vaccine targets, this method can classify various regions of a pathogen's genome or proteome as potential vaccine targets or not.

(b). **Unsupervised learning:** This involves training a machine learning algorithm on a set of unlabeled data to identify patterns or clusters within the data. In the context of identifying vaccine targets, unsupervised learning can be used to detect conserved regions within a pathogen's genome or proteome that may serve as potential vaccine targets.

(c). **Deep learning:** This involves training a neural network with multiple layers to learn complex representations of data. In the context of identifying vaccine targets, deep learning can be used to predict which parts of a pathogen's proteins are most likely to be recognized by the immune system.

Thus, it is evident that using machine learning for identifying potential vaccine targets provides significant benefits such as speed, accuracy, and flexibility. These algorithms can quickly and accurately analyze vast amounts of data, allowing efficient recognition of potential vaccine targets. Furthermore, machine learning can detect patterns and relationships in data that may not be evident to human, resulting in more accurate predictions. In terms of flexibility, machine learning algorithms can be applied to various data types, such as genomic and proteomic data. This allows the identification of potential vaccine targets for various pathogens.

3.3 Techniques Used for Optimizing Vaccine Targets Using Machine Learning

As explored in previous sections, machine learning has substantially improved vaccine development by effectively identifying and optimizing vaccine targets. These targets are specific components of a pathogen that the immune system recognizes and combats. Moreover, machine learning assists in predicting immunogenicity, designing antigens, selecting adjuvants, and optimizing vaccines comprehensively. This technology has the potential to facilitate a quicker and more efficient response to emerging infectious diseases [1].

Here are some techniques used for optimizing vaccine targets using machine learning:

(a). **Epitope prediction:** Epitopes are specific components of a pathogen that the immune system recognizes and targets. Machine learning algorithms can predict epitopes based on the pathogen's genetic sequence by analyzing the data and identifying regions likely to be recognized by the immune system. This information can then aid in designing vaccines targeting these specific epitopes.

(b). **Immunogenicity prediction**: Immunogenicity refers to a vaccine's capacity to elicit an immune response. Machine learning algorithms can be used to predict the immunogenicity of different vaccine candidates based on their chemical properties and structure [46]. This helps in the identification of the most promising vaccine candidates for further testing.

(c). **Antigen design:** Antigens are the molecules that stimulate an immune response. Machine learning can enhance antigen design, making them more effective in eliciting strong immune reactions [47]. This process involves analyzing extensive data on antigen structure and function to identify patterns associated with robust immune responses.

(d). **Adjuvant selection**: Adjuvants are substances added to vaccines to enhance their effectiveness. Machine learning can be utilized to identify the most effective adjuvants in stimulating an immune response [22]. This process involves analyzing data on adjuvant structure and function, identifying patterns associated with strong immune responses.

(e). Vaccine optimization: Machine learning can be used to optimize vaccines by predicting how different combinations of antigens and adjuvants will interact with each other and with the immune system [20]. This helps in the design of vaccines that are more effective at stimulating an immune response.

4.0 PREDICTIVE MODELLING FOR VACCINE DEVELOPMENT

Predictive modelling for vaccine development employs statistical and computational techniques to identify potential candidates and predict their efficacy. This method analyses extensive data from sources such as genomic sequences, immunological assays, and clinical trials to create models that accurately forecast the immune response to a specific vaccine. Ultimately, predictive modelling for vaccine development is a potent tool with the potential to transform vaccine design and development. Using big data and sophisticated computational methods, can hasten the discovery process, enhance vaccine formulations, and ultimately boost global health outcomes.

4.1. Application of Predictive Modelling in Vaccine Development

Predictive modelling is a powerful tool in vaccine development that involves the use of mathematical algorithms and statistical analysis to predict the efficacy, safety, and immunogenicity of a vaccine candidate. This approach can help in the identification of the most promising vaccine candidates, optimize dosing regimens, and accelerate the development process.

One of the key applications of predictive modelling in vaccine development is in the design of clinical trials. By using mathematical models to simulate different scenarios, the optimal sample size, duration, and endpoints for a clinical trial can be estimated. This can help to reduce the cost and time required for clinical testing, while also improving the accuracy and reliability of the results.

Another important application of predictive modelling is in the assessment of vaccine safety. By analyzing data from preclinical studies and early-stage clinical trials, the potential safety concerns and predict adverse events that may occur in larger populations can be identified. This can help to guide decision-making around vaccine development and ensure that only safe and effective vaccines are brought to market.

Lastly, predictive modelling can also be used to optimize vaccine dosing regimens. By simulating different dosing schedules and routes of administration, the most effective and efficient way to deliver a vaccine to achieve maximum immunogenicity with minimal side effects can be recognized.

