ViralVacDB: A manually curated repository of viral vaccines

Sadhana Tripathi [§], **Neelam Sharma** [§], **Leimarembi Devi Naorem**, **Gajendra P.S. Raghava** [*]

Department of Computational Biology, Indraprastha Institute of Information Technology, Okhla Phase 3, New Delhi 110020, India

Over the years, numerous vaccines have been developed against viral infections; however, a complete database that provides comprehensive information on viral vaccines has been lacking. In this review, along with our freely accessible database ViralVacDB, we provide details of the viral vaccines, their type, routes of administration and approving agencies. This repository systematically covers additional information such as disease name, adjuvant, manufacturer, clinical status, age and dosage against 422 viral vaccines, including 145 approved vaccines and 277 in clinical trials. We anticipate that this database will be highly beneficial to researchers and others working in pharmaceuticals and immunoinformatics.

Keywords: virus; vaccines; viral diseases; database; approved vaccines; clinical trials

Introduction

Viruses are small infectious agents that can infect all living organisms such as animals, plants, bacteria and archaea. They are minute microorganisms with sizes ranging from 20 nm to 200 nm in diameter [1]. They are predominantly known to have a wide variety of genomic structures. They can have single-stranded (ss) or double-stranded (ds) nucleic acids [2], for instance parvovirus (ssDNA) [3], herpes simplex virus (dsDNA), dengue virus (ssRNA) [4] and reovirus (dsRNA) [5], with a circular, linear or segmented arrangement [6]. They are of different types such as enveloped, naked or non-enveloped, helical and icosahedral [1]. They use the host cell to start the replication cycle by attaching to the outer membrane and then penetrate within the cell. A virus replicates its genome and produces new viral proteins using the host machinery [7]. During the process of replication, viruses tend to become contagious and infect host cells causing disease [8]. Such viruses are responsible for a wide range of diseases like the common cold, mumps, chickenpox and cold sores. Some of the deadliest viral pandemics and epidemics with widespread implications have occurred in the previous four decades. These include plague, pandemic influenza (flu), severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Ebola virus, human immunodeficiency virus (HIV), influenza A virus subtype H1N1 (A/H1N1) and Middle East respiratory syndrome coronavirus (MERS-CoV) [9,10].

In the past, numerous strategies were adopted to prevent viral infections, including avoiding viral exposure, quarantine, control of vectors and elimination of non-human reservoirs [11]. To control viral infections, several antiviral drugs have been developed for the treatment of influenza, herpes, hepatitis B and C and HIV [12,13]. One of the major challenges in managing viral infection is drug resistance, because the frequency of mutation in the virus is too high [14]. Thus, most antiviral drugs become ineffective against new virus strains. In addition, antiviral drugs are not capable of providing long-term immunity against a causative agent and do not provide virus-specific immunity [15]. Vaccines, over the years, have proved to be an effective

* *Corresponding author.Tripathi, S. (sadhana20214@iiitd.ac.in), Sharma, N. (neelams@iiitd.ac.in), Naorem, L.D. (leimarembi@gmail.com), Raghava, G.P.S. (raghava@iiitd.ac.in).*
§ Equal contribution.

https://doi.org/10.1016/j.drudis.2023.103523

and better approach to curb viral infections [16]. A vaccine usually contains weakened or inactivated parts of a particular organism (antigen) that elicit an immune response within the host [17]. It tends to develop a long-term immunological memory against the targeted pathogens [18]. Several types of viral vaccines are available to treat different human viral diseases and can offer lifelong protection [19]. According to the Centers for Disease Control and Prevention (CDC), viral diseases such as smallpox, polio, hepatitis A, hepatitis B and rubella have been fully or nearly eradicated by using vaccines [20]. There are different types of vaccines that trigger the immune response in the host in several ways. For instance, live attenuated vaccines produce a strong antibody response and are targeted against smallpox, measles, mumps and rubella. Inactivated vaccines such as influenza vaccine, rabies vaccine and hepatitis A virus vaccine consist of pathogenic particles that are inactivated using chemicals, heat or radiation [21]. In addition, protein subunit vaccines use fragments of protein to elicit a protective response against a disease-causing virus [22]. Vaccines can be administered via different routes, for example intramuscular, subcutaneous, intradermal, intranasal, intravenous and oral [23]. Adjuvants also play an important part in enhancing the immunity and effectiveness of the vaccine [24].

Nevertheless, the information regarding viral vaccines has been scattered throughout the literature and other online resources. It is challenging to search for this information, because it is not properly documented on a single platform. To the best of our knowledge, there is no complete database that is dedicated to viral vaccines. In the current study, we have developed ViralVacDB (https://webs.iiitd.edu.in/raghava/viralvacdb/) – a comprehensive database of viral vaccines. We have manually curated and compiled all the viral-vaccine-related information such as type, approval status, route of administration, associated disease and other essential details such as manufacturing country, approving organization, dosage, target strain and trade name. We envisage that ViralVacDB will certainly be helpful to the scientific community working in pharmaceuticals and immuno-informatics.

