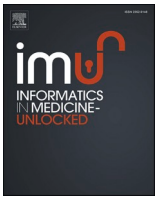
Informatics in Medicine Unlocked 37 (2023) 101164

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: www.elsevier.com/locate/imu



COVID-19 Vaccines: Computational tools and Development

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19 vaccines
Vaccines
Computational tools

ABSTRACT

The 2019 coronavirus outbreak, also known as COVID-19, poses a serious threat to global health and has already had widespread, devastating effects around the world. Scientists have been working tirelessly to develop vaccines to stop the virus from spreading as much as possible, as its cure has not yet been found. As of December 2022, 651,918,402 cases and 6,656,601 deaths had been reported. Globally, over 13 billion doses of vaccine have been administered, representing 64.45% of the world's population that has received the vaccine. To expedite the vaccine development process, computational tools have been utilized. This paper aims to analyze some computational tools that aid vaccine development by presenting positive evidence for proving the efficacy of these vaccines to suppress the spread of the virus and for the use of computational tools in the development of vaccines for emerging diseases.

1. Introduction

In December 2019, the Severe Acute Respiratory Syndrome-CoV-2 (SARS-CoV-2), also known as COVID-19, began in Wuhan, China, and over time, it spread across the globe. Ever since the pandemic began, scientists have been working tirelessly to develop vaccines that will protect individuals from contracting the deadly virus. Managing cases of COVID-19 and its associated comorbidities has been more challenging and has resulted in more deaths [1]. In December 2022, according to the World Health Organization (WHO), 651,918,402 cases and 6,656,601 deaths were recorded in over 200 nations and a total of 13,073,712,554 (13 billion) doses of the COVID-19 vaccines had been administered globally [2]. Since the outbreak, several vaccines have been developed and licensed for use in most countries. In comparison with previous vaccines, the COVID-19 vaccines have been developed rapidly, and the approval for the use of the vaccines took less than a year after development. The first dose of the vaccines was administered in December 2020 in the United Kingdom. Other vaccines are either still in the development stage, the preclinical stage, or the clinical phase, or are awaiting final review and approval to be released for use. The COVID-19 vaccines aim to provide immunity against the virus. Vaccines function by infusing weak pathogens into the immune system, which stimulates the immune system to generate antibodies and develop immunity to the disease they prevent. Vaccines typically contain genetic instructions that code for the disease or the same germs that cause the disease, thereby killing or weakening these germs [3,4]. As of December 2022, there were 175 vaccines in clinical development and 199 vaccines in pre-clinical development [5]. Computational immunology helps expedite vaccine development, but it is not a potential solution [6]. The design and development of vaccines are quite complicated, but advancements in bioinformatics have made the design of vaccines and drug development quite easy. Vaccine design falls into two categories: the traditional approach (expensive and time-consuming) and the modern approach [7]. The modern approach aims to maximize efficacy and, at the same time, minimize prospective negative effects [8]. The traditional approach to developing vaccines has several drawbacks, which have caused several modern technologies like recombinant DNA technology, next-generation technology, rational vaccination, structural biology, conjugate vaccines, and epitope-based vaccinations to come into existence. Recombinant DNA technology aids in the development of effective, safe, and less costly vaccines [7]. In this review, we give a brief overview of the development of the COVID-19 vaccines, highlighting the various computational tools utilized and their unique features. These tools are mostly resources and databases that aid in the development of the COVID-19 vaccines.

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https://doi.org/10.1016/j.imu.2023.101164
Received 1 July 2022; Received in revised form 2 January 2023; Accepted 3 January 2023
Available online 10 January 2023

2. Stages of COVID-19 Vaccines Development

Vaccine development is typically a lengthy process that takes between 10 and 15 years to complete, as it must go through multiple phases to assure its safety and effectiveness for the intended purpose [9]. Due to the global urgency of the pandemic, the timescale for the development of vaccines was compressed. Before the development of the COVID-19 vaccine, the mumps vaccine was the fastest vaccine ever developed, taking approximately four years. Historically, the development of vaccines has always involved a series of sequential steps, which can take decades. However, due to the COVID-19 pandemic, vaccines are needed immediately to stop the spread of the virus, and scientific collaborations and unprecedented financial investments are transforming the process. The development of vaccines must go through several phases of testing, but because of the urgent need for COVID-19 vaccines, some of the phases in the development process have been happening in parallel while still maintaining strict safety and clinical standards. The purpose of clinical trials is to explore innovative methods for enhancing the treatment and quality of life of patients with various diseases. The outcomes of clinical trials lead to the development of innovative therapies, diagnostic tools, and clinical procedures [10]. During clinical trials, many vaccines are examined simultaneously [11]. Vaccine development usually has three phases in clinical trials, with each phase assessing safety [12]. Table 1 outlines the various phases of COVID-19 vaccine development.

2.1. Types of vaccine platforms

The COVID-19 vaccines that have been developed employ various vaccine platforms. As of December 2022, 242 vaccine candidates were in clinical trials, but 12 of these vaccines stopped progressing [12]. Table 2 shows the various types of vaccines and the number of candidate vaccines in clinical trials [12].

Table 1
Stages of the COVID-19 vaccine development.

