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A comprehensive overview of vaccines developed for pandemic viral pathogens over the past two decades including those in clinical trials for the current novel SARS-CoV-2

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The unprecedented coronavirus disease 2019 (COVID-19) is triggered by a novel strain of coronavirus namely, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). Researchers are working around the clock to control this pandemic and consequent waves of viral reproduction, through repurposing existing drugs as well as designing new vaccines. Several countries have hastened vaccine design and clinical trials to quickly address this outbreak. Currently, more than 250 aspirants against SARS-CoV-2 are in progress, including mRNA-replicating or non-replicating viral vectored-, DNA-, autologous dendritic cell-based-, and inactivated virus-vaccines. Vaccines work by prompting effector mechanisms such as cells/molecules, which target quickly replicating pathogens and neutralize their toxic constituents. Vaccine-stimulated immune effectors include adjuvant, affinity, avidity, affinity maturation, antibodies, antigen-presenting cells, B lymphocytes, carrier protein, $CD4^+$ T-helper cells. In this review, we describe updated information on the various vaccines available over the last two decades, along with recent progress in the ongoing battle developing 63 diverse vaccines against SARS-CoV-2. The inspiration of our effort is to convey the current investigation focus on registered clinical trials (as of January 08, 2021) that satisfy the safety and efficacy criteria of international wide vaccine development.

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Senthilkumar obtained his M.Sc. chemistry at Bharathidasan University, where he was involved in mechanistic studies of anticancer drugs. He then explored new drug discovery and development from marine and medicinal plants, and their synthesis which is been developed at IIT Madras, IISc Bangalore and IIT Kanpur. He developed variegated drug candidates at IIT Madras, such as phosphate binder resin, sevcar (two patents); and tolvaptan, hyponatremia and cystagon; and drugs from Terminalia arjuna. He then engaged in the peptidomimetic domain for antitumor screening at IISc Bangalore. Then back at IIT Madras worked on transitmycin, which is in phase-II pre-clinical trials. He has also discovered new blood, breast, and liver cancer drugs, and diabetic treatments. Recently, he also discovered, arjunetin, that is a better candidate for COVID-19 treatment than FDA approved drugs.

Introduction

One of the most successful therapeutic strategies to prevent or control various diseases is by "vaccination" protocol.[1,2] Millions of lives have been saved because of vaccinations, which cover a number of diseases including certain types of cancer, HIV and many viral infections.[3] Vaccination was initially accomplished by Edward Jenner, who was the pioneer for smallpox in the late 18th century.[4] In the 1980s, the development of vaccines to fight against pathogenic microorganisms was tentatively introduced. Vaccines are now employed to improve and increase the protection capability (immunity) of the body to fight severe infection and disease,[5] and moreover, primarily intend to make immunity stronger and reduce resistivity of diseases by reducing the reproduction of target pathogens. The majority of vaccines actively exist in the immune system, since anti-bodies are constantly generated in the body to sustain a healthy immunity system.[6,7]

General components of vaccines

A vaccine consists of an antigen, stabilizer, adjuvant, antibiotic, preservative, and chemical reagents such as formaldehyde.[8] The advantages and disadvantages of vaccinations[9a] are listed in Table 1.

Antigen. The component matching the structural array of disease-oriented organisms, wherein, they are identified by the immune system as 'foreign' and cause an active immune response.

Stabilizer. This module is employed to assist the vaccine by sustaining its efficiency during storage. Instability of the vaccine can lead to reduced antigenicity and decreased infectivity of live attenuated vaccine (LAV). Magnesium chloride ($MgCl_2$) for oral polio vaccine (OPV), magnesium sulfate ($MgSO_4$) in measles vaccines, and lactose and gelatin associated with sorbitol, are current representatives of stabilizing factors.

Adjuvant. They are responsible for enhancing the efficacy of the vaccine by motivating the generation of antibodies. Chemically, adjuvants are a highly heterogeneous group of compounds (including Al salts).

Antibiotics. Used in lower amounts during the development phase, to circumvent bacterial infection during tissue culture cells where the viruses are grown. MMR (measles, mumps, rubella) and IPV (inactivated polio vaccine) associated vaccines have a minimum amount (<25 μg) of neomycin for each dose.

The MMR vaccine was developed by Maurice Hilleman in 1971. Mumps, like measles infections, are caused by an RNA based virus from the Paramyxoviridae family. Moreover, measles and mumps belong to the genus Rubulavirus, it is a human disease with no animal reservoirs. Generally, the MMR vaccine exhibits side effects of a painful arm from the shot, minor rashes, generally in teen/adult women who have no earlier immunity; then the rubella vaccine component can result in joint and tendon stiffness. This vaccine is also associated with the minor threat of seizures/jerking instigated by fever, but is not connected with any enduring effects. The threat of febrile seizures increases as infants get older, hence this vaccine is recommended at a young age. Some people may experience cheek/neck inflammation, impermanent low platelet counts that generally do not require treatment and are also not life threatening.[9b]

In 1955, Jonas Salk initiated an inactivated polio vaccine (IPV), after that, Albert Sabin further developed the live, OPV. Even though poliovirus has three serotypes, both vaccines are trivalent and offer good resistivity against poliomyelitis, a limited number of countries have continuously provided IPV. Sabin's OPV vaccine is underused in most countries due to minimising oral management, but it advances immunity in the intestine, which is capable of spreading to others, and is associated with lower cost.[9c]

Preservatives. They are added in multi-dose vaccines, which can be used to control bacterial and fungal growth, including thiomersal (sodium(2-carboxylatophenyl)sulfanyl-ethyl mercury), formaldehyde, or phenolic derivatives. In fact, formaldehyde is responsible for inactivating the viruses (*e.g.* IPV) and removing toxicity in bacterial strains, including the toxin employed in diphtheria and tetanus vaccines.

Types of vaccines

Various kinds of vaccines are available and those which are administered to infants and adults can be classified (Fig. 1) as follows:

- Live-attenuated.
- Inactivated.
- Toxoid.
- Conjugate.
- Subunit.

Live attenuated vaccines. These vaccines are adapted from the existing bacteria or virus, they have been weakened, and thus will not result in serious disease in people with strong immunity. LAV vaccines are more similar to the actual infection. A few representative examples are the MMR and varicella (chickenpox) vaccines. Albeit, it is efficient, but not everyone

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Table 1 Advantages and disadvantages of vaccines

Advantages	Disadvantages
Protection of inhabitants against disease	Uncertainty about complete protection
Preventing epidemic and pandemic diseases	May have some possible side effects
Prevents diseases spreading to others	Requires NHS/individual outlay
Avoids large cost for the treatment of infected patients	Injections are not pleasant/more immune booster injections are inconvenient

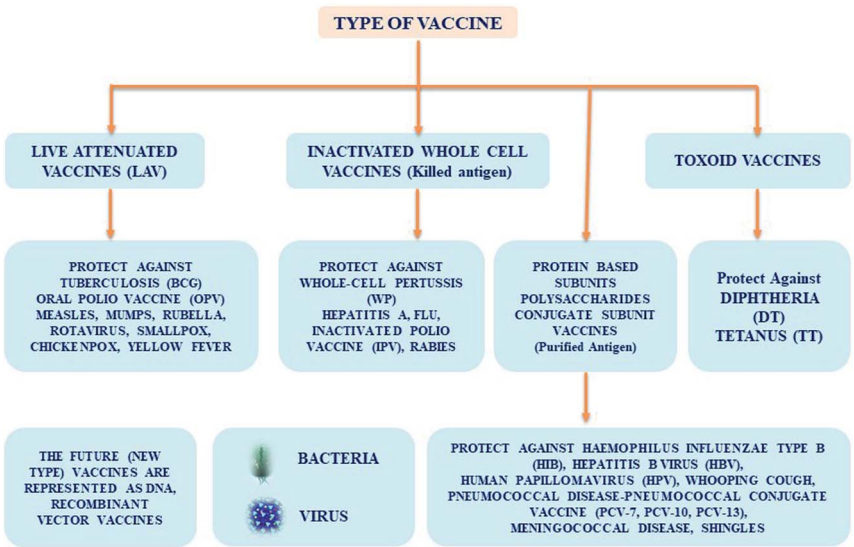


Fig. 1 Pictorial representation of vaccine types.

can be administered these vaccines, including children and patients undergoing chemotherapy as their immune system is too weak.

Inactivated vaccines. These vaccines are made from inactivated or dead organisms. The polio vaccine is an example of an inactivated vaccine, which generates an immune response through various routes different to the live attenuated vaccine. It requires a higher dosage to increase and/or sustain immunity.

Toxoid vaccines. This vaccine prevents the disease resulting from the toxins released by a virus into the body. Since the toxic substances administered are weak they are unable to cause the illness, while the immune system which encounters this toxoid vaccine, becomes able to repel the natural toxin. The DTaP vaccine for diphtheria and tetanus toxoids falls into this category.

Conjugate vaccines. They defend the system against different kinds of bacteria which have antigens that are surface coated with polysaccharide units. It is obvious, that this sugar coated unit masks the antigen. These vaccines append (or conjugate) themselves to the polysaccharide units on the antigens. *Haemophilus influenzae* type B (Hib) vaccine is an example of the conjugate type.

Subunit vaccines. These vaccines are made up of simple fractions of the virus/bacteria or subunits, rather than the complete germ. Since the subunit vaccines have an essential antigen only and are not the molecular array constituting the germ, they have less side effects. The DTaP vaccine-pertussis (whooping cough) module is a paradigm of subunit vaccines.