Viral vaccines

History

The first vaccine against smallpox was developed by Edward Jenner in the year 1796 using cowpox pustule inoculants [25]. Louis Pasteur later proposed a term vaccine that can be used for preventative disease inoculations [26]. The live-attenuated vaccine against rabies for humans was developed in 1885 [27]. In 1955, Jonas Salk developed the first safe and effective inactivated polio vaccine (Salk vaccine) against poliomyelitis [28]. Dr Maurice Hilleman discovered live-attenuated vaccines against measles in 1963, mumps in 1967 and rubella in 1969, which were later approved by the FDA. In 1971, a combined vaccine against measles, mumps and rubella was discovered [29]. The first licensed recombinant DNA vaccine against hepatitis B virus was developed in 1986 [30]. According to WHO, smallpox was eradicated worldwide with the help of immunization by 1980 [31]. The first live-attenuated vaccine against chickenpox was licensed in 1995 [32]. In 2003, a nasally administered vaccine named FluMist® against influenza was approved [33]. Gardasil® is the first recombinant vaccine against human papillomavirus, which was approved in 2006 [34]. In 2015, a recombinant, live-attenuated, tetravalent dengue vaccine named CYD-TDV was approved [35]. The first vaccine for Ebola was approved by the FDA in 2019 [36]. In 2020, the Pfizer-BioNTech mRNA-based vaccine was FDA-authorized against COVID-2019 [37]. The timeline of viral vaccine development is depicted in Figure S1 (see Supplementary Material online).

Protection induced by vaccines

A vaccine is a biologically derived product containing an antigenic strain that mimics a natural infection [21]. The innate immune response is generated at an early stage, providing the first line of defense against pathogens. It is fast, reacts within hours and has no immunological memory [38]. The adaptive immune response is the second line of defense which is activated at a later stage. It is characterized by the release of a diverse set of immunoglobulins against the target antigen and also generates immunological memory [38]. The main goal of vaccines is to develop long-term protection against the targeted pathogen by establishing immunological memory, which gets reactivated on subsequent exposure to a pathogen [21]. Figure 1 shows the infection induced by the virus as well as the immunity generated in the host after the administration of the vaccine against the same pathogen. Viruses can enter the body through the mouth, nose, eyes or wounds. After the entry of the virus into the host, it establishes the infection by attaching itself to the cells and binds to their receptors. Then, it replicates within the cell and makes multiple copies of itself by hijacking the host machinery. The newly formed viruses burst out of the infected host cell and start spreading to other cells. Thus, infecting the individual and leading to the symptoms of various diseases such as influenza, chicken pox and the common cold [39]. Vaccines are administered to provide immunity to the host against viral infections. They contain a part of the virus that triggers the immune response by imitating the infection in the body. This leads to the production of effector cells, memory T cells and B cells. These memory cells elicit the generation of antibodies when attacked by the same antigen in the future. Sometimes, administering vaccines can result in minor side effects like body pain and fever that are less severe than the actual infection required for building immunity [40]. The infectivity induced by the virus and the immunity induced after the administration of the vaccine is represented in Figure 1.

Types of vaccines

There are various types of vaccines against viruses that are prepared using different approaches. Each type of vaccine is designed to trigger an adequate immune response against the pathogen. Vaccines largely depend on the active part (i.e., antigenic strain) to elicit an immune response. Based on which part of the virus has been used to develop the vaccine, there are several vaccine types, such as whole pathogen, subunit, nucleic acid and viral vector. Whole pathogen vaccines are made up of either weakened or inactive forms of the virus. Subunit vaccines use a specific part like a protein or sugar of the outer membrane of the virus. Nucleic acid vaccines comprise the genetic material,