Phase	Activity	Number of people involved	Conventional timeline	COVID-19 timeline
Pre-clinical Phase	Data collection for safety and feasibility support and evaluation of toxic and pharmacological effects.	None (non-human testing)	5–10 years	6–9 months
Clinical Phase-Phase I	Study of healthy people and evaluation of the safety and immune response at different doses	20-100 people	1–3 years	3 months
Clinical Phase-Phase II	Safety evaluation, efficacy assessment, and vaccine schedule	100-300 people	2–3 years	8 months
Clinical Phase-Phase III	Evaluation of safety and efficacy	300-3000 people	2–4 years	Sometimes combined with Phase II
Regulatory Review (RR)	Review of trial data and licensing application information for government authorization	Nil	1–2 years	Few months
Final Phase or Phase IV	Monitoring the effectiveness of the vaccine in real world conditions and vaccine testing	Lots of people	Nil	Nil

Table 2
Types of vaccine platforms.

Vaccine Type	Platform	Phase	Number of vaccines
Protein-based Vaccines	Protein Subunit	Phase 3	36 Vaccines
		Phase 2	24 Vaccines
		Phase 1	17 Vaccines
	Virus-Like Particles	Phase 3	3 Vaccines
		Phase 2	4 Vaccines
		Phase 1	2 Vaccines
Whole-virus Vaccines	Live-Attenuated Vaccines	Phase 3	1 Vaccine
	Inactivated Virus Vaccines	Phase 3	18 Vaccines
		Phase 2	5 Vaccines
		Phase 1	5 Vaccines
Viral Vector Vaccines	Replicating Viral Vector (VVr)	Phase 3	1 Vaccines
		Phase 2	3 Vaccines
		Phase 1	3 Vaccines
	Non-Replicating Viral Vector (VVnr)	Phase 3	10 Vaccines
		Phase 2	7 Vaccines
		Phase 1	12 Vaccines
Nucleic Acid Vaccines	DNA	Phase 3	3 Vaccines
		Phase 2	6 Vaccines
		Phase 1	6 Vaccines
	RNA	Phase 3	20 Vaccines
		Phase 2	23 Vaccines
		Phase 1	21 Vaccines

2.2. Widely used and approved vaccines

As of December 2022, the WHO had approved 50 COVID-19 vaccines, including 11 Emergency Use Listing (EUL) vaccines, in about 201 countries [13,14]. These vaccines were approved, authorized, licensed, awarded emergency use authorization, or made available for use outside of clinical trials. Even after approval, these vaccines will continue to be monitored (Phase IV) to guarantee their safety and efficacy. The WHO EUL (used during public health emergencies) is a mechanism for gaining access to unlicensed (still in development) vaccines, therapeutics, and in vitro diagnostics in the event of a public health emergency to expedite the availability of products to those in need. WHO evaluates the quality, safety, and performance of drugs still in development, as well as efficacy data gained throughout development, and conducts a risk-benefit analysis to determine whether or not the drug may be used outside of clinical trials [15]. The approved COVID-19 vaccines and 11 EUL vaccinations [13,14] are detailed in Table 3, including the vaccine's name, its category, the number of trials conducted for that vaccine, and the number of countries where these vaccines have been approved for EUL.

Table 3
The WHO-approved vaccines. The rows in bold are the EUL vaccines.