Common characteristics of vaccines

Live attenuated vaccines are typically grown in animal cell lines under poor development conditions. The development of an inactivated vaccine involves use of thermal or chemical methods in the beginning, and its mode of action involved in conferring immunity is not fully known. However, the live attenuated or execution of entire organism-supported vaccines have shown a lot of success in the control and inhibition of severe transmittable diseases in human, including animal infectious cattle plague, classic swine fever, equine infectious anaemia, measles, mumps, polio, rubella, smallpox, and so on. In recent times, the use of LAVs, subunit and peptide based vaccines have become possible because of progressive technologies in molecular biology. LAVs are based on the mechanism of action associated with the immune response. Inactivated vaccines, based on antibodies have been mostly used to prevent and manage microbial infectious diseases. LAVs introduce stronger cell immune responses that are decisive to remove several intracellular viral pathogens. However, these pathogens sometimes bypass inactivated vaccines[9d] by mutating peripheral antigens. On the other hand, subunit and peptide based vaccines are less efficient in drawing a strong $CD8^+$ immune response.

Progressive vaccination involves the use of non-viral distributed nucleic acid-supported vaccines, which imitate live microorganism infection- or immunization. This leads to T-helper cellular immune responses. In addition, this vaccine development[9e,f] is harmless and consumes less. It does not require extreme infectious organisms, so is safe from infectivity through live transmittable agents and the discharge of harmful pathogenic organisms. These vaccines fill the gap between a virus outbreak and design of a desirable vaccine, wherein they are classified as DNA/RNA based pentose-carbon sugar motif. The remarkable growth of RNA-associated vaccines resulted in the growth of mRNA based vaccines. It is quite significant to note that mRNA vaccines provide many valuable benefits when compared to viral vectored- and DNA vaccines.[10]

Proceedings of vaccination against viral diseases

In 1970, to evade the prevalent spread of foot and mouth disease, scientists discovered a vaccine using a single protein from the virus. Despite their achievements in virology, in particular vaccine studies and their development, the lack of understanding of immunological mechanisms of action during induced defensive immunity, has prevented the use of existing vaccines during global pandemic outbreaks of related diseases with similar viral pathogens. The immune system protects against various pathogens, including distinctive units of T-helper cells that are useful to protect against various unusual pathogens. Besides, the follicular T-helper cells (T_{FH} cells) generate interleukins (ILs) and support the partition of B cells (they are lymphocytes, and take part in the humoral immune response) and generation of Memory B cells. Furthermore, Memory T cells can be sub classified as $CD4^+/CD8^+$ T cells (Cluster of Differentiation) and their functionalities are (a) central memory and (b) effectors memory, which provide various responses upon vaccination against different pathogens.[11] Different vaccines attempted for identical pathogens depend on the perceptions of the scientist,[12] many healthcare professionals do not pay sufficient attention to vaccines, which may result in uncertainty in their efficacy, side effects and toxicity. Table 2 lists the various vaccines discovered that are available in the current market for protection against viral infections. They are listed on the basis of various factors,[13,14] including the apparent protection level, plausible mechanism of action, possibility of usage for other diseases.[15,16]

Mode of action stimulated by vaccines

Normally antibodies prevent/minimize infections from extracellular pathogens:

(a) use enzymatic active sites to fuse to toxins to break their diffusion;

(b) prophylactic action preventing viral replication;

(c) facilitate opsonophagocytosis of extracellular bacteria;

(d) inducing the complement cascade.

$CD8^+$ T cells do not inhibit infection but work to minimize, regulate, and remove intracellular pathogens through:

(a) direct destruction of infected cells (discharge of perforin – a pore forming cytolytic protein present in cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells), granzyme (serine proteases delivered through cytoplasmic granules inside cytotoxic T cells and NK cells);

(b) destroy infected cells with antimicrobial cytokine release.

$CD4^+$ T cells do not inhibit infection, however they contribute in the minimization, regulation, and refinement of extra- and intra-cellular pathogens with their control and cytokine-development capabilities. The main examples of $CD4^+$ T cells are:

(a) Follicular T-helper (Tfh) cells yielding predominantly interleukin (IL)-21 and providing assistance to B-cells;

(b) T-helper 1 (Th1) effector cells yield interferon (IFN)-γ, (TNF)-α/TNF-β, IL-2, and provide a major role in controlling intracellular pathogens *e.g.*, viruses and bacteria such as *M. tuberculosis*;

(c) Th2 effector cells generate IL-4, IL-5, IL-13, and impact extracellular pathogens such as bacteria and helminths;

(d) Th9 effector cells generate IL-9 and also defend against extracellular pathogens;

(e) Th17 effector cells generate IL-17, IL-22, and IL-26 and participate in mucosal protection (for example against, *S. pneumoniae, B. pertussis, M. tuberculosis*).

Main effectors of vaccine responses

Vaccines prevent disease by inducing effector modes of action in cells/molecules to reduce the development of pathogens and deactivate their toxic effects. Vaccine-stimulating immune effectors are resourceful antibodies generated by B lymphocytes' ability to interact to a particular toxin/pathogen. A pictographic representation of vaccine immunological function is shown in Fig. 2.

Isotype switching. Control of immunoglobulin (Ig) expression and production from IgM yielding IgG, IgA, or IgE that ensues through B-cell differentiation by DNA recombination.

Marginal zone. The zone between the spleen's red pulp and white pulp is known as marginal zone. Its main function is to catch particulate antigens from the circulation and distribute them to lymphocytes.

Pattern recognition receptors. These germline-encoded receptors sense the existence of infection through the identification of pathogenic microbe molecular arrays, and stimulate innate immune responses.

Regulatory T cells-t. T cells secrete cytokines (IL-10, transforming growth factor [TGF]-β/surface markers) and react to reduce immune system response through different modes of action, this sustains immune homeostasis and tolerance to self-antigens.

Resident memory T cells. Effector memory T cells exist in particular tissues (such as the lungs, gut, and skin) and are an instant and early line of protection against various viral and bacterial pathogens.

Somatic hypermutation. This is a process which intercalates unsystematic mutations in the B-cell receptor region (*i.e.*,

Table 2 The various antiviral vaccines available in the last two decades, and their characteristics

Characteristic vaccines							
S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
1	AJ vaccines	Picovax IPV vaccine, Danish Medicines Agency	Inactivated Polio Vaccine (IPV)	IPV provides serum immunity to each poliovirus (three types) and defence against any ensuing paralysis causative disease (poliomyelitis). The mucosal immunity level in the intestine is less than that afforded by OPV, this difference may slightly show in the pharyngeal mucosal lining. Prevents poliovirus in the nervous system; immunostimulant	Diphtheria, whooping cough, tuberculosis, tetanus, polio and bladder cancer	2019	17
2	Grippol plus	Quadrivalent AbbVie	Polymer supported inactivated influenza vaccine 3-valent, egg derived adjuvanted influenza vaccine, polyoxidonium as a distinct adjuvant	Vaccine primes advanced meticulous anti-influenza immunity formation; immunostimulant	To treat influenza virus infection (A/H1N1 + A/H3N2)	2018	18
3	Ys-On-001	Yivyka polyinosinic-polycystidylic acid/ inactivated rabies virus Yisheng Biopharma	Cancer vaccines anti-neoplastics	B-cell stimulant, cytokines stimulant, dendritic cell stimulant, immune-modulator, macrophage modulator, natural cell stimulant, regulatory T lymphocyte inhibitor, Th1 cell stimulant	Cancer vaccines pancreatic cancer	2017	19
4	Adimmune's quadrivalent flu vaccine (4142)	Adimflu-S (QIS)BioB2B Taiwan	Monovalent vaccine, egg-based inactivated split virus, influenza H1N1 vaccine	Immunostimulants; inactivated virus from chick embryo culture split virus	Influenza A (H1N1) vaccine during pregnancy	2017	20
5	Quadrivalent influenza vaccine (J0&BB02)	Vaxigrip Tetra QIVSanofi Pasteur	Split influenza virus vaccine	Induces the humeral antibodies against hemagglutinins inhibition (HAI) within 2–3 weeks; antibodies neutralize the influenza viruses	Potent immunization against the four influenza virus strains (A and B types have two each)	2017	21
6	NBP-608	SKY Zoster	Attenuated zoster-, varicella-type vaccine	Inducing both humoral and cellular immune response, which creates an IgG humoral immune response; varicella-zoster specifically activate $CD4^+$ T-helper and $CD8^+$ T-lymphocyte cells	Varicella-zoster virus (VZV), a human neurotropic alpha-herpes-virus. Major infection causes varicella (chickenpox)	2017	22
7	HBV-ISS (Dynavax)	Heplisav-B	Hepatitis B virus used for vaccine development	Immune-stimulatory DNA sequence (ISS) ISS-1018, adjuvant proceeds TLR-9 agonist, which is used for potential prevention and treatment of HIV infection	Treatment of HBV-, HIV viruses	2017	23

Table 2 (*Contd.*)