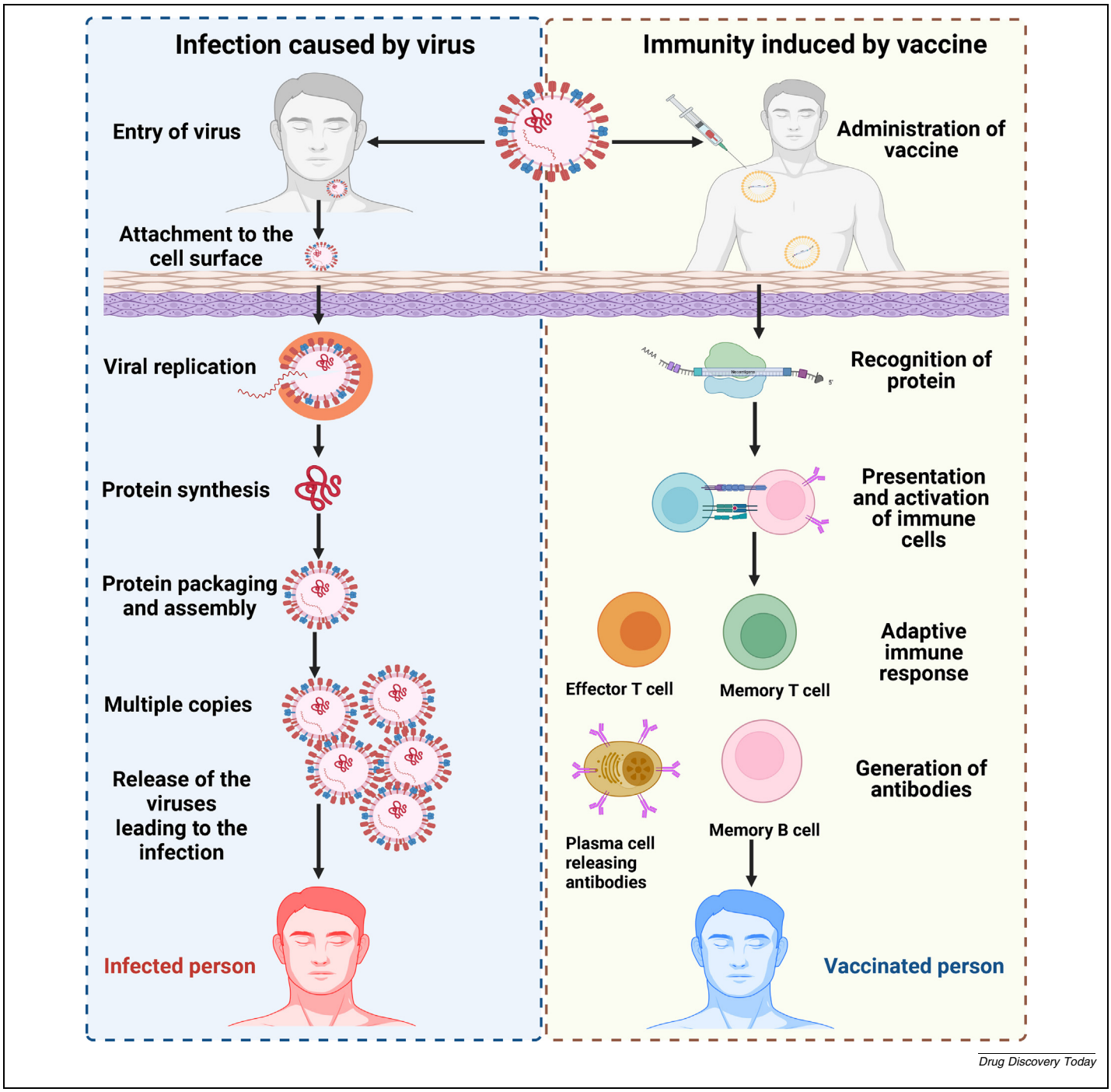

FIGURE 1

Illustration of the infection induced by the virus as well as the immunity generated in the host after the administration of vaccine.

i.e., DNA or RNA of the virus. Viral vector vaccines contain the genetically modified virus, which is harmless and is used to provide immunity. The complete details about different types of vaccines, their pros and cons along with the examples are listed in Table S1 (see Supplementary Material online).

Route of administration

Viral vaccines can be administered into the host body either via needle or needle-less techniques. Needle-mediated techniques consist of intramuscular, intradermal, intravenous and subcutaneous methods and needle-less techniques focus on intranasal and oral delivery to administer the vaccines [41]. Intramuscular administration is the most common mode of delivering the vaccine by injecting it directly into the host muscle through the skin. For example, HIL-214 for norovirus and Moderna's COVID-19 vaccine are administered intramuscularly. Some vaccines such as YF-VAX® for yellow fever and CYD-TDV Dengvaxia® for dengue fever are administered into the subcutaneous layer

of the skin. Some are injected via the dermis (upper layer of the skin), such as ZyCoV-D, CORVax12 and INO-4800 against COVID-19. Further, through intravenous injection, vaccines can be directly infused into the vein, like CHKV-24 against chikungunya fever. By contrast, a needle-free technique of administering vaccines is more favorable. Vaccines FluMist® and Fluenz against influenza are delivered via the nasal mucosa [42]. The most easiest way to administer vaccines is via oral route, which does not need any kind of expertise in handling needles or syringes. Polio vaccine against poliomyelitis is given orally to infants [43].

Approving organizations

Each novel vaccine candidate undergoes an evaluation process for safety, immunogenicity and protective efficacy before being licensed for human use [44,45]. Regulatory agencies like the European Medicines Agency (EMA) (https://www.ema.europa.eu/en), the FDA (https://www.fda.gov/) and WHO (https://www.who.int/) monitor the safety, effectiveness and quality of newly developed vaccines.

Available resources for viral vaccines

Several researchers have made various efforts to develop a number of resources that gather information regarding viral vaccines. For instance, Huvax (https://violinet.org/huvax/stat.php), part of the Vaccine Investigation and Online Information Network (VIOLIN) (https://www.violinet.org/) database, is a web-based licensed human-vaccine database and covers ~243 licensed vaccines against 21 viral diseases (as per information on the web server). Another knowledgebase, Vaccine Knowledge Project (https://vk.ovg.ox.ac.uk/vk/), contains information on 12 viral diseases with their corresponding vaccines; and the Immunization Advisory Center (https://www.immune.org.nz/) maintains evidence-based information on several diseases that can be prevented by vaccination as well as the advantages and disadvantages of immunization. However, the information is scattered throughout the scientific literature, and the existing vaccine repositories hold limited data for the vaccines. To get a complete overview, users must extensively search literature and websites, which is time-consuming and makes the vaccine search challenging. Hence, there is a crucial lack of a comprehensive database that is dedicated only for vaccines against human viral diseases and represents all the information in a user-friendly manner. To overcome these challenges, we have made an attempt to curate all the available information on viral vaccines and collate it in a single platform.

ViralVacDB

We have developed ViralVacDB – a manually curated repository on viral vaccines for humans. It contains a searchable list of viral vaccines and other related information such as vaccine type, administration route, dosage, age restriction, clinical phase and associated target strain. The database holds the information for 422 vaccines against 26 human viral diseases. For the vaccines listed in ViralVacDB, we have performed a thorough analysis of the vaccines and collected the information against 24 fields such as year of manufacture, approval, adjuvant, trade name and vaccine status. Out of 422 vaccines, 145 are approved and 277 are in clinical trials. All this information contained in this database is made freely accessible (https://webs.iiitd.edu.in/raghava/viralvacdb/). In this review, we have discussed and provided insights into major components of viral vaccines such as history, mechanisms, types, route of administration and approving agencies. We anticipate that ViralVacDB will provide assistance for the researchers working in the field of vaccine discovery and development.