Vaccine Manufacturer	Vaccine Name	Vaccine Platform	Number of trials	Status
Anhui Zhifei Longcom	Zifivax	Protein Subunit	21 trials in 5 countries	Approved in 4 countries
Bagheiat-Allah University of Medical Sciences	Noora vaccine	Protein Subunit	3 trials in 1 country	Approved in 1 country
Bharat Biotech	**Covaxin**	**Inactivated**	**16 trials in 2 countries**	**Approved in 14 countries**
	iNCOVACC	VVnr	4 trials in 1 country	Approved in 1 country
Biological E Limited	Corbevax	Protein Subunit	7 trials in 1 country	Approved in 2 countries
CanSino	**Convidecia**	**VVnr**	**14 trials in 6 countries**	**Approved in 6 countries**
	Convidecia Air	VVnr	5 trials in 4 countries	Approved in 2 countries
Center for Genetic Engineering and Biotechnology (CIGB)	Abdala	Protein Subunit	5 trials in 1 country	Approved in 6 countries
Chumakov Center	KoviVac	Inactivated	3 trials in 1 country	Approved in 3 countries
Gamaleya	Gam-COVID-Vac	VVnr	2 trials in 0 countries	Approved in 1 country
	Sputnik Light	VVnr	7 trials in 3 countries	Approved in 26 countries
	Sputnik V	VVnr	25 trials in 8 countries	Approved in 74 countries
Gennova Biopharmaceuticals Limited	GEMCOVAC-19	RNA	2 trials in 1 country	Approved in 1 country
Health Institutes of Turkey	Turkovac	Inactivated	8 trials in 1 country	Approved in 1 country
Instituto Finlay de Vacunas Cuba	Soberana 02	Protein Subunit	7 trials in 2 countries	Approved in 4 countries
	Soberana Plus	Protein Subunit	5 trials in 1 country	Approved in 2 countries
Janssen (Johnson & Johnson)	**Jcovden**	**VVnr**	**26 trials in 25 countries**	**Approved in 113 countries**
Livzon Mabpharm Inc	V-01	Protein Subunit	7 trials in 3 countries	Approved in 1 country
Medicago	Covifenz	VLP	6 trials in 6 countries	Approved in 1 country
Medigen	MVC-COV1901	Protein Subunit	15 trials in 4 countries	Approved in 4 countries
Moderna	mRNA 1273.214	RNA	2 trials in 2 countries	Approved in 1 country
	Spikevax	**RNA**	**70 trials in 24 countries**	**Approved in 88 countries**
	Spikevax Bivalent Original/Omicron BA.1	RNA	5 trials in 4 countries	Approved in 38 countries
	Spikevax Bivalent Original/Omicron BA.4/BA.5	RNA	2 trials in 1 country	Approved in 33 countries
National Vaccine and Serum Institute	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	Protein Subunit	3 trials in 2 countries	Approved in 1 country
Novavax	**Nuvaxovid**	**Protein Subunit**	**22 trials in 14 countries**	**Approved in 40 countries**
Organization of Defensive Innovation and Research	FAKHRAVAC (MIVAC)	Inactivated	3 trials in 1 country	Approved in 1 country
Oxford/AstraZeneca	**Vaxzevria**	**VVnr**	**73 trials in 34 countries**	**Approved in 149 countries**
Pfizer/BioNTech	**Comirnaty**	**RNA**	**100 trials in 31 countries**	**Approved in 149 countries**
	Comirnaty Bivalent Original/Omicron BA.1	RNA	3 trials in 5 countries	Approved in 35 countries
	Comirnaty Bivalent Original/Omicron BA.4/BA.5	RNA	4 trials in 1 country	Approved in 33 countries
PT Bio Farma	IndoVac	Protein Subunit	4 trials in 1 country	Approved in 1 country
Razi Vaccine and Serum Research Institute	Razi Cov Pars	Protein Subunit	5 trials in 1 country	Approved in 1 country
Research Institute for Biological Safety Problems (RIBSP)	QazVac	Inactivated	3 trials in 1 country	Approved in 2 countries
Sanofi/GSK	VidPrevtyn Beta	Protein Subunit	3 trials in 2 countries	Approved in 30 countries
Serum Institute of India	**Covishield (Oxford/AstraZeneca formulation)**	**VVnr**	**6 trials in 1 country**	**Approved in 49 countries**
	COVOVAX (Novavax formulation)	**Protein Subunit**	**7 trials in 3 countries**	**Approved in 6 countries**
Shenzhen Kangtai Biological Products Co	KCONVAC	Inactivated	7 trials in 1 country	Approved in 2 countries
Shifa Pharmed Industrial Co	COVIran Barekat	Inactivated	6 trials in 1 country	Approved in 1 country
Sinopharm (Beijing)	**Covilo**	**Inactivated**	**39 trials in 18 countries**	**Approved in 93 countries**
Sinopharm (Wuhan)	Inactivated (Vero Cells)	Inactivated	9 trials in 7 countries	Approved in 2 countries
Sinovac	**CoronaVac**	**Inactivated**	**42 trials in 10 countries**	**Approved in 56 countries**
Sk Bioscience Co Ltd	SKYCovione	Protein Subunit	7 trials in 6 countries	Approved in 1 country
Takeda	TAK-019 (Novavax formulation)	Protein Subunit	3 trials in 1 country	Approved in 1 country
	TAK-919 (Moderna formulation)	RNA	2 trials in 1 country	Approved in 1 country
Valneva	VLA2001	Inactivated	9 trials in 4 countries	Approved in 33 countries
Vaxine/CinnaGen Co.	SpikoGen	Protein Subunit	8 trials in 2 countries	Approved in 1 country
Vector State Research Center of Virology and Biotechnology	Aurora-CoV	Protein Subunit	2 trials in 1 country	Approved in 1 country
	EpiVacCorona	Protein Subunit	4 trials in 1 country	Approved in 4 countries
Walvax	AWcorna	RNA	4 trials in 3 countries	Approved in 1 country
Zydus Cadila	ZyCoV-D	DNA	6 trials in 1 country	Approved in 1 country

3. Computational tools in modern vaccine development

Utilizing computational tools before conducting initial laboratory research generates more benefits because they are less expensive and take less time to operate. These computational tools study and model molecular interactions during antigen presentation and processing using purely statistical and machine learning technologies. Fig. 1 shows the workflow for vaccine design and development with the use of