Thus, predictive modelling is a valuable tool in vaccine development, assisting investigators in designing efficient clinical trials, assessing safety concerns, and optimizing dosing regimens. Consequently, it has become an increasingly significant component of the vaccine development process in recent years.

4.2. Types of Predictive Models Used in Vaccine Development

There are several types of predictive models used in vaccine development. These models help in the understanding of the immune system and its response to different vaccines. Some of the most common types of predictive models used in vaccine development include:

(a). **Preclinical Models:** Preclinical models, such as animal and in vitro models, are essential in vaccine development. Animal models involve using laboratory animals, like mice, rats, and non-human primates, to study the immune response to a vaccine in a living organism [48-50]. These models also help test the safety and efficacy of a vaccine before human trials. In vitro models, on the other hand, examine the immune response to a vaccine in a controlled laboratory setting. This involves assessing the immune cells' response to a vaccine antigen in culture and analyzing the interaction between the vaccine antigen and specific proteins or molecules.

(b). **Computational Models:** Computational models employ mathematical algorithms and computer simulations to forecast the immune response to a vaccine [51, 52]. These models help identify potential targets for vaccines, optimize vaccine design, and anticipate the response of various populations to a vaccine.

(c). **Epidemiological models:** Epidemiological models use data from outbreaks and epidemics to predict disease spread and assess vaccine effectiveness in controlling an outbreak [53]. They also identify high-risk populations and prioritize vaccination efforts. Ultimately, these predictive models greatly contribute to vaccine development by improving investigators' understanding of immune responses and identifying potential targets for new vaccines.

4.3. Advantages of Using Predictive Modelling in Vaccine Development

Predictive modelling in vaccine development has numerous advantages that can help accelerate the process of creating safe and effective vaccines [54, 55].

Firstly, predictive modelling allows for the identification of potential vaccine candidates with a higher likelihood of success. This is done by analyzing large amounts of data from previous studies and clinical trials, as well as genetic and molecular information about the pathogen being targeted. By using this data, vaccinologists can create models that predict which vaccine candidates are most likely to be effective, reducing the need for costly and time-consuming experimentation.

Secondly, predictive modelling can also help optimize vaccine design by predicting how different formulations and dosages will affect immune responses. This can help in fine-tuning vaccines to maximize efficacy while minimizing potential side effects.

Finally, predictive modelling can aid in the development of personalized vaccines tailored to an individual's specific genetic makeup [72, 73]. By analyzing an individual's genetic data, models that predict which vaccine formulations will be most effective for an individual can be created.

Overall, the use of predictive modelling in vaccine development has the potential to greatly improve the efficiency and effectiveness of the vaccine development process.

5.0 CHALLENGES AND LIMITATIONS OF MACHINE LEARNING AND AI TECHNOLOGIES IN VACCINE DEVELOPMENT

Machine learning and AI technologies demonstrate significant potential in vaccine development; however, they also encounter numerous challenges and limitations [14, 15]. A primary obstacle is the availability of reliable data. Accurate training of machine learning algorithms necessitates vast amounts of high-quality data, which is often limited or incomplete in vaccine development. Furthermore, the diversity of pathogens and their rapid evolution present a considerable challenge for machine learning algorithms to accurately predict a vaccine's efficacy. Additionally, ethical concerns arise regarding the use of AI in vaccine development [56]. The use of AI raises concerns regarding transparency, accountability, and bias. It is essential to guarantee that AI algorithms are transparent and unbiased to prevent unintended consequences in vaccine development.

Moreover, machine learning algorithms' effectiveness depends on the quality of the data they are trained on. In vaccine development, there is a risk that the data used for training an algorithm may not adequately represent the population's diversity. This issue could result in biased predictions and inaccurate outcomes.

5.1 Ethical Considerations in Using Machine Learning and AI Technologies in Vaccine Development

The development and efficacy of vaccines have improved with the advent of artificial intelligence (AI) technologies. While these technologies offer significant benefits, they also raise ethical issues and considerations that must be addressed to ensure responsible and just usage. This section considers some specific examples of ethical issues in employing AI technologies in vaccine design and development [58].

One significant concern in using AI technologies is the potential for bias and discrimination [56, 57]. AI algorithms can only be as unbiased as the data they are trained on. If the data utilized for training an algorithm is biased, it will result in a biased algorithm. This can cause discrimination against specific groups, such as ethnic minorities or individuals with certain medical conditions, in vaccine design and development. The employment of AI technologies in this field necessitates the gathering and analysis of vast amounts of sensitive data, including personal health information. Guaranteeing privacy and data security is crucial to avoid unauthorized access or misuse of such information.