Data collection and curation

To provide comprehensive information on viral vaccines, we have manually curated data from a wide range of repositories and sources. The major resources from which we extracted information about viral vaccines include the FDA, WHO, CDC (https://www.cdc.gov/) and Central Drugs Standard Control Organization (CDSCO) (https://cdsco.gov.in/opencms/opencms/en/Home/); information regarding ongoing clinical trials was retrieved from Clinicaltrials.gov (https://clinicaltrials.gov/) and research articles. We have collected the latest information up until November 2022. The gathered information for 422 viral vaccines has been cataloged in a user-friendly tabulated manner.

Data analysis

Presently, ViralVacDB contains 422 viral vaccines against 26 human viral diseases retrieved from existing databases, websites and research articles. Of these, 145 vaccines are already licensed by approving authorities, and 277 vaccines are in the clinical phase. This user-friendly web-based repository contains major fields such as vaccine name, type, eligible age group, vaccine strain, adjuvants, manufacturer name, manufacturing country, year of manufacture, clinical phase, clinical status, dosage, dosage category, administration route and country. The distribution of viral vaccines based on various aspects is depicted in Figure 2. The pie chart indicating the distribution of different types of vaccines is shown in Figure 2a. It was found that 38% of vaccines belong to the whole pathogen group, then there are subunit vaccines (26%), viral vector vaccines (19%) and nucleic-acid-based vaccines (17%). Figure 2b represents the number of vaccines with respect to their route of administration. The bar plot shows that 282 vaccines are administered intramuscularly, 41 are given subcutaneously and 20 are given intranasally, followed by other routes. Figure 2c shows the name of the viruses causing various infections. It can be seen from the plot that 214 vaccines treat infections caused by SARS-CoV-2, followed by 67 for chikungunya virus, 31 for hepatitis, 19 for influenza virus and others. Figure 2d represents the distribution of vaccines for treating several viral diseases. Among them all, vaccines against respiratory diseases are majorly present (59%), followed by exanthematous diseases covering ~18%, hepatitic (7%), hemorrhagic (5%) and other diseases.

Database architecture and web interface

The database has been built using a standard platform based on Linux, Apache, MySQL and PHP (LAMP). MySQL (version 5.7.31) was used at the back-end for managing the data, and Apache (version 2.4.46) as the HTTP server to design the framework of this database. The responsive front-end web interface was devel-

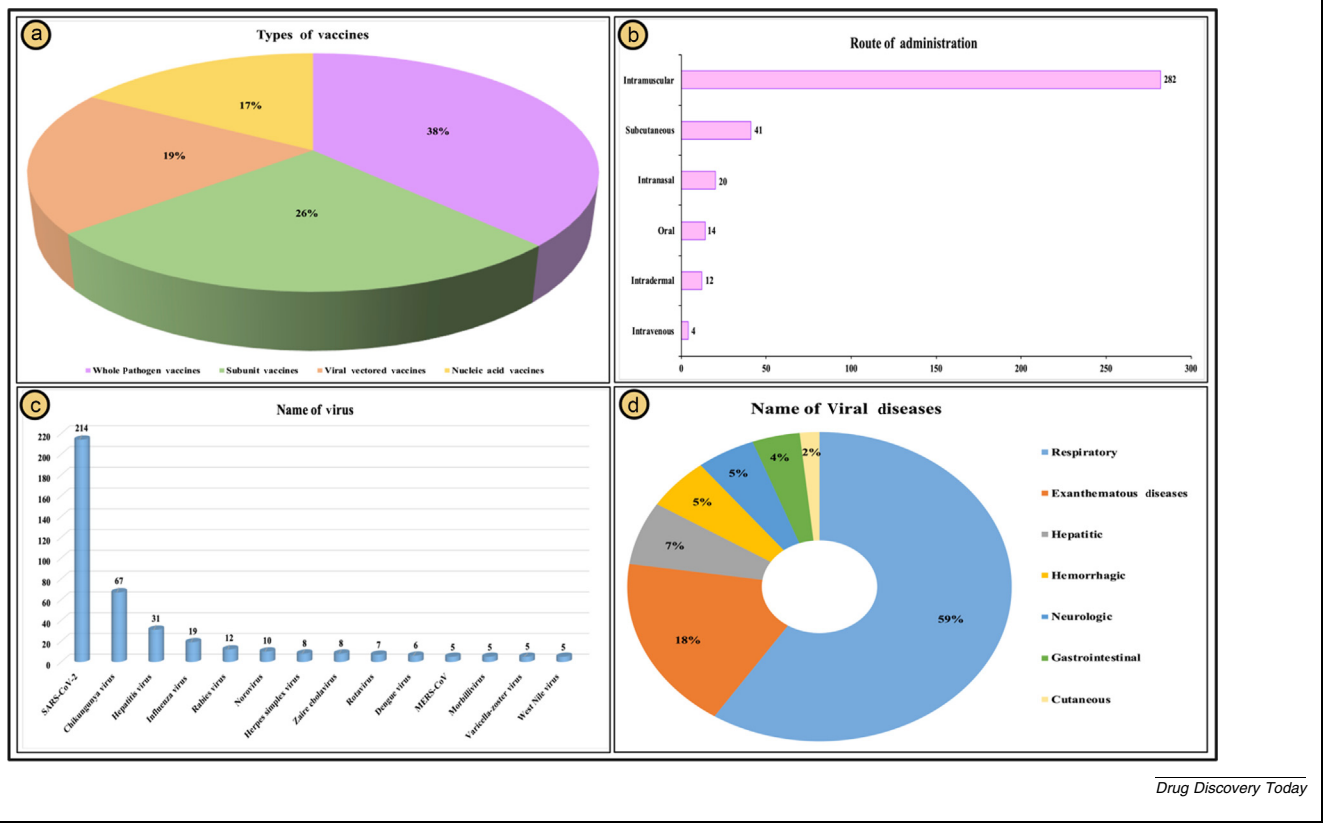

FIGURE 2

Schematic representation of distribution of viral vaccines based on **(a)** types of vaccines, **(b)** route of administration, **(c)** name of virus and **(d)** viral disease.

oped using bootstrap, a popular responsive development framework that includes HTML (version 5), PHP (version 7.3.21), CSS (version 3) and Javascript (version 1.8), which are compatible with smartphones, tablets and desktops. Different modules were integrated into ViralVacDB for data compilation, retrieval and exploration. The complete architecture of ViralVacDB and its different modules is depicted in Figure 3.