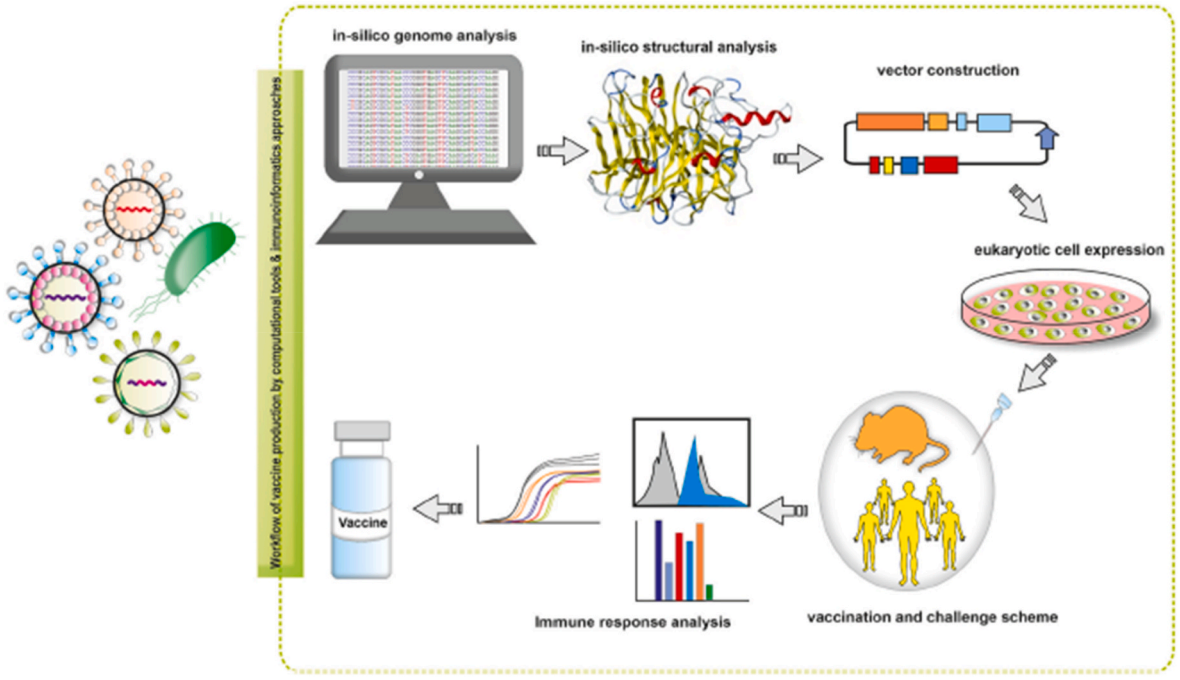

Fig. 1. A workflow for the design and development of vaccines using computational tools and immunoinformatics approaches [16].

computational tools and immunoinformatics approaches. In the past, developing vaccines took a considerable amount of time, which is why many scientists have turned to computational and informatics approaches and structural analysis to predict the recognition of novel pathogens by B- and T-cells or to develop targeted immunotherapies against tumor cells [16]. These various computational tools are discussed [7].

3.1. Sidechain and backbone modeling tools

Sidechains are diverse receptors located on cells that serve as the cells' gatekeepers. The distinctive characteristics of each sidechain permit only substances with identical structures to enter cells. Sidechains are receptors, which means they are molecules that bind to a specific substance and cause a specific effect in the cell. The side-chain modeling tool is an important part of computational biology for designing antibodies and determining how they will be built. The side chains with rotamer library (SCWRL) and side-chain accuracy prediction (SCAP) tools have been successfully used for modeling, determining, and analyzing mutations available *in silico* modeling of protein side chains [17–19] and they can also be employed for particular antibody recognition and affinity tuning. Fig. 2 shows the application of a side-chain modeling tool to the resurfacing of non-epitope regions of an antigen. Backbone modeling tools assist with antibody alterations, and backbone-dependent rotamer libraries are capable of utilizing a range of antibody modeling tools. Other tools are DRAGON and GADGET, which use an antibody-protein folding program to estimate a protein's secondary structure and ligand-binding location. A bioinformatics tool also used is RAMBLE, which has various permutations for checking disulfide bond connectivity, chain structure, and tryptone side-chain alignment [20]. Another tool, RAPPER, is an *in silico* strategy for generating 3D models of proteins to be used for comparative modeling with a high degree of accuracy. This tool also identifies target sequences by exploring a protein's conformational structure [21]. Comparative modeling often provides a useful 3D model of a protein related to at least one known protein structure that is known in the absence of an experimentally determined structure. The 3D structure of a protein sequence is predicted by comparative modeling based on its alignment with one or more known protein structures [22]. The application of RAPPER for comparative modeling makes use of positional restraints and

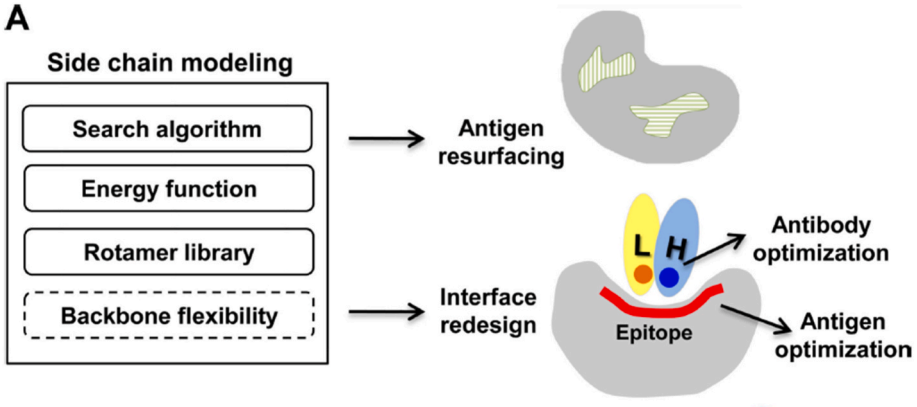

Fig. 2. Application of side-chain modeling tools to resurfacing of non-epitope regions of an antigen, antibody optimization, and engineering of an antigen epitope [17].

knowledge-based sampling to generate accurate models [23].

3.2. Multigraft and multivalent scaffolding tools

These are major vaccine development strategies. A multivalent ligand is made up of numerous copies of ligands that can bind to different locations on the receptor. Scaffolding broadens the scope of vaccine creation based on epitope engineering and the presence of a scaffold in the protein of interest. Due to the presence of a scaffold in the target protein, multivalent scaffolding technology is applied to the creation of epitope vaccines. It is also considered that scaffolds display antigens in a highly organized and repetitive manner, triggering robust immune responses. For the development of multi-graft immunogens, protein structure is predicted using composite modeling with multiple templates. Identifying a specific scaffold including many epitopes can be fairly difficult because epitopes are selected by antibodies without constraint [24]. A protein scaffold consisting of a designed ankyrin repeat protein (DARPins) cysteine knot can be utilized to represent a functional location. To increase the binding affinity, avidity, and specificity of the ligand-receptor, multivalent interactions of biological molecules are performed by distinct biochemical activities [25]. A multi-graft interface is a paradigm that is employed to graft epitopes to improve antibody binding selectivity and possibly influence antibody nature. SAGE (Strategy for Alignment and Grafting of Epitopes) is an automated computational tool used for inserting immune-generating epitopes into a scaffold [26].