Characteristic vaccines

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
8	GSK-1437173A	Shingrix GSK	Non-live, recombinant subunit vaccine; varicella vaccine herpes zoster (Hz/su) 2q4vaccine candidates	Antigen IgE and adjuvant system AS01B develop VZV-specific immune response in a weakening immune system. Generates a long-term immune response, Shingrix helps to address age-related decline in shingles immunity	To prevent herpes zoster (HZ) infection	2017	24
9	DTPa-hepB-IPV-Hib	EasySix, Hexaxim Panacea Biotech	6 in 1 combination Infanrix hexa whole cell pertussis antigen	The body produces its own antibodies to protect against bacteria and viruses causing different infections	Diphtheria, DTP, Hepatitis B, Hib, IPV, Pertussis, Polio, Tetanus vaccine	2017	25
10	Ad5-EBOVJ07BX02	ErveboBIB, CanSinoBIO	Glycoprotein recombinant adenovirus type 5 Ebola virus vaccine	Recombinant replication deficient human Ad5 vector stimulating immune responses and defending against the Ebola virus	To treat Ebola virus	2017	26
11	Tetravalent inactivated influenza vaccine (TIV)	Vaxiflu-4 Zydus Cadila	Influenza vaccine	To increase immunity by generating antibody proteins, which defend against infection caused by the virus present in the vaccine	Treating influenza viruses-H1N1, H3N2, Type B (Brisbane and Phuket)	2017	27
12	Flu Vac Qs 2019–20 (4 Yr Up) CD,BL-125408	Flucelvax Quadrivalent Seqirus, Inc	Cell based flu vaccines	Vaccine motivates the body to produce its own immunity (antibodies) against the virus	To prevent influenza A and B viruses	2016	28
13	Quadrivalent influenza vaccine (QIV) (GQM-10)	Vaxigrip TetraSanofi	Inactivated influenza vaccine (split version)	To enhance the protection from circulating influenza B viruses	To protect against influenza (flu) viruses	2016	29
14	Live attenuated influenza vaccine (LAIV) J07BB03	FluMist Quadrivalent Influenza Tetra-Medimmune	Attenuated virus	LAIVs induce T cell antibody-reactions against the surface protein of HA and NA; LAIVs provide hetero-subtype protection in humans	To prevent common flu; influenza A-(H1N1), (H3N2), and B-viruses	2016	30
15	Enterovirus type 71 vaccine (Vero cells)	Inlive SINOVAC	Inactivated EV 71 virus antigen vaccine	Generate immune reactions against EV71 virus	To prevent hand-foot-mouth disease (HFMD) caused by EV-71	2016	31
16	Inactivated influenza vaccine	Cadiflu-S CBL Biologicals Pvt. Ltd	Inactivated vaccine	To develop immunity against the disease by forming antibodies	To prevent influenza and protect against its effects	2016	32
17	Inactivated quadrivalent influenza vaccine (split version)	Afluria Quad 2020 Seqiruspty Ltd	Influenza quadrivalent vaccine 2020	Against influenza-A and influenza-B type viruses	To prevent influenza A and B viruses	2016	33
18	Riv-4 (RIV4)	Flublok-QSonofi Pasteur	Quadrivalent recombinant influenza vaccine	Humoral immune response measured by hemagglutination inhibition antibodies	To prevent influenza A (H1N1) and B (H3N2)	2016	34
19	Gam Evac Combi	Combined Vector Based Vaccine	Heterologous VSV and adenovirus type-5 vectored Ebola virus	Heterologous prime-boost vaccine humoral immune response, cell facilitated immune response to Ebola	To prevent Ebola viral disease (EVD)	2015	35

Table 2 (*Contd.*)

Characteristic vaccines

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
20	In32 Activated Sabin polio vaccine	Ai Bi Wei IMB China	Inactivated Poliomyelitis (IPV)	Inactivated vaccines offer immunity by delivering an inactivated antigen. This vaccine cannot cause disease, thus, it may be administered to an immuno-compromised host	To prevent polio in new born babies	2015	36
21	Rotavirus Orv-116E	ROTAVAC 5D Vero cells Derived Bharath Biotech	Rotavirus vaccine live attenuated monovalent vaccine	Rotarix (vaccine prevents rotavirus infectivity) reproduces in the small intestine and induces immunity; the particular mechanistic action of immunology by rotarix against rotavirus gastroenteritis is unknown	To prevent rotavirus gastroenteritis	2015	37
22	NBP-607-QIV	SKY cell flu Quadrivalent SK Bioscience	Cell cultured quadrivalent inactivated subunit influenza vaccine	Immunity for influenza viruses A and B subtypes. Sero-protection is generally obtained within three weeks	To treat influenza virus infections	2015	38
23	GC-3110A, GC-3110B	GCflu Quad GC Pharma	Quadrivalent influenza virus vaccine	Hemagglutination inhibition antibody response	To treat influenza virus infections	2015	39
24	Chimerivax-dengue (CYD-TDV)	Dengvaxia Sanofi Pasteur	Live attenuated tetravalent chimeric vaccine	Antibody dependent improvement	To prevent Dengue virus-1, 2, 3 and 4 fever in humans	2015	40
25	H5N1 influenza (avian flu) vaccine (Rx)	Audenz Vn-101 Sonali Pasteur GSK	Egg based H5N1 vaccines, inactivated influenza virus vaccine	Induces immunity (antibodies), which act against viral HA in the vaccine, after interrupting viral attachment to human respiratory cells, provides immunity to influenza A virus subtype H5N1	To treat influenza virus	2014	41
26	9-Valent HPV vaccine [9v HPV]	GARDASIL 9	Recombinant virus	Prevent HPV through humoral immune responses induced by the vaccine	Prevention of cervical, vuvar, vaginal, anal, or pharyngeal, head and neck cancer; by preventing papilloma virus (HPV) infection	2014	42
27	Cell cultured-H5N1 vaccine KD-295	GSK	Emulsion cell culture influenza HA vaccine (Prototype)	Antibody titer calculated through hemagglutination inhibition (HI): high-titer virus generation led to suspension of growth of MDCK (Madin–Darby Canine Kidney) and Vero cells in a serum-free distribution	To prevent influenza A virus H5N1	2014	43

Table 2 (*Contd.*)

Characteristic vaccines

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
28	Live modified vaccine virus Ankara Ankara-Bavarian Nordic (MVA-BN)-J07BX	IMVANEX/IMVAMUNE JYNNEOS	Non-replicating small pox vaccine	Non-replicating and capable of generating humoral and cellular immune response to orthopox-viruses	To prevent smallpox	2013	44
29	Japanese encephalitis vaccine BBIL/JEV	JENVAC Bharath Biotech	Inactivated Vero cell-derived viral vaccine	JENVAC is sufficient to elicit an immune response	To protect against Japanese encephalitis virus (JEV)	2013	45
30	Fluzone quadrivalent BL 103914/J07B B	FLUZONE Quadrivalent Sanofi Pasteur Inc.	Inactivated quadrivalent influenza virus vaccine type A and type B (split version)	Stimulates the production of specific antibodies	Prevents influenza diseases, type A and B	2013	46
31	FLU-Q-QIV flu laval quadrivalent GSK-2282511A	FluLaval™ Quadrivalent Glaxo Smith Kline (GSK)	Influenza virus vaccine	Vaccines which improve immunity against the viral pathogen leading to influenza: they induce the generation of antibodies	Prevents influenza diseases, type A and B	2013	47
32	DTa-IPV-HePB-HibHexavalent vaccine6-in-1 vaccine J07CA09	Hexyon, Infanrix, Vaxelis	Hexavalent vaccine	Booster vaccination	To treat DTaP, hepatitis B, polio, haemophilus influenza diseases	2013	48
33	GSK-2282512a BL 125127	Fluarix Quadrivalent (FLU Q-QIV) Glaxo Smith Kline Biologicals	Inactivated influenza vaccine, quadrivalent, seasonal	Increases immunity for treatment of disease originating from influenza-A subtype and type B viruses	Prevents disease triggered by influenza A subtype and type B viruses	2012	49
34	ChimeriVax™-JE	IMOJEV Sanofi	Live attenuated Japanese encephalitis vaccine (JEV), monovalent	IMOJEV is highly immunogenic and able to induce continuing immunity through both preclinical and clinical trials	To prevent yellow fever virus	2012	50
35	Prepandemic influenza vaccine (H5N1) J07BB01	Vepacel	Inactivated flu strain known as A/Vietnam/1203/2004 (H5N1) whole virion, derived from inactivated Vero cells	Overall the vaccine primes the immune system	Protect against influenza H5N1 (bird flu)	2012	51
36	Medi-3250STN: 125020	FLUMIST Quadrivalent Med-Immune	Influenza vaccine, live attenuated influenza vaccine (LAIV)	To provide immunity against influenza virus caused by subtypes A and B	Protects against influenza	2012	52
37	Hepatitis E hecolin (HEV-239)	Hecolin Xiamen Innovax Biotech	Non enveloped virus with positive sense HEV vaccine, a recombinant vaccine	HEV 239 treatment induces a strong anti-HEG IgG response, through early antibody mobilisation	Fights against hepatitis-E virus	2012	53
38	Measles/rubella vaccine	German measles	Live attenuated (weakened) viruses	Immunostimulant, produces antibodies (associated proteins fight and kill measles, mumps, and rubella (MMR) viruses	Prevent MMR viruses	2011	54
39	Human inactivated influenza vaccine (H1N1) 2009 vaccine. Pandemic influenza strain A/California/7/2009/nyMC X-179A	HNVAC (Bharath Biotech)	Inactivated Influenza A virus vaccine (H1N1). Cell culture derived vaccine	Active immunization agent, which acts against the influenza A (H1N1) 2009 virus	Activity against influenza A	2010	55

Table 2 (*Contd.*)