It is imperative to ensure that AI algorithms' decisions are transparent, explainable, and accountable. For example, there is some concern that reliance on AI could lead to a decrease in human oversight and accountability, potentially leading to unsafe or ineffective vaccines.

This is particularly important for critical decisions, such as vaccine efficacy and safety. The use of AI technologies in vaccine design and development raises questions about intellectual property rights [58]. Who owns the intellectual property rights to a vaccine designed using AI technologies? Should these rights be shared among all stakeholders involved in its development? Additionally, concerns about access and equity arise. Will vaccines designed using AI technologies be accessible to everyone, regardless of their socioeconomic status or geographic location?

To address ethical issues and considerations, developing guidelines and regulations promoting responsible and just use of AI technologies in vaccine design and development is essential. These guidelines should ensure unbiased, transparent, and accountable AI algorithms while maintaining privacy and data security [59].

5.2 Limitations and Challenges Faced When Using Machine Learning and AI Technologies in Vaccine Development

Besides these ethical considerations, there are also several challenges associated with the use of AI technologies in vaccine design and development.

AI algorithms require high-quality data for precise predictions [60]. In vaccine design, this involves gathering extensive data from diverse populations, which can be challenging. A significant limitation is the absence of comprehensive data on immune responses to infectious diseases [61]. AI algorithms depend on large datasets to recognize patterns and make predictions; however, current data on the immune system's reaction to pathogens is limited. This hinders AI systems from accurately predicting the effectiveness of potential vaccines. Additionally, the immune system's complexity poses another challenge. The immune system, with its highly complex and dynamic nature, comprises numerous cell types and signaling pathways that respond to infections. AI algorithms might face challenges in capturing this complexity and accurately modelling the immune response [62].

Another challenge is algorithm validation. AI algorithms must be validated using rigorous scientific methods to ensure that they are accurate and reliable. This requires extensive testing on real-world data sets, which can be time-consuming and costly.

A third challenge is regulatory approval. AI technologies are subject to regulatory approval, and the regulatory landscape for AI in healthcare is still evolving. Navigating intricate regulatory frameworks is a challenge that must be overcame to ensure their AI algorithms are approved for use in vaccine design and development. Despite these challenges, AI technologies continue to demonstrate potential in vaccine design and development. Biomedical scientists, immunologists, vaccinologists, biostatisticians, and AI experts are addressing these limitations by improving data collection methods, developing sophisticated algorithms, and integrating ethical considerations.

5.3 Strategies to Overcome These Limitations and Challenges

This section x-rays some specific steps that could be taken to overcome these limitations and challenges:

One of the biggest challenges in using AI for vaccine design is the availability and quality of data. AI algorithms rely on vast amounts of high-quality data to learn and make accurate predictions. In the case of vaccines, there might be limited data available on the targeted disease or pathogen, particularly for emerging or rare diseases. To overcome this limitation, data augmentation techniques to generate synthetic data or merge multiple datasets to enlarge the sample size can be employed by investigators [63]. Furthermore, efforts can be made to enhance the quality of existing data through standardization and curation. At times, comprehending the reasoning behind an AI system's prediction or decision can be challenging, potentially affecting trust and acceptance from regulators and healthcare providers. To tackle this interpretability and transparency issue, employing explainable AI techniques that offer insights into the algorithms' functionality and the features utilized for making predictions is essential [64, 65]. This approach will enhance transparency and foster trust in the technology.

The use of AI in vaccine design also raises ethical considerations regarding privacy, bias, and fairness. If AI algorithms use biased data, they might exacerbate existing disparities in healthcare access and outcomes [66]. To mitigate these concerns, investigators should ensure their data is representative and unbiased while designing algorithms that prioritize fairness and equity.

In summary, despite the limitations and challenges in using AI technologies for vaccine design and development, addressing data quality and quantity, interpretability, transparency, and ethical considerations can harness AI's potential to expedite the deployment of safe and effective vaccines.

6.0. FUTURE DIRECTIONS FOR MACHINE LEARNING AND AI TECHNOLOGIES IN VACCINE DEVELOPMENT

By enabling faster and more accurate identification of vaccine candidates, predicting potential side effects, and optimizing dosages, AI technologies have already revolutionized vaccine design and development. There are still potentials and possibilities in these areas. Specific future possibilities in the use of AI technologies in vaccine design and development will include in the areas of identification of vaccine candidates, prediction of potential side effects, and optimization of dosages.

AI algorithms can be used to analyze large amounts of genomic data from pathogens and identify potential vaccine targets for emerging infection threats and pandemic. Machine learning models are being trained already on past successful vaccines to predict which antigens are most likely to elicit an immune response. This approach has already been used to develop a vaccine for H7N9 influenza virus, which was able to induce a protective immune response in animal models.