3.3. Epitope prediction tools

Epitope prediction is the first crucial stage in vaccine development since the epitope serves to stimulate immune responses from B-cells and T-cells, and prediction algorithms can be used to design a successful vaccine. For analyzing peptide reactions in epitope prediction, computational approaches such as SVMs, motif-based systems, QSAR (Quantitative Structure-Activity Relationship Analysis), structure-based, neural networks, and Hidden Markov Models (HMMs) can be used [27]. Based on statistical theory, SVMs are used to categorize data into two groups: binders and non-binders [28]. However, HMM assists in locating sequences with binder-like properties and recognizing peptide patterns that are difficult to recognize due to the installation of a Bayesian neural network. Several approaches, including hydrophilicity profile, flexibility profile, surface probability, and HMM, are utilized for the prediction of B-cell epitopes [29]. T-cell epitopes are important for the design of vaccines because of the vital role they play in cellular response, and these epitopes can be identified through T-cell receptors on several cells, including B-cells [30]. The process and selection of antigens are crucial to the development of vaccines.

4. COVID-19 Vaccine development computational tools

Combining multiple computational vaccine design techniques is crucial for reducing the time and expense of identifying and developing vaccine candidates and enhancing vaccine safety and efficacy [31]. Computational tools accelerate the vaccine design and development process for international pandemics caused by viruses such as COVID-19 [16]. Several studies have discussed the application of computational methods and resources to COVID-19 vaccine discovery and development. Hwang et al. (2021) reviewed several computational approaches used in bioinformatics, and PK modeling approaches were highlighted as viable *in silico* tools for Sars-CoV-2. Bharadwaj et al. (2021) discussed how current technologies like Artificial Intelligence (AI), Machine Learning (ML), Big Data, and the Internet of Things (IoT) in the area of computer science, in association with basic knowledge of immunoinformatics, virology, and a deep understanding of molecular and structural biology, have helped reduce the time required for the development of the coronavirus vaccines. AI is characterized as a modern technology that is incorporated to develop the competency of instruments or devices to the applicability of intelligence as it gives authentic health reports. It is a recognized approach to interpreting the virus and improving disincentives, and it is also essential to viral evolution, understanding, structure, and transmission through computational biology, structural biology, and mathematical design. Genetic, biological, and environmental information, which are all compiled in AI, may lead to the evolution of treatment for coronavirus diseases. AI can also explore the vast information about convenient drugs that can be used across COVID-19, and even the combinations of those drugs can be invented in less time for COVID-19 treatment. ML can be utilized to determine the factors responsible for the death and how these mortality rates can be controlled. The collection of large datasets from COVID-19 patients during a global pandemic is managed and analyzed using artificial intelligence, data science, and machine learning, which will benefit the design and development of biomarkers, drug candidates, and therapeutic targets. Abbasi et al. (2022) carried out research on designing *in silico* multi-epitope subunit vaccine candidates and discovering potential vaccine candidates through a novel computational pipeline that combines reverse vaccinology, molecular docking, and simulation techniques. The study also shortlisted a protein-named spike protein from SARS-CoV-2 as a potential vaccine candidate, which was also examined for the presence of B and T-cell epitopes. This study utilized various strategies to design six multi-epitope subunit vaccines, including immunogenic epitopes, suitable adjuvants, and linker sequences, and also proposed that the vaccine designs can be employed for further in vitro and in vivo studies to build efficient and safe vaccines against various COVID-19 strains [32]. Kangabam et al. (2021) and Chatterjee et al. (2020) examined the various computational methods, databases, and bioinformatics resources that are accessible for systematic sequence structural research on Sars-CoV-2 vaccine design and development. These computational tools are databases and resources that help in the design of the COVID-19 vaccines and extensively maintain various genomic, epidemiological, and biological data that are related to COVID-19 [33]. Table 4 shows six computational tools that are being utilized in the COVID-19 vaccine design. These computational tools have been implemented in various fields, including antigen selection, epitope prediction, toxicology, and allergenicity prediction [8].

4.1. CoronaVIR (Computational resources on Coronavirus)

The CoronaVIR is a web-based resource for maintaining predicted diagnostic, drug, and vaccine candidates for COVID-19. It is a multi-omics website comprising comprehensive insights on genomic, diagnostic, therapeutic, and proteomic understanding of the coronavirus. The information contained in CoronaVIR was manually extracted from already-existing literature and databases and comprises important data obtained with the use of several computational tools. The CoronaVIR database comprises five modules: the General module, the Genomic module, the Diagnosis module, the Immunotherapy module, and the Drug Design module. This database contains data on 53 genome sequences of coronavirus, various coronavirus strains, protein sequences, nucleotide sequences, and sequences of antigenic peptides that are computationally predicted and may induce antibody-mediated immunity to fight coronavirus diseases. It also provides information about 65 unique predicted primer sets and 12 experimentally validated primer sets, drug targets, repurposing drugs, and monoclonal antibodies. Patiyal et al. proposed potential diagnostic primers, peptides, RNA-based vaccine candidates, and potential drug molecules. The 17 epitopes as potential vaccine candidates against COVID-19 were suggested by the same study, based on different prediction methods. For the identification of potential vaccine candidates, Patiyal et al. also generated 109 9-mer peptides from different proteins of SARS-CoV-2 that can stimulate both arms of the immune system and utilized a wide range of immunoinformatics tools for B-cell epitope prediction, T-cell epitope prediction, 111 MHC binders, and vaccine adjuvants. The study, using

Table 4
Computational tools/databases utilized in COVID-19 vaccine design and discovery.