Characteristic vaccines

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
40	Influenza A virus (H1N1), monovalent vaccine	2009 Influenza A (H1N1), Sonali Pasteur	Monovalent vaccine, adjuvant	Active immunization for preventing disease caused by influenza virus A (H5N1)	To prevent influenza A viral disease	2010	56
41	Quadrivalent flu vaccine	FLUCELVAX	Cellular influenza vaccine	Active immunization for preventing influenza subtypes A and B causative diseases	To defend against four different strains of influenza for both subtypes A and B	2010	57
42	Influenza vaccine (whole virion). Inactivated combination	Vaxiflu-S Fluzone Zydus Cadila Healthcare Ltd	Inactivated influenza vaccine (NZ)	Active immunization for preventing Vaxiflu-X	To assist in protection against influenza	2010	58
43	H1N1 pandemic influenza vaccine H5N1 strain of the flu virus A/Vietnam/1203/2004Flu strain/California/07/2009 (H1N1) virus	Celvapan Baxter International	Whole virion in Vero cell-based influenza vaccine, inactivated	Motivates the immune system to produce antibodies when exposed to the virus	To protect against the influenza strains of H5N1 virus	2009	59
44	Influenza A virus vaccine H5N1	Fluval P-H5N1 Omninvest	Fluart innovative vaccine	Fluval affords active immunization against four virus strains; two for influenza A subtype, and two for B type	To prevent influenza a (H5N1)	2009	60
45	Non adjuvant influenza A (H1N1) 2009 monovalent vaccine. Influenza hemagglutinin (HA) A/California/07/2009 (H1N1) V-like virus	Panenza Sanofi-Pasteur	Non-adjuvanted pandemic vaccine	Induces a high immune (antibody) response, three weeks post-vaccination	To prevent influenza A (H5N1)	2009	61
46	Monovalent, cell culture-derived, inactivated subunit influenza vaccine. Produced from A/California/07/2009 (H1N1) with adjuvant MF-59	Celtura	MF-59 adjuvanted cell cultured derivative A/H1N1 pandemic influenza vaccine	MF-59 induces a strong response in adults and substantially develops the response with growth of HA-specific Tfh ($CD4^+$, ICOS+, CXCR5+, IL-21+) cells	Induces an immune response for protection against influenza virus	2009	62
47	Pandemic (H1N1) ASO3 adjuvanted influenza vaccine	Pandremix GSK	Combination of H1N1 virus antigen and adjuvant system of H1N1	Enhances the natural immunity of the body	To prevent influenza A (H1N1), swine flu viral infections	2009	63
48	Influenza vaccine (H1N1) flu strain from A/California/7/2009 (H1N1) derived strain NYMC-181 J07BB02	Focetria	Surface antigen (hemagglutinin and neuraminidase) inactivated adjuvant	Vaccine acts by priming the immune system	To protect against influenza type A (H1N1) 2009 virus	2009	64
49	Cell culture-derived adjuvanted influenza virus vaccine (Grippol TC	Grippol NeoSolvay pharmaceutical AbbVie	Cell based adjuvanted influenza vaccine	Activates the endosomal receptor, which leads non-specific activation of the surface TLRs, which induce the intracellular signals contributing to the antiviral mechanism	To prevent influenza virus infections	2009	65
50	Inactivated H5N1 influenza (avian flu) vaccine A/Vietnam/1194/2003/(H5N1) RG	Pan-flu (Sinovac Biotech)	Single shot vaccine against H1N1 influenza	Body reacts by creating antibodies	To prevent H5N1 pandemic influenza	2008	66

Table 2 (*Contd.*)

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
Characteristic vaccines							
51	Pandemic influenza vaccine	Panvax H1N1 vaccine	Split virion inactivated vaccine	Panvax, is an inactive viral part of H1N1, the immune system responds by developing antibodies to the virus particle	Influenza virus (H1N1), swine flu infections	2008	67
52	Pre-pandemic influenza vaccine H5N1 (split virion, adjuvanted, inactivated) AS03-H5N1 vaccine A/Vietnam/1194/2004; or A/Indonesia/5/2005 GSK-1562902a	Prepandrix GSK	Split virion, inactivated, adjuvanted; hemagglutinin, antigen, adjuvanted	Potential immunization against influenza A subtype H5N1 virus	Influenza (H5N1) virus, swine flu infection	2008	68
53	Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) J07BB02	Optaflu Flucelvax TETRA Novartis	Influenza virus surface antigens, hemagglutinin and neuraminidase subunit vaccines	Optaflu comprising different strain surface regions of the flu virus. Vaccine causes immune system to recognize the unknown viral components and produce antibodies against them	Prevent influenza viral infection	2008	69
54	Smallpox (vaccinia) vaccine ACAM2000	Acam-2000 Sanofi Pasteur Biologics Co.	The vaccine is made from a live virus, vaccinia	Possessing potent immunization against smallpox	Prevention of smallpox	2007	70
55	Inactivated quadrivalent influenza vaccine (split virion)	Afluria Seqirus Pty. Ltd.	Quadrivalent split virion, influenza virus hemagglutinin as the active ingredient.	Immunity against 3 (type A (2) and type B (1)) or 4 (type A (2) and type B (2)) microbial strains. Suitable for the annual flu season	To stop infection caused by influenza virus	2007	71
56	H5N1 avian flu vaccine, avian influenza or bird flu, vaccine is derived from A/Vietnam/1203/2004 influenza virus	Fluzone Sanofi Pasteur	Inactivated influenza virus vaccine	Provides protection against the H5N1 influenza virus stimulating the immune response	To prevent infection caused by influenza virus	2007	72
57	Adjuvanted H5N1 pre-pandemic vaccine	Daronix, GSK	Second generation pandemic vaccine	Prepare the body's immune system to prevent a flu epidemic	Prevent common flu disease	2007	73
58	Influenza vaccine surface antigen, inactivated, prepared in cell culture: A/California/7/2009 (H1N1) pdm09-like strain, A/Switzerland/9715293/2013 (H3N2)-like strain, B/Phuket/3073/2013-like strain	Optaflu	Vaccine containing flu surface antigen	Enhances the body's defence system, priming the immune system to make antibodies against the flu virus	To prevent infection caused by influenza virus	2007	74
59	Birch pollen allergy vaccine	Oralgen Birch Pollen ALK-Abello	Peptide based vaccine	Suppression of allergic reactions after immunization with fusion protein, which is caused by releasing the immune messenger interleukin-10 (IL-10), an autologous cytokine, functioning to decrease the overacting immune response	To prevent allergy	2007	75

Table 2 (*Contd.*)

S. no.	Generic name	Trade name	Type	Mode of action	Treatment for other diseases	Year of approval	Ref.
	Characteristic vaccines						
60	Influenza vaccine, split virion, inactivated hemagglutinin of A/California/7/2009 Hemagglutinin of A/Victoria/210/2009 Hemagglutinin of B/Brisbane/60/2008	Anflu Sinovac	Split virion, inactivated	Body generates immuno-reactions against influenza virus	To prevent infection caused by influenza virus	2006	76
61	Rec hepatitis B vaccine	Supervax	Hepatitis B vaccine, immunoglobulin (HBIG)	Active immunization of hepatitis B vaccine induces the immune system to create anti-HBs without an active infection risk	To prevent infection against hepatitis B virus	2006	77
62	Antirabies vaccine	RABIRIX Bharath Biotech	Vero cell based rabies vaccine (PVRV)	Inactivated virus vaccine boosts immunization against rabies	To prevent infection against rabies virus	2006	78
63	Live herpes zoster vaccine	Zostavax Merck	Live attenuated virus vaccine	Enhancing VZV – specific immunity against zoster	Treatment for herpes zoster/postherpetic neuralgia (PHN), a neuropathic pain	2006	79
64	Rotavirus vaccine, live rotavirus 116E strain derived in Vero cells	RotaTeq Bharath Biotech	Live attenuated, oral, monovalent	Active immunization for infants from the age of 6 weeks	To protect against rotavirus gastro-enteritis disease in infants and young children	2006	80
65	Human papillomavirus quadrivalent (type 6, 11, 16, and 18) vaccine (HPV vaccine) J07BM01	Gardasil, Cervarix Merck	Protein subunit quadrivalent, recombinant	Body's immune system identifies the viral proteins in Gardasil, develops antibodies against them	To protect against either two or four or nine types of HPV (cervical, vaginal and vulvar in females)	2006	81
66	Rotavirus vaccine with five strains of rotavirus, from both human and animal sources	ROTARIX	Live, attenuated, oral	Usually to develop immunity against rotavirus-based disease	Rotarix vaccine assists to prevent this disease in children	2005	82
67	Hepatitis B (r DNZ) vaccine, adjuvanted, absorbed J07BC01	Fendrix GSK	Adjuvanted, absorbed, recombinant DNA technology	Vaccine works by priming the immune system	Prevents hepatitis B virus infection	2005	83
68	MR vaccine freeze-dried, live, attenuated, measles-rubella combined vaccine	Mearubik, Mitsubishi Tanabe Pharma Corporation	Live vaccine for measles, rubella	Immune system induced to produce antibodies (proteins that fight and also kills the rubella virus)	To prevent rubella virus	2005	11
69	Inactivated hepatitis A and hepatitis B (rDNA) – HAB adsorbed vaccine	Bilive Sinovac	Recombinant DNA technology	Suboptimal immune response to the vaccine	Prevents hepatitis B viral infection	2005	84
70	Virosomal influenza vaccine, Invivac influenza vaccine	Invivac Solvay Pharmaceuticals	Adjuvant	The virosome mechanism remains complex; it is the transporter as well as an immune stimulant	To treat influenza	2004	85
71	Influenza virus (live) (LAIV), inactivated influenza vaccine (IIV)	Flumist	Wild-type	Disease-causing viruses has been attenuated and inactivated, using the influence of heat/chemicals such as formaldehyde	Protects against infection from influenza viruses	2003	86
72	Hepatitis A and B Vac DB10989, DB11627	Ambirix	Vaccine based	B-lymphocytes anti-HBs antibodies	Immunization against hepatitis A and B viral infectivity	2003	87

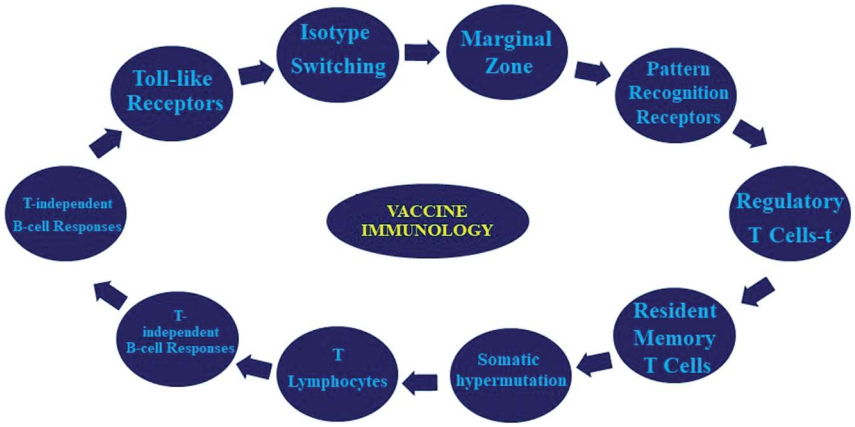


Fig. 2 General features of vaccine immunology.

immunoglobulin) at a particularly high rate throughout the proliferation of B-cells. This mechanistic process occurs as an effect of the cytidine deaminase enzyme and results in antibody diversification.