Web server facility

To serve the scientific community, we have provided the facilities to browse and explore the comprehensive information in the database. Users can perform different tasks like: (i) extensive searching of vaccines; (ii) data browsing based on categories such as disease name, administration route, vaccine type, transmission route and vaccine status; (iii) see an overview of viral diseases and associated viruses; and (iv) obtain general information. The database consists of several major modules, as discussed below.

Search module

Basic search. This facility allows the users to search the major fields against the vaccines. Fields such as vaccine name, disease name, manufacturer, administration route, clinical phase or vaccine type can be explored by default. It allows users to customize the search criteria by selecting the desired fields.

Advanced search. This is a complex search where the user can provide multiple queries simultaneously with the help of different Boolean operators (like AND, OR and NOT). Both the search modules assist the users to download the obtained results in a comma-separated format. The details of each vaccine entry are linked to a unique vaccine ID which provides all the information in a tabular format.

Browse module

To retrieve information from the database in a simple and effortless manner, users can browse the different major fields such as: (i) disease name – displays different viral diseases with vaccine counts; (ii) administration route – shows the vaccines with their route of administration; (iii) vaccine type – exhibits different types of vaccines along with their count; (iv) transmission route – helps in browsing the major categories of viral diseases like respiratory, gastrointestinal, hemorrhagic as well as the number of vaccines against these diseases; and (v) vaccine status – enables users to browse vaccines based on their status of being approved or clinical phase.

Viral diseases

This module provides detailed information on different types of viral diseases and their causative agents. The viral diseases are grouped into eight major categories: respiratory, gastrointestinal,

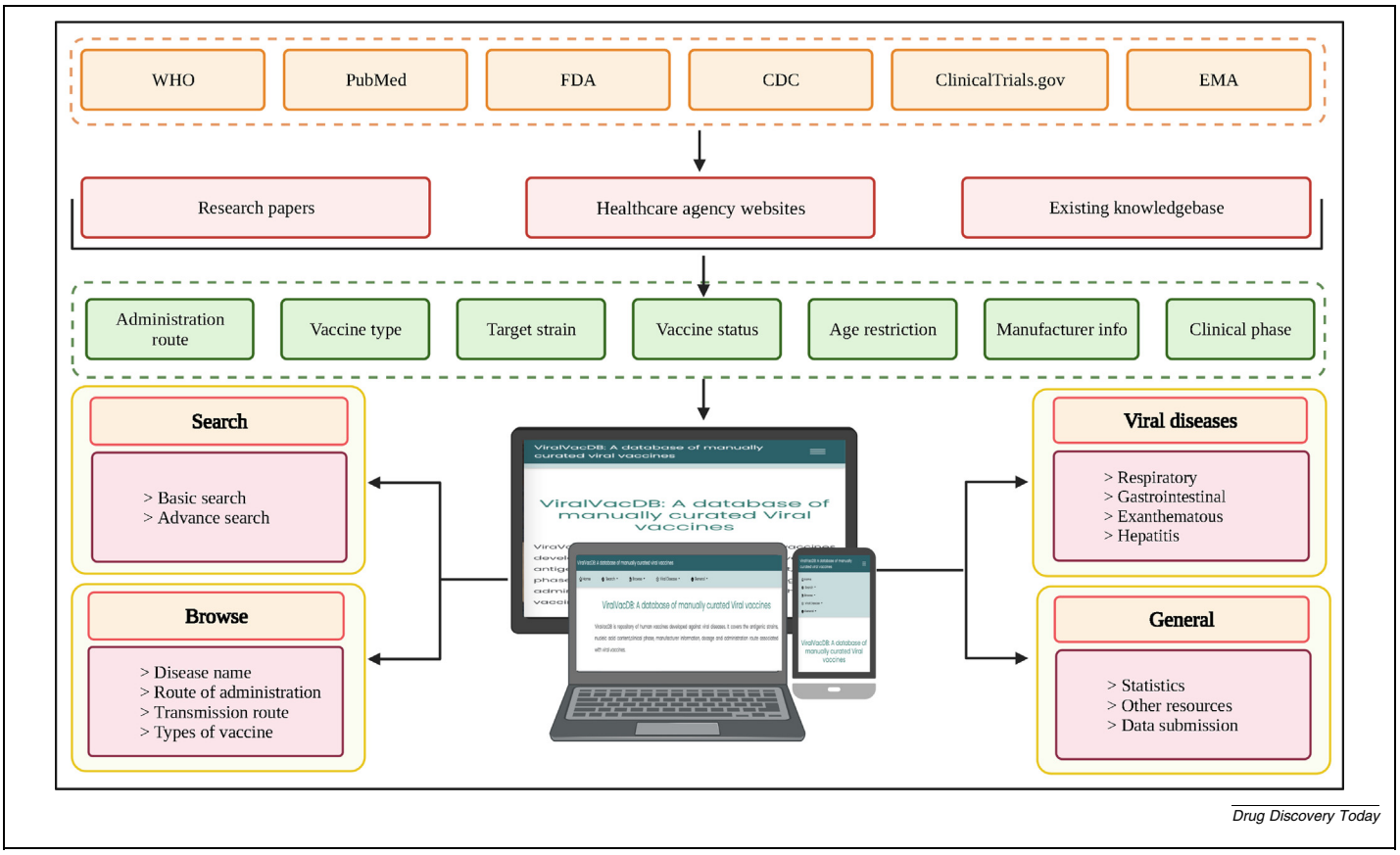

FIGURE 3
Complete architecture of ViralVacDB and its modules.