Tool	URL	Year Released	Utility	Reference
CoronaVIR	https://webs.iiitd.edu.in/raghava/coronavir/	2020	Comprises comprehensive insights on genomic diagnostic, therapeutic, and proteomic understanding of the coronavirus.	[31,33,34].
DBCOVP	http://covp.immt.res.in/	2020	Comprises of structurally pathogenic glycoproteins, membrane, spikes, envelope proteins, and nucleocapsid proteins from 137 coronavirus strains that belong to the beta coronavirus genera.	[33,35].
CoVdb	http://covdb.popgenetics.net	2020	Contains about 5709 coronavirus strains that belong to several species hosts retrieved from 60 countries	[33,36]
IEDB	http://tools.iedb.org/	2019	Comprises T-cell epitope data and verified antibody directories that are related to humans and primaries in infections.	[31,37,38].
ViPR	https://www.bv-brc.org/	2012	Contains major pathogenic viruses with single-stranded positive-sense RNA, single-stranded negative-sense RNA, double-stranded RNA, and double-stranded DNA	[31,39]
COVIEdb	http://biopharm.zju.edu.cn/coviedb/	2020	Contains information on the prediction of potential B-cell and T-cell epitopes for SARS-CoV, SARS-CoV-2, and MERS-CoV that could be used to make a pan-coronavirus vaccine	[33,40,41]

the *in silico* method, also discovered 477 siRNA-based therapeutics and nucleotide-based vaccine adjuvants for COVID-19 [42].

4.2. DBCOVP (A database of Coronavirus virulent glycoproteins)

DBCOVP is a comprehensive database of structurally pathogenic glycoproteins, membrane proteins, spikes, envelope proteins, and nucleocapsid proteins from 137 coronavirus strains that belong to the betacoronavirus genera. It is a knowledge-based resource that explores the functional and immunological properties of coronavirus virulent glycoproteins for applications in vaccine target discovery. Currently, the database contains 185 protein sequences from human, bay, rat, rabbit, and hedgehog species that belong to the 5 subgenera of the beta coronavirus. The Summary module, Structural Details module, Physiochemical Properties module, and Epitope Module comprise the DBCOVP database. This database contains various strains, associated organisms, taxonomic lineages, subcellular localization, genomic location, ontologies for genes, functional domains, family classification, protein and nucleotide sequences, and references to other databases such as NCBI, UniProt, and KEGG. It also includes data on immunogenic promiscuous epitopes. The database makes available in-built bioinformatics tools like the Phylogeny tool used for the development of phylogenetic trees using Muscle and PhyML, the MSA tool (multiple sequence alignment) used for aligning two or more protein sequences with the muscle, the Compare tool (comparative genomic analysis) used for comparing annotation features of proteins, and a BLAST (Basic Local Alignment Search Tool) alignment search. The main purpose of the DBCOVP database is to enable researchers to carry out knowledge discovery from the available coronavirus antigen data, with a specific concentration on immunology and vaccine applications. This database will serve as a one-stop shop for virologists and vaccine researchers interested in studying SARS-CoV-2 pathogenesis and accelerating rational vaccine design through in vitro and in vivo experimental validation of promiscuous vaccination targets. Sahoo et al. predicted the binding Class I and Class II HLA alleles, the allergenicity, the conservancy score, the antigenicity, the toxicity, the charge, and the molecular weight of the predicted peptides. To choose the most promising epitopes for each protein sequence to induce a strong immune response, the most promiscuous T-cell epitopes and B-cell epitopes that were recognized by many HLA alleles and included the highest immunogenicity, antigenicity, and nontoxic values for humans, were selected. The result of this indicated that more than 80% of the world's population was covered by all the predicted epitopes and the HLA alleles that bind them, which is essential for a vaccine candidate since the emerging SARS-CoV-2 strain has affected people all over the world. The predicted epitopes' 3D structure was determined, and a docking technique was used to study the binding interaction with the most conserved HLA allele [43].

4.3. CoVdb (Annotation data resources of Coronavirus genes and genomes)

This database is an online proteomic, genomic, and evolutionary analysis website that contains about 5709 coronavirus strains that belong to several species of hosts retrieved from about 60 countries and provides detailed data about the function of the gene, subcellular localization, topology, and structure of a protein. There are built-in search tools for observing and studying relationships among several COVID genomes stored in the phylogenetic tree. The CoVdb contains a search engine for browsing taxonomies and supporting filtering, as well as BLAST. It also supports tools like the Protein Tool, Aln Browser Tool, Pop Analyzer, and Phylogenetic Tree Tool. The Aln browser tool makes it simple to extract several sequence alignments of different strains at specific positions and then uses the alignment to build a phylogenetic tree. The Pop analyzer and Phylo Tree tool permit visual and interactive exploration of phylogenetic trees that were developed based on their genomic or proteomic sequences for vaccine design and tracing origins. In a study, the CoVdb repository was explored by Zhu et al., and coronavirus genomes were retrieved and identified to obtain a general view of possible recombination events within coronaviruses reported. CoVdb also provided population genetic analysis and the annotation of the recombination events [44]. In another study, Zhu et al. utilized the CoVdb repository to discover, retrieve, and annotate consensus sequences of COVID-19 strains [45]. This database makes it easy for researchers to find and pull out all the genomic information on COVID-19, as well as do comparative genomics, protein structure, and evolutionary analysis.