T lymphocytes. Cells that mature in the thymus, and become stimulated in the spleen or nodes if their T-cell receptors interact with an antigen marked with MHC molecules, and they obtain supplementary co-stimulation indications motivating them to kill the infected cell (mainly $CD8^+$ T cells)/secondary (mainly $CD4^+$ T cells) roles.

T-Independent B-cell responses. This B cell differentiation pathway is mostly triggered by polysaccharides, in the marginal zone and extra-follicular regions of the spleen or nodes. It provides a fast response (days), and generates transient (over months) low affinity antibodies without impacting immune memory.

T-Dependent B-cell responses. This B cell differentiation occurs due to protein antgens which recruit T and B cells into germinal centers of the spleen/nodes. It is slower (weeks), but provides enduring stimulation (years) with high affinity antibodies formation and immune memory.

Toll-like receptors. A cluster of 10 receptors (TLR1 to TLR10) existing at immune cell external regions, which identify pathogens and trigger characteristic immunity.

The main target of immunization through vaccination is to inhibit specific infections and their unavoidable difficulties. The best vaccine is the one which concomitantly accomplishes the following criteria such as:

(a) Actively inhibit the infective disease or else minimize the adverse effects of the disease;

(b) Offer a strong and continuing defence against a specific disease;

(c) Improves immunity through a minimum quantity of administrations;

(d) Deliver abundant antigens to afford wide-ranging safety against infection;

(e) Never results in side effects, or keeps them to a minimum;

(f) Remains stable under storage conditions, preferably mild storage conditions, for its shelf-life;

(g) Can be produced on a huge scale;

(h) Should be economical and easily available.

Herein we consider the COVID-19 pandemic, the main resolution of vaccination against SARS-CoV-2 are:

(a) Inhibition of characteristic clinical symptoms so hospitalization is avoided, and reduces severe infectivity;

(b) Prevention of disease spreading before the corresponding antibodies are produced (sero conversion)

(c) Producing a strong neutralizing immune response able to link with the viral protein spike (S) that must prevent it from attaching to human cells.

From this perspective, the various immunological response effects which neutralize antibodies and $CD8^+$ T cells are most significant.

The antibodies of anti-SARS-CoV-2 alert the host organism's immune response to the presence of the virus; such antibodies are immunoglobulins, which are appropriately split into IgA, IgM, IgG, and less frequently IgD. Prior serological antibody model responses to viral infections have usually proven the subsequent sequence of these antibodies resulting from virus infection: the antibodies of IgA are primary, which are followed by IgM, IgG-type continues at high levels for a longer time than the preceding ones (IgA and IgM). For certain viruses, sometimes the antigen (the virus itself) co-occurs with antibodies, particularly with the antibodies of primary IgA and IgM. Further, viruses have a "serological window," *i.e.*, a period between the initial arrival of the antigen (in the blood) and the antibody response, thus phase intervals of infection occur. Eventually, IgG-type antibodies are specific to the novel coronavirus (SARS-CoV-2) and can be examined through chemiluminescence immunological routes, which is an automated laboratory process using enzyme-linked immunosorbent assays with higher arrangement. The examination mostly identifies the body's immune response to SARS CoV-2 infection.

Significant characteristics of (corona) virus

Before 2019, there were two pandemics caused in the past two decades by coronavirus; namely SARS during 2002–2003 and Middle East Respiratory Syndrome (MERS) in 2011. According

to the International Committee on Taxonomy of Viruses (ICTV), the coronaviruses (CoVs) are sub-classified as Othocoronavirinae, which in turn consist of four categories – alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. The alpha- and beta-CoVs transmit disease in mammals such as bats, pigs, cats and mice. Gamma- and delta-CoVs usually infect birds. In addition, the seven different types of human CoVs – which include HCoV-229E, HCoV-NL63 – belong to alpha-CoVs. The HCoV-OC43, HCoV-HKU1, SARS-, MERS- CoVs, and the current pandemic SARS-CoV-2 belong to beta-CoVs, and the genus of such beta coronavirus occurrences are zoonotic infections. The December 2019 outbreak coronavirus, which leads to the respiratory-associated syndrome, originated from Wuhan, China, and is called the novel corona virus disease 2019 or nCOVID-19, and its genome is fully sequenced.[88] The genetic sequential arrangement of SARS-CoV-2 has an identical genomic array of SARS-/MERS-CoV.[89,90]

Initially, the taxonomy of coronaviruses are split in to three groups, on account of genetic and serological interactions, the first set (Group-1) comprised several viruses including the porcine epidemic diarrhoea virus (PEDV), porcine transmissible gastroenteritis virus (TGEV), canine coronavirus (CCoV), feline infectious peritonitis virus (FIPV), the previously identified coronavirus of HCoV-229E, and HCoV-NL63. Whilst the second combination (Group-2) consists of murine hepatitis virus (MHV), bovine coronavirus (BCoV), human coronavirus OC43 (HCoV-OC43), rat sialodacryoadenitis virus (SDAV), porcine hemagglutinating encephalomyelitis virus (PHEV), canine respiratory coronavirus (CRCoV), and equine coronavirus (ECoV). In a similar pattern, the third group (Group-3) contains the avian infectious bronchitis virus (IBV) and Turkey coronavirus (TCoV). Now, the SARS coronaviruses (SARS-CoV) cannot be associated with any of these representative groups, however they possess some similarities along with the second group coronaviruses.[91a]

The battle between scientists and viral infections is a perpetual process and thus the identification of specific potential drugs with high efficiency and low toxicity is a continuous aim. Globally, this is the first time, that scientific researchers, diplomats, politicians, and capitalists have convened to work towards a common objective. The FDA approved drugs chloroquine and hydroxychloroquine to be utilized in critical illness cases, but clinical practices were still becoming overwhelmed by CoV cases. The suggestion to employ extensive use of these antiviral drugs was not sufficient. Certain polymerase nucleoside/nucleotide inhibitors are promising agents. Favipiravir a selective viral RdRp inhibitor, has been tested in clinical trials against COVID-19. Furthermore, the antiviral drugs lopinavir, ritonavir, remdesivir, nelfinavir, serine based protease inhibitors of nafamostat, camostat, efficient lipid reducing statin, rosovastatin, TNF alpha inhibitors, interleukin 1 receptor antagonists; Janus associated kinases (JAK) as well as monoclonal antibodies, tocilizumab, baricitinib and ruxolitinib *etc.*, along with their combinations and other antiviral components, are also under investigation in clinical studies to combat COVID-19. In the future, researchers are requested to accumulate their results to provide more knowledge to repurpose significant drugs appropriately, and provide cheap drugs with the minimum toxicity profile.[91b,c]

The manufacture of SARS-CoV-2 vaccines through various approaches

Vaccines have to be approved based on sufficient evidence. Many scientific researchers have reviewed the current literature and worked towards the development of a specific treatment for COVID-19. Current studies have exposed several beneficial opportunities, a few of them are more established and are in preclinical trials in addition to some in clinical trials.[92,93] Vaccines endeavor to represent the antibody to the antigen, and they should help the immune system (innate and adaptive immune responses, Fig. 3).

Virus vaccines

A number of vaccines are being developed for SARS-CoV-2, including inactivated and weakened, replicating and non-replicating viral vectors, and the tentative use of nucleic acid in the form of DNA and RNA. Now, we can distinguish each vaccine characteristic as follows:

Weakened virus. Viruses cause disease by reproducing in a rapid manner. A weakened virus reproduces inside the human or animal host very poorly thereby decreasing its virulence and disease causing ability. One pharmaceutical company in the USA (Codagenix, New York) is collaborating with an Indian research team (Serum Institute at Pune) for the manufacture of SARS-CoV-2 with changed genetic sequence – making viral proteins with lower potency.

Inactivated virus. Chemicals such as formaldehyde, or thermal heating, are applied to inactivate a virus which is then used as a vaccine.

Viral-vector vaccines. In this technique other virus types are modified to render them safe and then used as a vaccine. They combine the qualities of DNA vaccines with those of live attenuated vaccines. The viral vector vaccine consists of a live attenuated virus which is genetically modified to carry the DNA encoding protein antigens from a different organism. For example, the virus belonging to measles/adenovirus is genetically modified and thus made safe. Currently there are products for veterinary use but not for human use. There are two types of viral vectors,[94] one is still able to replicate inside the cells, while the other is non-replicating, since the key genes have been rendered inoperative.

Replicating viral vector (weakened measles). One of the approved Ebola vaccines is a typical paradigm for a viral-vector vaccine. Even if replication occurs inside cells, this vaccine is safe and will intensify the immune response.