In the near future, AI could accurately predict potential vaccine side effects by analyzing extensive data from clinical trials and post-market surveillance. Machine learning models can identify patterns in adverse event reports and determine which patients are most at risk for developing side effects. This would aid in designing safer vaccines and identifying patients who may require closer monitoring after vaccination.

In the future, AI may optimize vaccine dosages and personalize vaccine regimens by analyzing clinical trial data and identifying optimal doses for various patient populations. Machine learning models, trained on previous trial data, can predict patient population responses to different doses, enabling the development of more effective vaccines.

6.1 Potential Future Applications of Machine Learning and AI Technologies in Vaccine Development

Some potential future applications of AI technologies in vaccine design and development include: identification of potential vaccine targets, rational vaccine design, optimization of vaccine formulations, production process optimization and quality assurance, and real-time monitoring of vaccine safety

AI technologies can be used to identify potential vaccine targets by analyzing large amounts of data from various sources, including genomic, proteomic, and clinical data. For example, machine learning algorithms can be used to analyze the genetic sequences of viruses and identify regions that are highly conserved across different strains. These conserved regions can then be targeted for vaccine development.

AI technologies can also be used to design vaccines rationally by predicting the structure and function of viral proteins and identifying regions that are most likely to elicit an immune response. For example, computational methods can be used to predict the three-dimensional structure of viral proteins and identify regions that are exposed on the surface and likely to interact with antibodies.

Machine learning and AI technologies can also be used to optimize vaccine formulations by predicting the optimal combination of antigens, adjuvants, and delivery systems that will elicit a robust immune response. For example, machine learning algorithms can be used to analyze data from clinical trials and identify factors that contribute to vaccine efficacy, such as dose, route of administration, and timing.

Accelerated clinical trials can be made possible by AI technologies. This can be achieved by predicting which candidate vaccines are most likely to succeed in clinical trials. For example, machine learning algorithms can be trained on data from previous clinical trials to predict which vaccines are most likely to succeed based on factors such as safety, immunogenicity, and efficacy.

Furthermore, it is possible to monitor the safety of vaccines in real-time by analyzing data from electronic health records and social media platforms. For example, machine learning algorithms can be used to identify adverse events associated with vaccines and alert public health officials in real-time.

6.2 Areas Where Further Research is Needed to Improve the Use of Machine Learning and AI Technologies in Vaccine Development

Further research is needed to address the challenges associated with integrating diverse data sources, developing accurate predictive models, optimizing clinical trials, designing effective vaccines, and ensuring ethical considerations are met [1, 14, 15].

Data Integration: One of the biggest challenges in vaccine development is integrating data from different sources. Machine learning algorithms can help in integrating data from various sources such as clinical trials, electronic health records, and genomic data [67]. However, further research is needed to develop algorithms that can integrate these diverse data sources seamlessly.

Predictive Modelling: Predictive modelling can help in identifying potential vaccine candidates by analyzing large datasets. Machine learning algorithms can be used to predict which vaccines are likely to be successful based on factors such as antigenicity, immunogenicity, and efficacy [68]. However, further research is needed to develop more accurate predictive models that take into account the complexity of the immune system and the variability of human responses.

Optimization of Clinical Trials: Clinical trials are a crucial part of vaccine development, but they can be time-consuming and expensive. Machine learning algorithms can help in optimizing clinical trials by identifying patient subgroups that are most likely to respond positively to a vaccine or by predicting adverse events before they occur [69, 70]. However, further research is needed to develop algorithms that can handle the large amounts of data generated by clinical trials and take into account factors such as patient demographics, genetics, and environmental factors.

Automated Vaccine Design: Machine learning algorithms can be used to design new vaccines by predicting which antigens are most likely to elicit an immune response. However, further research is needed to develop algorithms that can design vaccines that are effective against multiple strains of a virus or bacteria [41].

Ethical Considerations: The use of machine learning and AI technologies in vaccine development raises ethical concerns such as privacy, bias, and transparency [70, 71]. Further research is needed to develop ethical guidelines for the use of these technologies in vaccine development and to ensure that they are used in a way that benefits all members of society.

CONCLUSION

In conclusion, the use of machine learning algorithms and emerging AI technologies in vaccine target optimization and development holds immense potentials for a comprehensive and positive transformation of the immunology and vaccinology fields. These tools have the ability to rapidly identify potential targets, predict their efficacy, and optimize vaccine formulations for maximum effectiveness. However, further research is needed to fully harness the power of these technologies and to ensure their safe and ethical implementation. As we continue to explore the possibilities of AI in healthcare, it is important to prioritize collaboration between experts in computer science, immunology, vaccinology, and pharmaceutical sciences in order to devise effective and responsible vaccine solutions.