4.4. IEDB (Immune epitope database and analysis resource)

A database that the National Institute of Allergy and Infectious Diseases (NIAID) sponsors makes available T-cell epitope data and verified antibody directories that are related to humans and primates in infections like allergies. IEDB makes use of artificial neural networks and is used for B-cell and T-cell epitope prediction. The database also makes available various immunoinformatic tools used for putative epitope prediction from antigenic proteins and epitope data analysis. The IEDB includes T-cell epitope prediction, binding affinity to MHC class I and II binding, and linear and discontinuous B-cell epitope prediction. The

database contains several immunoinformatics tools for information on analyzing epitopes. In a study, Bhattacharya et al., 2020, Enayatkhani et al., 2021, Feng et al., 2021, and Kumar, 2020, evaluated promiscuous epitopes for immune responses against COVID-19 as candidate targets by mapping the known epitopes at the same position in SARS-CoV-2 and MERS-CoV present at the IEDB server. Similarly, using epitope conservancy, potential immunogenicity, and conservation analysis, the combination of *in silico* studies and IEDB prediction and analysis tools identified potential candidate vaccines from COVID-19 antigenic proteins that belong to B and T-cell epitopes [46–49]. IEDB is an important resource for developing COVID-19 vaccines using epitope-based subunits.

4.5. ViPR (Virus Pathogen resource)

The Virus Pathogen Resource (ViPR), which is operated by the National Institute of Allergy and Infectious Diseases (NIAID), is a database of pathogenic viruses. Although, as of October 31st, 2022, all the data and tools from the ViPR database were migrated to the Bacterial and Viral Bioinformatics Resource Center (BV-BRC https://www.bv-brc.org/). The BV-BRC is an information system that was designed to support research on bacterial and viral infectious diseases. It contains a plethora of tools for analyzing multiple human pathogenic viruses from different families, including all of the Coronaviridae family. It contains an Organism module, a Search module, Tools and services module, and a Workspace module. The Organism module comprises a list of bacterial pathogens, viral families, and featured viruses. BV-BRC also includes several analytical and visualization tools, which may be used to carry out tasks such as sequence alignment, phylogenetic tree construction, sequence variation (SNP) identification, BLAST search, genome annotator development, and metadata-driven comparative analysis. Users can select the Viruses module and select the Coronaviridae family tab (https://www.bv-brc.org/view/Taxonomy/11118#view_tab=overview), which is listed under single-stranded positive-sense RNA, or select the SARS-CoV-2 tab (https://www.bv-brc.org/view/Taxonomy/2697049#view_tab=overview) listed under featured viruses. Users can view detailed data on genomes, features, 3D protein structures, proteins, epitopes, domains and motifs, and experiments. The database currently comprises 6,709,783 genome sequences and 2393 3D Protein structures of the SARS-CoV-2 virus.

4.6. COVIEdb (resources for immune epitopes of Coronaviruses)

This database contains information about potential B-cell and T-cell epitopes for SARS-CoV, SARS-CoV-2, and MERS-CoV that could be used to make a pan-coronavirus vaccine. The B- and T-cell epitope predictions are based on their protein sequences. COVIEdb has four basic interfaces for easy and quick data retrieval: "B cell epitope," "T cell epitope," "Peptide," and "Validated." The B cell epitope interface keeps track of B-epitope details; the T-epitope interface keeps track of T-epitope details; the Peptide interface keeps track of previously predicted B and T cell epitopes, and the Validated interface keeps track of predicted B and T cell epitopes (currently 116 validated epitopes) that have been confirmed by experimental studies. Furthermore, based on the projected B cell and T cell epitopes, COVIEdb identified 77 peptides present in all coronaviruses that can activate T cells, with 10 of them having a B-score greater than 4. This database can help with COVID-19 vaccine research and identify potential therapeutic targets.

There are other tools that have not been used in the COVID-19 vaccine development but are being used in the development of vaccine candidates for other infectious diseases.

4.7. Vaxi-DL (https://vac.kamalrawal.in/vaxidl/)

Vaxi-DL [50] is a web-based, deep learning (DL) program that looks at how likely different protein sequences could be used as vaccine candidates. Vaxi-DL provides a deep learning platform that helps users to process FASTA format protein sequences or UniProt ID data in other to classify them into vaccine or non-vaccine candidates as output, directly from an online server or via a user email. It is meant to predict vaccine candidates for infectious diseases caused by bacteria, protozoa, fungi, and viruses. It looks at 18 biological and 9154 physical and chemical properties of known protein antigens in each model to figure out what they are. Vaxi-DL combines the strengths of deep learning systems and immunoinformatics to predict vaccine candidates with high speed, sensitivity, and accuracy. A multi-epitope vaccine against Chagas disease was designed using Vaxi-DL. Antigens can be predicted with Vaxi-DL, which is a strong and reliable tool. This tool can be used on its own to predict antigens or in combination with other tools to design vaccines.

4.8. ***Vax-ELAN*** (https://vac.kamalrawal.in/vaxelan/)

Vax-ELAN [51] identifies proteins that have the necessary features to be considered as vaccine candidates and ranks them accordingly. Vax-ELAN combines bioinformatics tools, immunoinformatics approaches, and supervised machine learning-based tools for discovering and designing vaccines. It also uses multiple strategies to scan protein sequences. The tool was tested on different pathogens, like *Mycobacterium tuberculosis*, Plasmodium vivax, Candida albicans, and the Influenza A virus, and several key vaccine candidates were found. The tool was also used to identify vaccine candidates against *Trypanosoma cruzi* disease and design a putative multi-epitope vaccine along with an *in silico* model of immune stimulation that predicts responses associated with protective immunity. Vax-ELAN uses features like subcellular localization, secretory or non-secretory proteins, stability, cleavage sites, adhesion property, CTL epitope prediction, MHC class-I binding, transmembrane helix prediction, essentiality, virulence, molecular weight, a lack of homology with host proteins, etc.