Non-replicating viral vector (adenovirus variety). In general, viral vectors are genetically transformed to generate defective replications which are termed non-replicating vectors. Numerous viruses like adenovirus, adeno-linked, measles, and human parainfluenza viruses has been extensively utilized as viral vectors. Ultimately, the virus attains an attenuated state in which they can activate the anticipated human immune

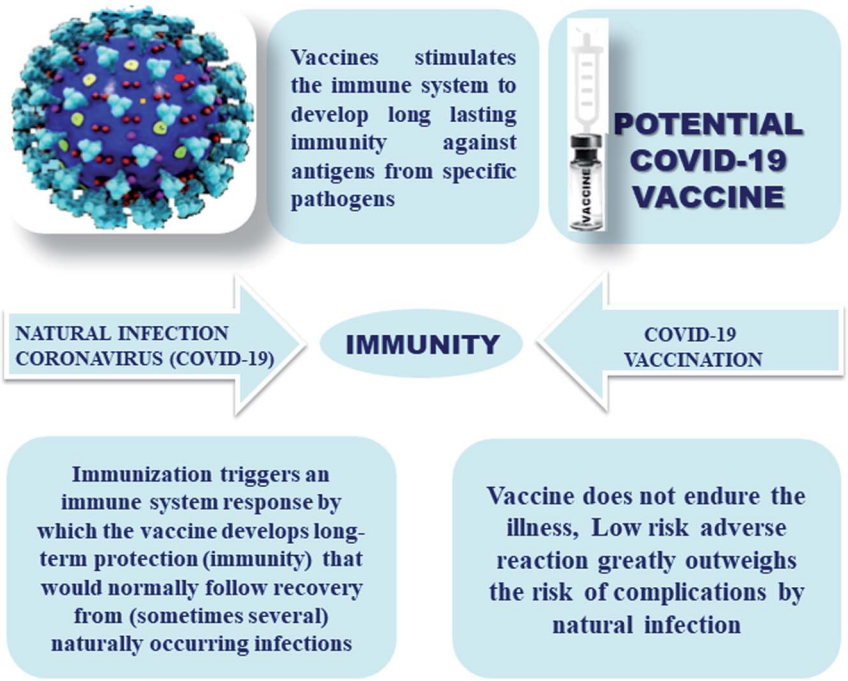


Fig. 3 Pictorial representation of characteristic immunity.

responses, however, they are unable to reproduce in human cells.

Nucleic-acid vaccines. A number of groups are aspiring to utilize gene sequences (based on DNA or RNA) for a coronavirus protein to instantaneously provide an immune response. The majority of these vaccines focus on the spike protein present in the virus.[95]

Protein-based vaccines. Several researchers have focused on injecting proteins present in coronavirus into the body. Also, protein fragments or shells of protein as copies of the coronavirus' surface could also be utilized.

Protein subunits. Nearly 28t groups are working on vaccines using subunits of viral proteins, predominantly on the spike protein at the receptor binding arena. Vaccines for protecting monkeys against SARS virus infection are available which have not been examined for humans. In fact, to employ such vaccines, adjuvant-immune-stimulation drug molecules should be administered together with the vaccine.[96]

Virus-like particles. Shells (outer regions) of an empty virus resemble the CoV structure, however, it is non-transmittable due to the absence of the genetic factors. Several research groups are engaged in vaccines based on virus-like particles that can activate a good immune response, however it is quite complex to synthesize such particles, and 70% of the teams directing their research in this way are from industry or private companies rather than academic laboratories.[97,98]

Table 3 and 4 provide a comprehensive overview of the current development of vaccines for SARS-CoV-2, their mode of action, their utility and the name of the manufacturer.[99] More than 10 vaccines have almost reached the approval stage, while many are in the preclinical stage. Fig. 4 portrays the number of vaccine aspirants which are under clinical (~63 drug aspirants) and preclinical (~172 drug aspirants) stages against nCOVID-19.[99a] Protein-based techniques seem to be the most popular among the various mechanisms (see https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines).

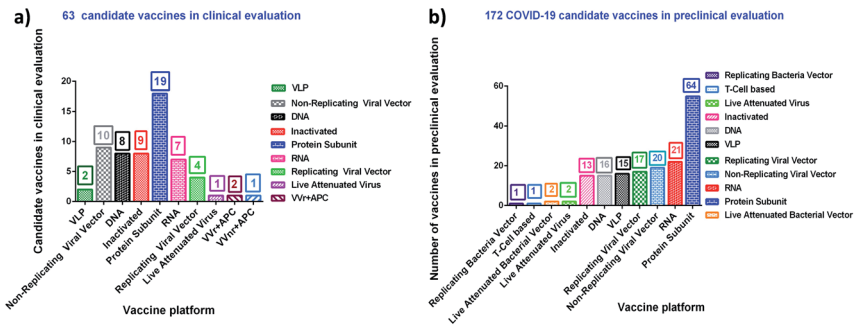
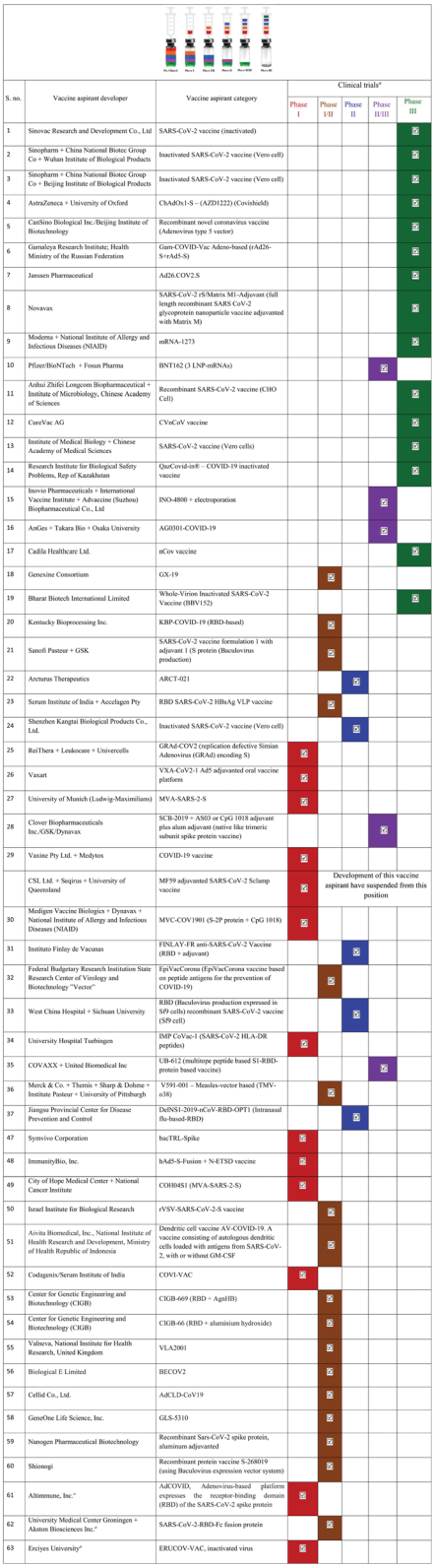


Fig. 4 nCOVID-19 vaccine aspirants at the clinical (63 drug aspirants) and preclinical (172 drug aspirants) stage.

Table 3 COVID-19 aspirant developers and their significant details[99a a]



S. no.	Vaccine aspirant developer	Vaccine aspirant category	Clinical trials[a]				
			Phase I	Phase I/II	Phase II	Phase II/III	Phase III
1	Sinovac Research and Development Co., Ltd	SARS-CoV-2 vaccine (inactivated)					☑
2	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Vero cell)					☑
3	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Vero cell)					☑
4	AstraZeneca + University of Oxford	ChAdOx1-S – (AZD1222) (Covishield)					☑
5	CanSino Biological Inc./Beijing Institute of Biotechnology	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)					☑
6	Gamaleya Research Institute; Health Ministry of the Russian Federation	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)					☑
7	Janssen Pharmaceutical	Ad26.COV2.S					☑
8	Novavax	SARS-CoV-2 rS/Matrix M1-Adjuvant (full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)					☑
9	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	mRNA-1273					☑
10	Pfizer/BioNTech + Fosun Pharma	BNT162 (3 LNP-mRNAs)				☑	
11	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Recombinant SARS-CoV-2 vaccine (CHO Cell)					☑
12	CureVac AG	CVnCoV vaccine					☑
13	Institute of Medical Biology + Chinese Academy of Medical Sciences	SARS-CoV-2 vaccine (Vero cells)					☑
14	Research Institute for Biological Safety Problems, Rep of Kazakhstan	QazCovid-in® – COVID-19 inactivated vaccine					☑
15	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	INO-4800 + electroporation				☑	
16	AnGes + Takara Bio + Osaka University	AG0301-COVID-19				☑	
17	Cadila Healthcare Ltd.	nCov vaccine					☑
18	Genexine Consortium	GX-19		☑			
19	Bharat Biotech International Limited	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)					☑
20	Kentucky Bioprocessing Inc.	KBP-COVID-19 (RBD-based)		☑			
21	Sanofi Pasteur + GSK	SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein (Baculovirus production)		☑			
22	Arcturus Therapeutics	ARCT-021			☑		
23	Serum Institute of India + Accelagen Pty	RBD SARS-CoV-2 HBsAg VLP vaccine		☑			
24	Shenzhen Kangtai Biological Products Co., Ltd.	Inactivated SARS-CoV-2 vaccine (Vero cell)			☑		
25	ReiThera + Leukocare + Univercells	GRAd-COV2 (replication defective Simian Adenovirus (GRAd) encoding S)	☑				
26	Vaxart	VXA-CoV2-1 Ad5 adjuvanted oral vaccine platform	☑				
27	University of Munich (Ludwig-Maximilians)	MVA-SARS-2-S	☑				
28	Clover Biopharmaceuticals Inc./GSK/Dynavax	SCB-2019 + AS03 or CpG 1018 adjuvant plus alum adjuvant (native like trimeric subunit spike protein vaccine)				☑	
29	Vaxine Pty Ltd. + Medytox	COVID-19 vaccine	☑				
	CSL Ltd. + Seqirus + University of Queensland	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	☑	Development of this vaccine aspirant have suspended from this position			
30	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	MVC-COV1901 (S-2P protein + CpG 1018)	☑				
31	Instituto Finlay de Vacunas	FINLAY-FR anti-SARS-CoV-2 Vaccine (RBD + adjuvant)			☑		
32	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)		☑			
33	West China Hospital + Sichuan University	RBD (Baculovirus production expressed in Sf9 cells) recombinant SARS-CoV-2 vaccine (Sf9 cell)			☑		
34	University Hospital Tuebingen	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)	☑				
35	COVAXX + United Biomedical Inc	UB-612 (multitope peptide based S1-RBD-protein based vaccine)				☑	
36	Merck & Co. + Themis + Sharp & Dohme + Institute Pasteur + University of Pittsburgh	V591-001 – Measles-vector based (TMV-s038)		☑			
37	Jiangsu Provincial Center for Disease Prevention and Control	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)			☑		
47	Symvivo Corporation	bacTRL-Spike	☑				
48	ImmunityBio, Inc.	hAd5-S-Fusion + N-ETSD vaccine	☑				
49	City of Hope Medical Center + National Cancer Institute	COH04S1 (MVA-SARS-2-S)	☑				
50	Israel Institute for Biological Research	rVSV-SARS-CoV-2-S vaccine		☑			
51	Aivita Biomedical, Inc., National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	Dendritic cell vaccine AV-COVID-19. A vaccine consisting of autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF		☑			
52	Codagenix/Serum Institute of India	COVI-VAC	☑				
53	Center for Genetic Engineering and Biotechnology (CIGB)	CIGB-669 (RBD + AgnHB)		☑			
54	Center for Genetic Engineering and Biotechnology (CIGB)	CIGB-66 (RBD + aluminium hydroxide)		☑			
55	Valneva, National Institute for Health Research, United Kingdom	VLA2001		☑			
56	Biological E Limited	BECOV2		☑			
57	Cellid Co., Ltd.	AdCLD-CoV19		☑			
58	GeneOne Life Science, Inc.	GLS-5310		☑			
59	Nanogen Pharmaceutical Biotechnology	Recombinant Sars-CoV-2 spike protein, aluminum adjuvanted		☑			
60	Shionogi	Recombinant protein vaccine S-268019 (using Baculovirus expression vector system)		☑			
61	Altimmune, Inc.[c]	AdCOVID, Adenovirus-based platform expresses the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein	☑				
62	University Medical Center Groningen + Akston Biosciences Inc.[c]	SARS-CoV-2-RBD-Fc fusion protein		☑			
63	Erciyes University[c]	ERUCOV-VAC, inactivated virus	☑				