CONFLICT OF INTEREST

The authors have no sponsorship, commercial interest, or conflict of interest in writing this review paper.

REFERENCES

1. Thomas S, Abraham A, Baldwin J, Piplani S, Petrovsky N. Artificial Intelligence in Vaccine and Drug Design. Methods Molecular Biology. 2410, 2022, 131-146.
2. McCaffrey P. Artificial Intelligence for Vaccine Design. Methods Molecular Biology 2412, 2022, 3-13.
3. Nevmerzhitskaya A, Gromova M, Pfleiderer M. Designing Vaccines: The Role of Artificial Intelligence and Digital Health, Part 1. BioProcess Int. 2021. Accessed April 22, 2023. https://bioprocessintl.com/manufacturing/information-technology/in-silico-vaccine-design-the-role-of-artificial-intelligence-and-digital-health-part-1
4. Kanampalliwar AM. Reverse Vaccinology and Its Applications. Methods Molecular Biology 2131, 2020, 1-16.
5. Heaton PM. Challenges of Developing Novel Vaccines with Global Health Importance. Front Immunol. 11:517290, 2020.
6. Rios A. Fundamental challenges to the development of a preventive HIV vaccine. Current Opinion in Virology 29, 2018, 26-32.
7. Karch CP, Matyas GR. The current and future role of nanovaccines in HIV-1 vaccine development. Expert Review Vaccines. 20(8), 2021, 935-944.
8. Goodfellow I, Bengio Y, Courville A. Deep learning (1st ed.). Cambridge, MA: MIT Press, 2016.
9. Goodswen SJ, Barratt JLN, Kennedy PJ, Kaufer A, Calarco L, Ellis JT. Machine learning and applications in microbiology. FEMS Microbioliology Review. 45(5): fuab015, 2021.
10. Murphy KP. Machine learning: A probabilistic perspective (1st ed.). Cambridge, MA: MIT Press., 2012
11. Russell SJ, Norvig P. Artificial Intelligence: A Modern Approach. 4th ed. Pearson; 2020.
12. Bhatia M, Manocha A, Ahanger TA, Alqahtani A. Artificial intelligence- inspired comprehensive framework for Covid-19 outbreak control. Artificial Intelligence Medicine 127:102288, 2022
13. Naseem M, Akhund R, Arshad H, Ibrahim MT. Exploring the Potential of Artificial Intelligence and Machine Learning to Combat COVID-19 and Existing Opportunities for LMIC: A Scoping Review. Journal of Primary Care and Community Health. 11:2150132720963634; 2020
14. Sharma A, Virmani T, Pathak V, Sharma A, Pathak K, Kumar G, Pathak D. Artificial Intelligence-Based Data-Driven Strategy to

Accelerate Research, Development, and Clinical Trials of COVID Vaccine. Biomed Res Int. 2022:7205241, 2022