exanthematous, hepatitis, cutaneous, hemorrhagic, neurologic and others. It covers extensive information about disease symptoms, transmission, zoonotic evidence, associated virus structure, family, genus, genomic and proteomic profiling, antigenic strains and targeted host organisms.

External links

In this module, we have provided cross-linking of our database ViralVacDB to other widely used resources including DrugBank (https://go.drugbank.com/), Ontobee (https://ontobee.org), PubChem (https://pubchem.ncbi.nlm.nih.gov) and NCBI (https://www.ncbi.nlm.nih.gov/). This module contains several fields, such as 'Pharma-based', 'Continent -wise', 'Adjuvant information' and 'Other resources'. Pharma-based information displays a table showing major pharmaceutical companies their origin, and headquarters along with a brief description. Continent-wise information contains the information related to different countries linked to their vaccination schedule, Covid Vaccine Tracker as well as health and vaccine portal. Furthermore, Adjuvant information displays various adjuvants for viral vaccines, its description and additional links to DrugBank, Ontobee, PubChem and PubMed IDs. Other resources cover additional vaccine-related websites and resources.

General information

This module provides users with general information about the database. It includes: (i) statistics – displays the graphical representation of viral diseases, vaccines types, route of administration and clinical phase; (ii) data submission page – facilitates the user to submit the data for any other human viral vaccine; (iii) help page – assists users in efficiently using the different modules through figures and descriptions; and (iv) contact/developers – in case assistance is required, users can reach out to the developers with given contact information.

Utility of ViralVacDB

ViralVacDB can be used to fetch extensive information regarding viral vaccines for humans on a single platform. The step-by-step procedure for extracting the needed information from the database is demonstrated in Figure 4. For example, if the user wants to search for a vaccine named 'Moderna' they should type the vaccine name in the search box provided and can select other fields as per their need (Figure 4a,b). By clicking on the search button, the result page will be displayed (Figure 4c) along with the other selected fields. Each entry is specified with a unique ID which is hyperlinked with the viral vaccine card that gives comprehensive information about each vaccine (Figure 4d).

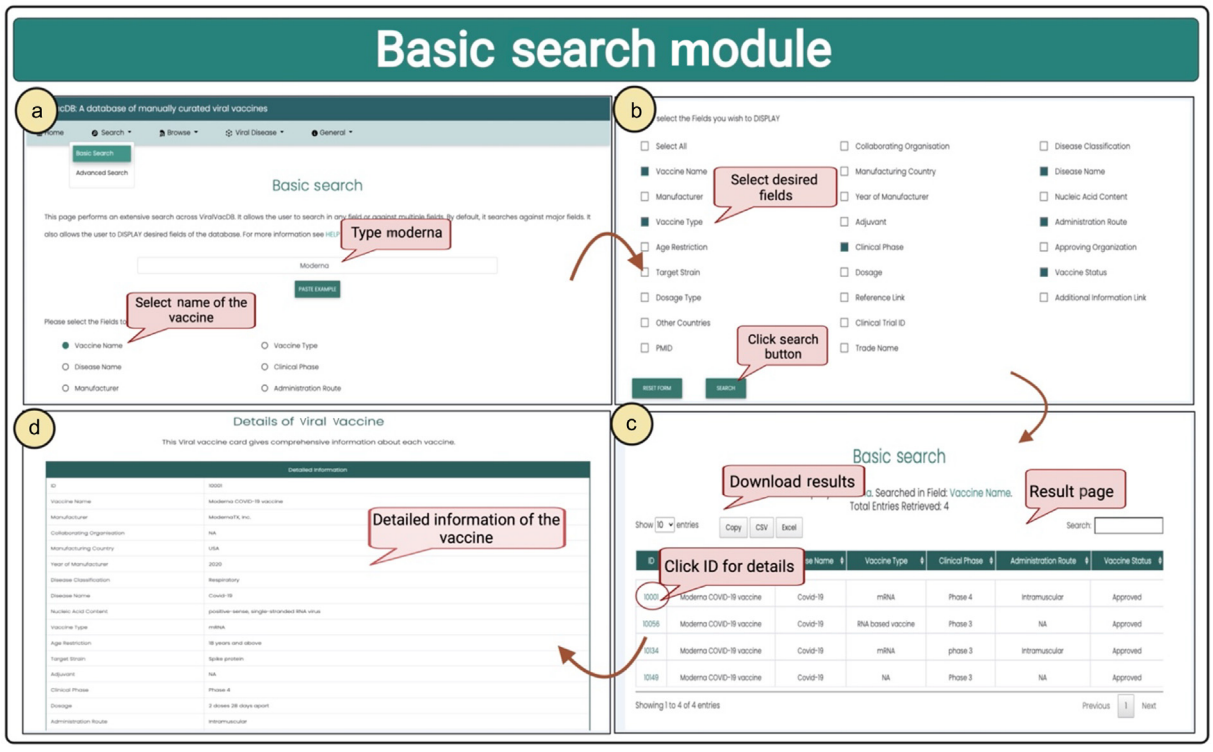

FIGURE 4

Screenshots of ViralVacDB showing **(a)** submission of a query on basic search page, **(b)** display of the other fields, **(c)** results page after submission of a query in the basic search and **(d)** the detailed information after the result page.