[a] Vaccine candidate list and relevant information shown according to the World Health Organization (WHO) statistical data for COVID-19 during 2019–2020. Clinical research data (last updated on January 08, 2021) may be variable.

Comparison between previous vaccines and COVID-19 vaccines

Comparing COVID-19 vaccine novelty may seem challenging, but it is normal for queries to arise on a vaccine's overall potential, safety, toxicity and its side effects *etc.*,[100a] and some of the efficacy, efficiency and safety of the COVID-19 frontrunner vaccines can be determined by comparison with other vaccines, like flu vaccines. For example, Pfizer/BioNTech released their COVID-19 vaccine initially in the UK and USA, and the rest of the world could see their effectiveness. However, prior to this demonstration the three prominent COVID-19 vaccines – Pfizer/BioNTech claims an efficacy of 95%, the Oxford/AstraZeneca provides 70%, and the Moderna is stated as 94.1% efficacy – were compared with other available vaccines such as the flu, polio, and measles, which helped provide their effectiveness and efficiency predictions.

It is important to discuss here that "effectiveness" and "efficacy" are different.[100b] Efficacy states how a vaccine performs in ideal lab circumstances, like those present in clinical trials. Whereas, effectiveness means how the vaccine works in normal, non-controlled conditions. For example, in a clinical trial, 90% efficacy refers to 90% lower disease rates in the group getting the vaccine compared with the sample group. But, the members in a group selected for a clinical trial have to be in good health and young and they usually have no underlying health conditions. Besides, medical researchers will not generally consider some demographics in these clinical research studies like children/pregnant women. Thus, once a vaccine is able to prevent disease in clinical trials, we may observe the effectiveness drop when directed to different demographics.

Vaccines do not necessarily need high effectiveness to protect several thousands of lives from disease. For instance, the vaccine for flu[100c] has 40–60% effectiveness according to CDC data. During 2018–19, this vaccine prevented millions of influenza cases and its associated illness, but determining the exact effectiveness rate is challenging. Dosages can also increase effectiveness for some vaccines. The two doses of a vaccine can give a protection boost, nevertheless this advantage is sometimes limited to only certain groups like children/organ transplanted people. The booster dosage may not provide an advantage in people aged 65 years.

Through comparing vaccines, like the ones for polio and measles, we see heavy dosages are needed to realize effectiveness.

Polio vaccines[100d] should be up to 100% effective. According to the CDC, "Two inactivated polio vaccine (IPV) dosages have 90% effectiveness; three dosages are 99–100% effective." The IPV vaccine prevents poliomyelitis (poliovirus), which can activate infection in the brain and spinal cord leading to paralysis.

The MMR vaccine[100e] defends against measles, mumps, and rubella, which tends to have up to 97% effectiveness at inhibiting measles once directed in two dosages. A single dose is around 93% effective, as reported by the CDC. They suggest to give the initial dose at "12–15 months of age, followed by the second dose at 4–6 years."

Table 4 Range of SARS-CoV-2 vaccine aspirants and their representative data[16a,b,99c]

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
1	IV	Inactivated virus	Vaccines of CoronaVac, PiCoVaccine, based on vaccine cultured in Vero cells, inactivated pathogen	Based on an inactivated pathogen, body generates a varied immune response against several viral antigens, producing neutralizing antibodies	Sinovac R&D Co. Ltd	Phase III NCT04456595, Phase 1/2 NCT04383574, NCT04352608	Vaccine being developed for treatment of SARS-CoV-2	101
2	IV	Inactivated virus	Inactivated vaccine, Vero cell based	Vaccine from non-living viral particles, bacteria, and other pathogens which are developed in a culture medium. No potential for infection, but induces an immune system response	Sinopharm + WIBP	Phase 3, Phase-I/II/III ChiCTR2000031809	Vaccine being developed for treatment of SARS-CoV-2	102
3	IV	Inactivated virus	Inactivated and similar to virus vaccine based on Vero cells	The foremost vaccine, does not exhibit any adverse side effects with favored immunogenicity and safety; also an inactivated new crown vaccine which completely neutralizes the antibodies in 28 days	Sinopharm + BIBP	Phase 3 ChiCTR2000032459	Vaccine being developed for treatment of similar viruses	92*d*
4	VVnr	Viral vector (non-replicating)	Covishield ChAdOx1-S-(AZD1222)	Adenovirus vector based on chimpanzee adenovirus	AstraZeneca + Oxford University	Phase 3 ISRCTN89951424, Phase2b/3 2020-001228-32, Phase 1/2 PACTR202006922165132 2020-001072-15	MERS, influenza, TB, Chikungunya, Zika, MenB, plague	103
5	VVnr	Viral vector (non-replicating)	Ad5-nCoV recombinant vaccine for CoV	Recombinant adenovirus type 5 vector based vaccine aspirant, which is genetically modified with replication-deficient groups, mimics SARS-CoV-2 spike protein	Beijing Biotechnology Institute/CanSino Biological Inc.	Phase 2 ChiCTR2000031781, Phase 1 ChiCTR2000030906	EBOV (Ebola virus)	104
6	VVnr	Viral vector (non-replicating)	Gam-COVID-Vac adeno-based (rad26-S+rAd5-S), Russian COVID-19 vaccine, adenovirus based, and non-replicating	Develop immunity against the coronavirus, and strengthens the immune system	Gamaleya Research Institute; Ministry of Health, Russian Federation	Phase-I/III NCT04436471, NCT04437875	Vaccine being developed for treatment of SARS-CoV-2	105
7	VVnr	Viral vector (non-replicating)	Ad26.COV2.S recombinant serotype 26, adenovirus vectors, multivalent vaccine	Activates specific acquired immunity for Ebola virus	Janssen Pharmaceutical	Phase 3 NCT04505722, NCT04614948	Vaccine being developed for treatment of similar viruses	106

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
8	PS	Protein subunit	SARS-CoV-2 rS/ Matrix M1-adjuvant (full size recombinant SARS CoV-2 GP nanoparticle based vaccine with Matrix Mas adjuvant)	Matrix-M, an adjuvant which improves the immune response and induces advanced neutralizing antibodies	Novavax	Phase 3 NCT04611802, NCT04583995	Ebola, Lassa, MERS, Nipah, Rift Valley Fever and Chikungunya	107
9	RNA	RNA based vaccine	Moderna mRNA-1273 vaccine, LNP encapsulated cell bank; mRNA, VAX (non-replicating viral vector)	A vaccine with mRNA encapsulated in LNP, encoding for perfusion stabilized spike (S) protein. Host generates an immune response against the spike protein on SARS-CoV-2	Moderna + NIAID	Phase 3 NCT04470427, Phase 2 NCT04405076, Phase 1 NCT04283461	Multiple agents	108
10	RNA	mRNA based vaccine	BNT162 (3 LNP-mRNAs)	BNT162 contains a nucleoside modified mRNA (modRNA) encoding the viral spike (S) glycoprotein	BioNTech + Fosun Pharma; Jiangsu Provincial CDC + Pfizer	Phase 2/3 NCT04368728	To be implemented	109
11	PS	Protein subunit	Recombinant COVID-19 vaccine, CHO (Chinese hamster ovary) cell system, prevents CoVs	Increases rate of new coronavirus neutralizing S protein antibody (IgG) and RBD protein antibody (IgG)	Anhui Zhifei Longcom Biopharmaceutical + IMCAS	Phase-I NCT04453852, NCTo4445194, Phase 3 NCT04646590	Vaccine being developed for treatment of SARS-CoV-2	110
12	RNA	mRNA based vaccine	CVnCoV vaccine	Nucleotides without chemical modifications in the mRNA	CureVac AG	NCT04449276 Phase 1, NCT04515147 Phase 2, NCT04674189 Phase 3	CureVac's vaccine candidate against SARS-CoV-2	111
13	IV	Inactivated virus	Vaccine for SARS-CoV-2 based on Vero cells	ELISA derived antibodies (IgGs) and neutralizing antibodies, target the spike protein, N protein virion and the specific positive CTL responses against N, S and virion antigens	IMB + CAMS	Phase 3 NCT04659239, Phase 1/2 NCT04470609, NCT04412538	To be implemented	112
14	IV	Inactivated virus	QazCovid-in®-COVID-19 inactivated vaccine	There are specific antibodies that activate upon receiving small dilutions given in the vaccine, they constantly counterbalance the novel coronavirus with a virulence dose of 3000 TCD50	RIBSP, Republic of Kazakhstan	Phase 1/2 NCT04530357	Vaccine being developed for treatment of SARS-CoV-2	113