15. Lv H, Shi L, Berkenpas JW, Dao FY, Zulfiqar H, Ding H, Zhang Y, Yang L, Cao R. Application of artificial intelligence and machine learning for COVID-19 drug discovery and vaccine design. Brief Bioinformatics. 22(6): bbab320; 2021. doi: 10.1093/bib/bbab320
16. Bali A, Bali N. Role of artificial intelligence in fast-track drug discovery and vaccine development for COVID-19. Novel AI and Data Science Advancements for Sustainability in the Era of COVID-19. 2022: 201–29.
17. Myers ML, Gallagher JR, Kim AJ, Payne WH, Maldonado-Puga S, Assimakopoulos H, Bock KW, Torian U, Moore IN, Harris AK. Commercial influenza vaccines vary in HA-complex structure and in induction of cross-reactive HA antibodies. Natural Communications 4(1), 2023: 1763.
18. Chaudhury S, Duncan EH, Atre T, Storme CK, Beck K, Kaba SA, Lanar DE, Bergmann-Leitner ES. Identification of Immune Signatures of Novel Adjuvant Formulations Using MachineLearning. Scientific Reports. 8(1); 2018: 17508.
19. O'Hagan DT, Lodaya RN, Lofano G. The continued advance of vaccine adjuvants - 'we can work it out'. Seminars in Immunology.50:101426; 2020.
20. Pulendran B, S Arunachalam P, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. Natural Reviews Drug Discovery. 20(6), 2021:454-475.
21. Hioki K, Hayashi T, Natsume-Kitatani Y, Kobiyama K, Temizoz B, Negishi H, Kawakami H, Fuchino H, Kuroda E, Coban C, Kawahara N, Ishii KJ. Machine Learning-Assisted Screening of Herbal Medicine Extracts as Vaccine Adjuvants. Frontiers in Immunology.13:847616; 2022.
22. Chaudhury S, Duncan EH, Atre T, Dutta S, Spring MD, Leitner WW, Bergmann-Leitner ES. Combining immunoprofiling with machine learning to assess the effects of adjuvant formulation on human vaccine- induced immunity. Human Vaccines and Immunotherapy Journal 16(2); 2020:400-411.
23. Wübbolding M, Lopez Alfonso JC, Lin CY, Binder S, Falk C, Debarry J, Gineste P, Kraft ARM, Chien RN, Maasoumy B, Wedemeyer H, Jeng WJ, Meyer Hermann M, Cornberg M, Höner Zu Siederdissen C. Pilot Study Using Machine Learning to Identify Immune Profiles for the Prediction of Early Virological Relapse After Stopping Nucleos(t)ide Analogues in HBeAg-Negative CHB. Hepatology Communications 5(1); 2020: 97-111.
24. Emanuel EJ, Wachter RM. Artificial Intelligence in Health Care: Will the Value Match the Hype? Journal of the American Medical Association. 321(23); 2019: 2281-2.
25. Kannan S, Subbaram K, Ali S, Kannan H. The Role of Artificial Intelligence and Machine Learning Techniques: Race for COVID-19 Vaccine. Archive of Clinical Infectious Diseases. 15(2):e103232; 2020.
26. Marroquin U, Saboya N, Sullon AA. Machine Learning-based predictive model for the prognosis of human papillomavirus (HPV) vaccination attrition. In: Proceedings of the 4th International Conference on Robot Systems and Applications (ICRSA '21). New York, NY, USA: Association for Computing Machinery; 2021:44-49.
27. Tomic A, Tomic I, Rosenberg-Hasson Y, Dekker CL, Maecker HT, Davis M SIMON, an Automated Machine Learning System, Reveals Immune Signatures of Influenza Vaccine Responses. Journal of Immunology. 203(3); 2019:749-759.
28. Agrebi S, Larbi A. Use of artificial intelligence in infectious diseases. Artificial Intelligence in Precision Health. 2020:415–38.
29. Khemasuwan D, Colt HG. Applications and challenges of AI-based algorithms in the COVID-19 pandemic. BMJ Innovations 7:387-398; 2021.
30. Sarker S, Jamal L, Ahmed SF, Irtisam N. Robotics and artificial intelligence in healthcare during COVID-19 pandemic: A systematic review. Robotic Automation System 146:103902; 2021.
31. Klén R, Purohit D, Gómez-Huelgas R, Casas-Rojo JM, Antón-Santos JM, Núñez-Cortés JM, Lumbreras C, Ramos-Rincón JM, García Barrio N, Pedrera-Jiménez M, Lalueza Blanco A, Martin-Escalante MD, Rivas-Ruiz F, Onieva-García MÁ, Young P, Ramirez JI, Titto Omonte EE, Gross Artega R, Canales Beltrán MT, Valdez PR, Pugliese F, Castagna R, Huespe IA, Boietti B, Pollan JA, Funke N, Leiding B, Gómez-Varela D. Development and evaluation of a machine learning-based in-hospital COVID-19 disease outcome predictor (CODOP): A multicontinental retrospective study. Elife. 11: e75985; 2022.
32. Albalawi U, Mustafa M. Current Artificial Intelligence (AI) Techniques, Challenges, and Approaches in Controlling and Fighting COVID-19: A Review. International Journal of