The comparison of the six COVID-19 vaccine design computational tools displayed in Table 5 revealed that the DBCOVP tool supports multiple functionalities. This led us to conclude that DBCOVP is the most essential tool for the design and discovery of COVID-19 vaccine candidates (see Table 6).

4.9. SWOT analysis of the computational tools used in Covid-19 Vaccine design and development

A SWOT analysis was carried out on four of the computational tools used in the COVID-19 vaccine development to understand the strengths, weaknesses, opportunities, and threats of these tools. We chose the computational tools with the most features and functionalities. This analysis could be used as a guide in choosing a suitable computational tool for designing more COVID-19 vaccine candidates.

5. Conclusion and future perspectives

The global coronavirus pandemic has been a major disaster. Scientists and health authorities have been working tirelessly to produce vaccines that will help curb the spread of the virus. The WHO has authorized up to 20 vaccines for use in an emergency. The distribution of vaccines is still ongoing in several countries. As of December 2022, over 13 billion doses of the vaccines have already been administered globally. The future of the COVID-19 vaccine gives way to more options and different storage and administration modes. The vaccines in development (next-generation vaccines) will not face the challenge of transportation and storage because they can be taken right from home. Altimmune, a biopharmaceutical company, is currently developing a coronavirus vaccine that can be administered as a nasal spray. This form of administration could reduce the risk of transmitting the virus to those who received the vaccine because of its direct action on the respiratory tract. In this review, we analyzed how computational strategies can

Table 5
Comparison of the computational tools.

Functionality	CoVdb	CoronaVIR	DBCOVP	IEDB	ViPR	COVIEdb
BLAST Tool	Not present	Not present	Present	Not present	Present	Not present
Phylogeny Tool	Present	Not present	Present	Not present	Not present	Not present
Compare Tool	Not present	Not present	Present	Not present	Not present	Not present
MSA Tool	Present	Not present	Present	Not present	Present	Not present
COVID-19 Tracker	Not present	Not present	Present	Not present	Not present	Not present
3D protein structure	Present	Present (12 structures)	Present	Not present	Present	Not present
Epitope details (MHC-I; MHC-II & B-Cell Epitope)	Not present	Present	Present	Present	Present	Not present
3D epitope structure	Not present	Not present	Present	Not present	Not present	Not present
Coronavirus Strains	Present (5709 strains)	Present (53 strains)	Present (137 strains)	Not present	Not present	Not present
Predicted B-Cell and T-Cell epitope details	Not present	Not present	Present	Present	Not present	Present

Table 6
SWOT Analysis of four Computational tools used in the Covid-19 Vaccine development.

SWOT Analysis of Computational Tools used in Covid-19 Vaccine Development				
	Strengths	**Weaknesses**	**Opportunities**	**Threats**
DBCOVP	• Detailed data on 185 structural proteins and 137 strains. • Functional annotation of proteins • The ability for users to perform knowledge discovery from Covid-19 antigen data with emphasis on vaccinology applications. • Perform multiple sequence alignment	Lack of provision for adequate information on sequence from other coronavirus strains.	Combining tools for epitope analysis into one automated tool.	Database crash and loss of data.
CoronaVIR	• Providing detailed information on whole-genome sequences and protein sequences of Coronavirus strains • Predicting potential coronavirus epitopes (B and T cell, MHC class I and class II binders) • Prediction of potential vaccine candidates based on epitopes.	• Inability to experimentally validate diagnostic primers. • Lack of functional annotation of encoded proteins.	• Develop tools to aid experimental validation of diagnostic primers. • Develop tools for the construction of phylogenetic trees.	Database crash and loss of data and information.
CoVdb	• Provides convenient analysis in comparative genomics, protein structure, and evolutionary biology. • Detection of SARS-CoV-2 using test strips.	Lack of annotation features on genome information, cleavage sites, RNA structures, and transcription regulation.	Provide continuous updates and maintenance of the database	Database crash and loss of data
ViPR	Analysis on multiple sequence alignment, BLAST comparison, phylogenetic inference, sequence variation determination, and comparative genomics statistical analysis.	Lack of information on associated glycoprotein, biological processes, epitope conservancy, and 3D epitope information.	Include more genome annotations, protein annotations, and tertiary protein structures.	Database crash

hasten vaccine development at several phases. Six computational tools that are utilized in COVID-19 vaccine design and development were highlighted. A comparison of these computational tools based on some major functionalities revealed that DBCOVP is the most effective and efficient tool and database for the design and development of COVID-19 vaccines. Vaccine researchers, vaccine users, public health policy-makers, and epidemiologists all benefit from the use of computational tools. Similar viral infections are predicted to emerge in the future due to increased contact between humans and animals as human society continues to expand and animal habitats shrink. Using these computational tools and resources, vaccines for new and emerging diseases could be made. These computational tools should also be improved to make them more effective for the design and development of vaccines. For future research and studies, the effect of these computational tools in the development of the COVID-19 vaccines should be further investigated to understand their mechanism of operation and how they improve the design and development of the vaccines. Further research should also be carried out to see if these tools could be relied on for the design and

development of vaccines for diseases that may be related to COVID-19 in the long run.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Our acknowledgement goes to Covenant University and Covenant University Center for Research, Innovation, and Discovery for support and assistance regarding the publication of this article.

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