Concluding remarks

This review, in conjunction with the database ViralVacDB, provides insights into the viral vaccines against viral diseases in humans. We have emphasized and covered the in-depth description of the history of vaccines, mechanism of action, types of vaccines, route of administration and approving agencies. Virus diseases range from small infections to outbreaks that alter the course of history. There exists enormous variation in viruses, their epidemiology and pathogenesis, which is the leading cause of morbidity and mortality in humans [46]. Over time, several approaches have been adopted and developed to prevent and curb viral spread. The most successful approach for managing viral infection is vaccines. The first vaccine was discovered for smallpox in 1796. Since then, we have seen the major development of several other successful viral vaccines [47]. Vaccination has transformed global health, by eradicating viral diseases such as smallpox [31] and nearly eliminating poliomyelitis that once claimed the lives of millions of people [48]. These vaccines help to manage the treatment of viral infection and provide long-term protection against viruses responsible for infection [49].

Advances in technology and immunological research have led to a better understanding of viral pathogenesis at the molecular level. This has also led to the rapid development of effective vaccines against viral infections [50]. These vaccines are designed to activate the immune response and develop lifelong immunity in minimal dosage with no or mild adverse effects [21]. Different types of vaccines such as live-attenuated, inactivated, subunit, nucleic-acid and viral-vector vaccines are used to provide protection against several viral diseases [22]. Vaccines can be administered through a number of routes like intramuscular, intravenous, subcutaneous, intradermal, oral and nasal. It has been found from our analysis that the intramuscular route of administration is the most common way of injecting viral vaccines into the host. There are several regulatory authorities, for example the FDA, WHO and EMA, that ensure the safety, efficacy, potency and good quality of vaccines before releasing them onto the market for human use. There are several other aspects that are associated with vaccines such as target strains, adjuvant, clinical phase, manufacturer information, approving organization, licensing countries and clinical status. This extensive information is dispersed throughout the literature and various websites. To save time and effort for the users, it would be beneficial if all the information pertaining to viral vaccines could be accessed from a single platform. Taking this into consideration, we developed ViralVacDB, which covers several aspects of 422 viral vaccines against 26 human viral diseases. All the comprehensive information can be accessed freely from the user-friendly interface (available at https://webs.iiitd.edu.in/raghava/

viralvacdb/). The database information will be updated periodically with newly approved vaccines along with other properties. We envisage that this database will be beneficial to the scientific community, clinicians and the general public.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

We are thankful to the Department of Biotechnology (DBT) for providing an infrastructure grant to the institute. NS is thankful to the Department of Science and Technology (DST-INSPIRE) for providing Senior Research Fellowship. NLD is thankful to DBT-RA program in Biotechnology and Life Sciences for providing Research Associate fellowship. ST, NS and NLD are thankful to Department of Computational Biology, IIIT-Delhi, for infrastructure and facilities. We would like to acknowledge that figures were created using BioRender.com.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Author contributions

GPSR conceived and coordinated the project. ST manually collected and curated all the data. NS, NLD and ST analyzed the data. ST, NLD and NS developed the web interface. NS, NLD, ST and GPSR wrote the manuscript. All authors have read and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2023.103523.