Environmental Research and Public Health. 9(10); 2022: 5901.
33. Arora G, Joshi J, Mandal RS, Shrivastava N, Virmani R, Sethi T. Artificial Intelligence in Surveillance, Diagnosis, Drug Discovery and Vaccine Development against COVID-19. Pathogens. 10(8); 2021:1048.
34. Cunningham AL, Garçon N, Leo O, Friedland LR, Strugnell R, Laupèze B, Doherty M, Stern P. Vaccine development: From concept to early clinical testing. Vaccine. 34(52); 2016: 6655-6664.
35. The College of Physicians of Philadelphia. Vaccine Development, Testing, and Regulation. Editor's note. Accessed 17th April, 2023; https://historyofvaccines.org/vaccines-101/how-are-vaccines-made/vaccine-development-testing-and-regulation; 2022.
36. Ong E, Cooke MF, Huffman A, Xiang Z, Wong MU, Wang H, Seetharaman M, Valdez N, He Y. Vaxign2: the second generation of the first Web-based vaccine design program using reverse vaccinology and machine learning. Nucleic Acids Research 49(W1); 2021; W671-W678.
37. Cai X, Li JJ, Liu T, Brian O, Li J. Infectious disease mRNA vaccines and a review on epitope prediction for vaccine design. Brief Functional Genomics. 20(5); 2021:289-303.
38. Ricci AD, Brunner M, Ramoa D, Carmona SJ, Nielsen M, Agüero F. APRANK:Computational Prioritization of Antigenic Proteins and Peptides From Complete Pathogen Proteomes. Frontiers in Immunology 12: 702552; 2021.
39. Gu WG, Zhang X, Yuan JF. Anti-HIV drug development through computational methods. The AAPS Journal. 16(4); 2014:674-80. doi: 10.1208/s12248- 014- 9604-9.
40. Vishweshwaraiah YL, Dokholyan NV. Toward rational vaccine engineering. Advanced Drug Delivery Reviews. 83:114142; 2022.
41. Sunita, Sajid A, Singh Y, Shukla P. Computational tools for modern vaccine development. Human Vaccines and Immunotherapy Journal. 16(3); 2020:723-735.
42. De Groot AS, Moise L, McMurry JA, Martin W. Epitope-Based Immunome-Derived Vaccines: A Strategy for Improved Design and Safety. Clinical Applications of Immunomics 2; 2008:39–69.
43. De Groot AS, Moise L, Terry F, Gutierrez AH, Hindocha P, Richard G, Hoft DF, Ross TM, Noe AR, Takahashi Y, Kotraiah V, Silk SE, Nielsen CM, Minassian AM, Ashfield R, Ardito M, Draper SJ, Martin WD. Better Epitope Discovery, Precision Immune Engineering, and Accelerated Vaccine Design Using Immunoinformatics Tools. Frontiers in Immunology. 11:442; 2020.
44. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunology 15(6); 2018: 586-594.
45. Rawal K, Sinha R, Abbasi BA, Chaudhary A, Nath SK, Kumari P, Preeti P, Saraf D, Singh S, Mishra K, Gupta P, Mishra A, Sharma T, Gupta S, Singh P, Sood S, Subramani P, Dubey AK, Strych U, Hotez PJ, Bottazzi ME. Identification of vaccine targets in pathogens and design of a vaccine using computational approaches. Scientific Reports. 11(1); 2021:17626
46. Dimitrov I, Zaharieva N, Doytchinova I. Bacterial Immunogenicity Prediction by Machine Learning Methods. Vaccines (Basel). 8(4); 2020:709.
47. Castro KM, Scheck A, Xiao S, Correia BE (2022). Computational design of vaccine immunogens. Current Opinion in Biotechnology.78:102821.
48. Kiros TG, Levast B, Auray G, Strom S, van Kessel J, Gerdts V. The Importance of Animal Models in the Development of Vaccines. Innovation in Vaccinology. 29; 2012: 251–64.
49. Chirkova T, Ha B, Rimawi BH, Oomens AGP, Hartert TV, Anderson LJ. In vitro model for the assessment of human immune responses to subunit RSV vaccines. PLoS One. 15(3): e0229660; 2020.
50. Cotugno N, Santilli V, Pascucci GR, Manno EC, De Armas L, Pallikkuth S, Deodati A, Amodio D, Zangari P, Zicari S, Ruggiero A, Fortin M, Bromley C, Pahwa R, Rossi P, Pahwa S, Palma P. Artificial Intelligence Applied to *in vitro* Gene Expression Testing (IVIGET) to Predict Trivalent Inactivated Influenza Vaccine Immunogenicity in HIV Infected Children. Frontiers in Immunology. 11:559590; 2020
51. Bonin CRB, Fernandes GC, Dos Santos RW, Lobosco M. A qualitatively validated mathematical-computational model of the immune response to the yellow fever vaccine. BMC Immunology 9(1); 2018:15.
52. González-Parra G, Cogollo MR, Arenas AJ. Mathematical Modeling to Study Optimal Allocation of Vaccines against COVID-19 Using an Age-Structured Population. Axioms. 11(3); 2022:109.
53. Webb G. A COVID-19 Epidemic Model Predicting the Effectiveness of Vaccination in the US. Infectious Diseases Reports. 3(3); 2021: 654-667.

54. Cheong Q, Au-Yeung M, Quon S, Concepcion K, Kong JD. Predictive Modeling of Vaccination Uptake in US Counties: A Machine Learning-Based Approach. Journal of Medical Internet Research. 23(11): e33231; 2021.
55. Dolgin E. Could computer models be the key to better COVID vaccines? Nature. 604(7904); 2022: 22-25.
56. Tzachor A, Whittlestone J, Sundaram L, hÉigeartaigh SÓ. Artificial intelligence in a crisis needs ethics with urgency. Nature Machine Intelligence 2, 2020; 365–366
57. Prakash S, Balaji JN, Joshi A, Surapaneni KM. Ethical Conundrums in the Application of Artificial Intelligence (AI) in Healthcare—A Scoping Review of Reviews. Journal of Personalized Medicine. 12(11); 2022: 1914.
58. Garfinkel SQK. ChatGPT Artificial Intelligence and the very real legal implications of this technology. Lexology. Accessed online 18/04/2023 at https://www.lexology.com/library/detail.aspx?g=71298ed8-482e-446d-8b45-148d517ddeda.
59. Pashkov VM, Harkusha AO, Harkusha YO. Artificial intelligence in medical practice: regulative issues and perspectives. Wiadomości Lekarskie Medical Advances 73(12 cz 2); 2020:2722-2727.
60. de Hond AAH, Leeuwenberg AM, Hooft L, Kant IMJ, Nijman SWJ, van Os HJA, Aardoom JJ, Debray TPA, Schuit E, van Smeden M, Reitsma JB, Steyerberg EW, Chavannes NH, Moons KGM. Guidelines and quality criteria for artificial intelligence-based prediction models in healthcare: ascoping review. NPJ Digital Medicine 5(1); 2022: 2.
61. Santangelo OE, Gentile V, Pizzo S, Giordano D, Cedrone F. Machine Learning and Prediction of Infectious Diseases: A Systematic Review. *Machine Learning and Knowledge Extraction*. 5(1); 2023: 175-198.
62. Chiu HR, Hwang CK, Chen SY, Shih FY, Han HC, King CC, Gilbert JR, Fang CC, Oyang YJ. Machine learning for emerging infectious disease field responses. Scientific Reports 12(1); 2022: 328.
63. Gonzalez-Dias P, Lee EK, Sorgi S, de Lima DS, Urbanski AH, Silveira EL, Nakaya HI. Methods for predicting vaccine immunogenicity and reactogenicity. Human Vaccines and Immunotherapy Journal 16(2); 2020: 269-276.
64. Markus AF, Kors JA, Rijnbeek PR. The role of explainability in creating trustworthy artificial intelligence for health care: A comprehensive survey of the terminology, design choices, and evaluation strategies. Journal of Biomedical Informatics 113: 103655; 2021.
65. Amann J, Vetter D, Blomberg SN, Christensen HC, Coffee M, Gerke S, Gilbert TK, Hagendorff T, Holm S, Livne M, Spezzatti A, Strümke I, Zicari RV, Madai VI; Z-Inspection initiative. To explain or not to explain? -Artificial intelligence explainability in clinical decision support systems. PLOS Digital Health. 1(2): e0000016; 2022.
66. Igoe KJ. Algorithmic Bias in Health Care Exacerbates Social Inequities -How to Prevent It. Harvard University Health Information Technology; Accessed 18/04/2023 at https://www.hsph.harvard.edu/ecpe/how-to-prevent- algorithmic-bias-in-health-care/; 2021.
67. Quazi S. Artificial intelligence and machine learning in precision and genomic medicine. Medical Oncology 39(8); 2022: 120.
68. Van Tilbeurgh M, Lemdani K, Beignon AS, Chapon C, Tchitchek N, Cheraitia L, Marcos Lopez E, Pascal Q, Le Grand R, Maisonnasse P, Manet C. Predictive Markers of Immunogenicity and Efficacy for Human Vaccines. Vaccines (Basel) 9(6); 2021:579.
69. Weissler EH, Naumann T, Andersson T, Ranganath R, Elemento O, Luo Y, Freitag DF, Benoit J, Hughes MC, Khan F, Slater P, Shameer K, Roe M, Hutchison E, Kollins SH, Broedl U, Meng Z, Wong JL, Curtis L, Huang E, Ghassemi M. The role of machine learning in clinical research: transforming the future of evidence generation. Trials. 22(1); 2021: 537.
70. Bærøe K, Miyata-Sturm A, Henden E. How to achieve trustworthy artificial intelligence for health. Bulletin of the World Health Organization. 98(4); 2020: 257-262. doi: 10.2471/BLT.19.237289.
71. Gerke S, Minssen T, Cohen G. Ethical and legal challenges of artificial intelligence-driven healthcare. Artificial Intelligence in Healthcare. 2020; 2020: 295-336.
72. Poland GA, Ovsyannikova IG, Jacobson RM. Personalized vaccines: the emerging field of vaccinomics. Expert Opinion in Biological Therapy. 8(11); 2008:1659-67.
73. Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: A review. Vaccine. 36(36); 2018: 5350-5357.