References

[1] Louten, J. (2016) Virus structure and classification*Essential Human Virology*. Elsevierpp. 19–29. Elsevier.
[2] Strauss, J.H. and Strauss, E.G. (2008) Overview of viruses and virus infection. *Elsevier*pp. 1–33.
[3] Pattison, J.R. and Patou, G. (1996) Parvoviruses. In: *Medical Microbiology* (4th edn)(Baron S., ed. .
[4] Ganeshpurkar, A. *et al*. (2019) RNA-dependent RNA polymerases and their emerging roles in antiviral therapy*Viral Polymerases*. Elsevierpp. 1–42. Elsevier.
[5] Kim, J.W. *et al*. (2018) Gene/viral treatment approaches for malignant brain cancer*Handbook of Brain Tumor Chemotherapy, Molecular Therapeutics, and Immunotherapy*. Elsevierpp. 211–227. Elsevier.
[6] Chaitanya, K.V. (2019) Structure and organization of virus genomes*Genome and Genomics*. Springer Singaporepp. 1–30. Springer Singapore.
[7] Pellett, P.E. *et al*. (2014) Basics of virology. *Handb. Clin. Neurol*. 123, 45–66.
[8] Lozach, P.Y. (2018) Early virus-host cell interactions. *J. Mol. Biol*. 430, 2555–2556.
[9] Louten, J. (2016) Virus transmission and epidemiology*Essential Human Virology*. Elsevierpp. 71–92. Elsevier.
[10] Mourya, D.T. *et al*. (2019) Emerging/re-emerging viral diseases & new viruses on the Indian horizon. *Indian J. Med. Res*. 149, 447–467.
[11] Andrei, G. (2021) Vaccines and antivirals: grand challenges and great opportunities. *Front. Virol*. 1.
[12] Razonable, R.R. (2011) Antiviral drugs for viruses other than human immunodeficiency virus. *Mayo Clin. Proc*. 86, 1009–1026.
[13] Arts, E.J. and Hazuda, D.J. (2012) HIV-1 antiretroviral drug therapy. *Cold Spring Harb. Perspect. Med*. 2 a007161.
[14] Strasfeld, L. and Chou, S. (2010) Antiviral drug resistance: mechanisms and clinical implications. *Infect. Dis. Clin. North Am*. 24, 413–437.
[15] Bryan-Marrugo, O.L. *et al*. (2015) History and progress of antiviral drugs: from acyclovir to direct-acting antiviral agents (DAAs) for Hepatitis C. *Med. Univ*. 17, 165–174.
[16] Bernasconi, V. *et al*. (2020) Developing vaccines against epidemic-prone emerging infectious diseases. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 63, 65–73.
[17] Clem, A.S. (2011) Fundamentals of vaccine immunology. *J. Glob. Infect. Dis*. 3, 73–78.
[18] Payne, S. (2017) Viral vaccines*Viruses*. Elsevierpp. 73–79. Elsevier.
[19] Excler, J.L. *et al*. (2021) Vaccine development for emerging infectious diseases. *Nat. Med*. 27, 591–600.
[20] https://www.cdc.gov/vaccines/parents/diseases/forgot-14-diseases.html. Accessed November 12, 2022.
[21] Pollard, A.J. and Bijker, E.M. (2021) A guide to vaccinology: from basic principles to new developments. *Nat. Rev. Immunol*. 21, 83–100.
[22] Brisse, M. *et al*. (2020) Emerging concepts and technologies in vaccine development. *Front. Immunol*. 11 583077.
[23] Zhang, L. *et al*. (2015) Effect of vaccine administration modality on immunogenicity and efficacy. *Expert Rev. Vaccines* 14, 1509–1523.
[24] Coffman, R.L. *et al*. (2010) Vaccine adjuvants: putting innate immunity to work. *Immunity* 33, 492–503.
[25] Smith, K.A. (2011) Edward jenner and the small pox vaccine. *Front. Immunol*. 2, 21.
[26] Riedel, S. (2005) Edward Jenner and the history of smallpox and vaccination. *Proc. (Bayl. Univ. Med. Cent.)*. 18, 21–25.
[27] Rappuoli, R. (2014) Inner workings: 1885, the first rabies vaccination in humans. *Proc. Natl. Acad. Sci. U S A* 111, 12273.
[28] Baicus, A. (2012) History of polio vaccination. *World J. Virol*. 1, 108–114.
[29] Tulchinsky, T.H. (2018) Maurice Hilleman: creator of vaccines that changed the world*Case Studies in Public Health*. Elsevierpp. 443–470. Elsevier.
[30] Zhao, H. *et al*. (2020) Hepatitis B vaccine development and implementation. *Hum. Vaccin. Immunother*. 16, 1533–1544.
[31] https://www.who.int/health-topics/smallpox#tab=tab_1. Accessed November 12, 2022.
[32] Jones, T. (2002) Varivax (Merck & Co). *Curr. Opin. Investig. Drugs*. 3, 54–57.
[33] (2003) Influenza virus vaccine live intranasal–MedImmune vaccines: CAIV-T, influenza vaccine live intranasal. *Drugs R D*. 4, 312–319.
[34] Sharma, R. and Sharma, C.L. (2007) Quadrivalent human papillomavirus recombinant vaccine: the first vaccine for cervical cancers. *J. Cancer Res. Ther*. 3, 92–95.
[35] Guy, B. *et al*. (2015) Development of the Sanofi Pasteur tetravalent dengue vaccine: one more step forward. *Vaccine* 33, 7100–7111.
[36] Hoff, N.A. *et al*. (2022) Immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccination in exposed and potentially exposed persons in the Democratic Republic of the Congo. *Proc. Natl. Acad. Sci. U S A* 119.
[37] Polack, F.P. *et al*. (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med*. 383, 2603–2615.
[38] Marshall, J.S. *et al*. (2018) An introduction to immunology and immunopathology. *Allergy Asthma Clin. Immunol*. 14(Suppl 2), 49.
[39] Cohen, F.S. (2016) How viruses invade cells. *Biophys. J*. 110, 1028–1032.
[40] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html. Accessed November 12, 2022.
[41] Kramps, T. and Probst, J. (2013) Messenger RNA-based vaccines: progress, challenges, applications. *Wiley Interdiscip Rev RNA* 4(6), 737–749.

[42] Vetter, V. *et al*. (2018) Understanding modern-day vaccines: what you need to know. *Ann. Med.* 50, 110–120.
[43] Zhu, Q. and Berzofsky, J.A. (2013) Oral vaccines: directed safe passage to the front line of defense. *Gut Microbes* 4(3), 246–252.
[44] Han, S. (2015) Clinical vaccine development. *Clin Exp Vaccine Res* 4(1), 46–53.
[45] Singh, K. and Mehta, S. (2016) The clinical development process for a novel preventive vaccine: An overview. *J Postgrad Med* 62(1), 4–11.
[46] Parvez, M.K. and Parveen, S. (2017) Evolution and Emergence of Pathogenic Viruses: Past, Present, and Future. *Intervirology* 60(1–2), 1–7.
[47] Rodrigues, C.M.C. and Plotkin, S.A. (2020) Impact of vaccines; health, economic and social perspectives. *Front. Microbiol.* 11, 1526.
[48] https://www.who.int/health-topics/poliomyelitis#tab=tab_1. Accessed November 12, 2022.
[49] Goldenthal, K.L. et al. (1996) *Control of Viral Infections and Diseases*.
[50] McCullers, J.A. and Dunn, J.D. (2008) Advances in vaccine technology and their impact on managed care. *P T.* 33, 35–41.