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
15	DNA	DNA based vaccine	INO-4800 + electroporation vaccine with DNA–plasmid based connecting electroporation device	DNA plasmids distribute by electro-permeabilization (electro-transfer), a computationally sequenced design to produce a specific immune response	Inovio Pharmaceuticals + IVI	Phase 1 NCT04336410, NCT04447781, Phase 2 ChiCTR2000040146, Phase 2/3 NCT04642638	Multiple agents, Cancer, HBV, HIV, HPV, Lassa, Nipah, Zika,	114
16	DNA	DNA based vaccine	AG0301-COVID19	Plasmid DNA vaccine developed through an intradermal gene transfer targeting the S protein, which increases the efficiency of gene expression and antibody production	AnGes + Takara Bio + Osaka University	Phase 2/3 NCT04655625, Phase 1/2 NCT04463472, NCT04527081	To be implemented	115
17	DNA	DNA based vaccine	nCov vaccine viral vector, membrane protein based vaccine	Progression of DNA vaccine with the viral membrane protein liable for CoV cell entry; plasmid DNA incorporated into the host cell changes the viral protein, leading to a strong immune response intervened by cellular and humoral immunity. Also used to produce live attenuated recombinant measles viral vector vaccine	Cadila Healthcare Ltd.	Phase 1/2 CTRI/2020/07/026352	To be implemented	116
18	DNA	DNA based vaccine	GX-19	Designed to make antigens by adding nucleic acids into the body, the antigens then produce an immune response	Genexine Consortium	Phase-1/2 NCT04445389	To be implemented	117
19	IV	Inactivated virus	Whole-virion inactivated vaccine (BBV152), Covaxin for SARS-CoV-2, India's trials on nCoV-19 vaccine	Isolated from asymptomatic COVID-19 patient at NIV Pune, India	Bharat Biotech International Limited	Phase 1/2 NCT04471519, Phase 3 NCT04641481; CTRI/2020/11/028976	Vaccine being developed for treatment of SARS-CoV-2	118
20	PS	Protein subunit	KBP-COVID-19 (RBD-based), plant based technology	A distinctive plant-based vaccine technology for the generation of antigens to various diseases	KBP., Inc.	Phase 1/2 NCT04473690	To be implemented	119

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
21	PS	Protein subunit	Adjuvanted vaccine of SARS-CoV-2 formulation spike protein (baculovirus production)	—	Sanofi Pasteur + Glaxo SmithKline plc.	Phase 1/2 NCT04537208		120
22	RNA	RNA based vaccine	ARCT-021	Powerful single dose, vaccine is based upon self-replicating mRNA, self-transcribing and replicating RNA along with its liquid-enabling and resolving nucleo-monomer facilitator altered RNA	Arcturus Therapeutics	Phase 1/2 NCT0448095	Vaccine being developed for treatment of SARS-CoV-2	121
23	VLP	Virus like particle	RBD SARS-CoV-2 HBsAg VLP vaccine	Neutralizing antibodies response in pigs, treated together with pseudo type lentivirus and live SARS-CoV-2 viruses. Immunoglobulin (IgG) response observed after booster immunization	SII + Accelagen Pty	Phase 1/2 ACTRN12620000817943	Vaccine being developed for treatment of SARS-CoV-2	122
24	VVnr + APC	Viral vector (non-replicating) + APC IV inactivated virus	SARS-CoV-2 vaccine (inactivated)		Shenzhen Geno-Immune Medical Institute	Phase 1/2 NCT04276896	Vaccine for SARS-CoV-2	123
25	VVnr	Viral vector (non-replicating)	GRAd-COV2 replication using defective simian adenoviral vector (GRAd), encodes full length CoV spike protein	Able to generate immune response (antibodies and T cells)	ReiThera + Leukocare + Univercells	Phase 2 ChiCTR2000039462	Ebola and RSV (respiratory syncytial virus)	124
26	VVnr	Viral vector (non-replicating)	VXA-CoV2-1 Ad5 adjuvanted oral vaccine platform	Vaccine mainly provides mucosal immunity, this vital factor targets mucosal pathogens, including the current coronavirus. Stimulates antigen-specific $CD4^+$ and $CD8^+$ T cells at low and high dosage levels	Vaxart	Phase 1 NCT04563702	Influenza infection H1N1	125

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
27	VVnr	Viral vector (non-replicating)	MVA-SARS-2-S	Immune responses and neutralizing antibodies directing the S antigen used to defend against infectivity. The double recombinant sMVA-CoV-2 vectors give S-specific $CD8^+$ and $CD4^+$ T cells to both S and N antigens in Balb/c mice, respectively	University of Munich (Ludwig-Maximilians)	Phase 1 NCT04569383	Infectious diseases and cancer	126
28	PS	Protein subunit	SCB-2019 + AS03/ CpG 1018 adjuvant plus alum adjuvant (similar to native trimeric subunit spike protein vaccine)	S-Trimer, antigen used to target the antibodies of novel CoV spike protein and is in ACE2-viable human convalescent sera samples, obtained from recovered COVID-19 patients	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 1 NCT04405908	Vaccine being developed for treatment of SARS-CoV-2	127
29	PS	Protein subunit	COVID19 vaccine	Effective T cells and neutralizing antibody response	Vaxine Pty Ltd. + Medytox	Phase 1 NCT04453852	Vaccine being developed for treatment of SARS-CoV-2	128
		Protein subunit	MF59 adjuvanted SARS-CoV-2 S clamp vaccine	Advanced antibodies are able to neutralize infectivity through live virus in the cell culture	CSL Ltd. + Seqirus + University of Queensland	Phase 1, development was suspended and the candidate vaccine was removed from the summary analysis	Vaccine production against similar viruses is on hold	
30	PS	Protein subunit	MVC-COV1901 (S-2P protein + CpG 1018)	High titer of neutralizing antibodies are prompted against pseudo type novel CoV in sera of immunized mice	Medigen Vaccine Biologics Corp + NIAID + Dynavax	Phase 1 NCT04487210	Vaccine being developed for treatment of SARS-CoV-2	129
31	PS	Protein subunit	FINLAY-FR anti-SARS-CoV-2 vaccine (RBD + adjuvant)	It has the capability to generate a substantial immune reaction	Instituto Finlay de Vacunas	Phase 2 RPCEC00000347, Phase 1/2 RPCEC00000332, Phase 1 RPCEC00000338	Vaccine being developed for treatment of SARS-CoV-2	130
32	PS	Protein subunit	EpiVacCorona, based on peptide antigens	This antigens-based preparation stimulates the immune reaction	Federal Budgetary Research Institution SRC VB VECTOR	Phase 1/2 NCT04527575	Vaccine being developed for treatment of SARS-CoV-2	131
33	PS	Protein subunit	RBD, baculovirus production expressed in Sf9 cells, recombinant SARS-CoV-2 vaccine (Sf9 cell)	Specific immune blotting RBD, S-WT and S-2P, motivates high neutralization titers	WCH, Sichuan University	Phase 2 NCT04640402, ChiCTR2000039994, Phase 1 NCT04530656	Vaccine being developed for treatment of SARS-CoV-2	132
34	PS	Protein subunit	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)		University Hospital Tuebingen (UKT)	Phase 1	Vaccine being developed for treatment of SARS-CoV-2	133

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
35	PS	Protein subunit	UB-612, multitope peptide based S1-RBD-protein based vaccine	This vaccine has the immunity potential to reduce future pandemic rates	COVAXX + United Biomedical Inc	Phase 1 NCT04545749	Vaccine being developed for treatment of SARS-CoV-2	134
36	VVr	Viral vector (replicating)	V591-001-measles-vector based (TMV-o38)	Attains the target immune response in humans	Merck & Co., Themis + Sharp & Dohme + Pasteur Institute + Pittsburgh University	Phase 1 CT04498247, Phase1/2 NCT04497298NCT04569786	Vaccine being developed for treatment of SARS-CoV-2	135
37	VVr	Viral vector (replicating)	DelNS1-2019-nCoV-RBD-OPT1, intranasal flu-based-RBD	SARS-CoV-2 RBD protein based vaccine used to motivate cross-reactivity or cross-neutralizing antibodies; moreover it blocks previous CoV pseudovirus and the advanced novel CoV pseudovirus into hACE2 expressing 293 T cells (IC_{50} = 4.1 and 11.63 μg ml^{-1})	Jiangsu Provincial CDC	Phase 2 ChiCTR2000039715, Phase 2 ChiCTR2000037782	Vaccine being developed for treatment of SARS-CoV-2	136
38	RNA	RNA based vaccine	LNP-nCoVsaRNA	The saRNA vaccine can activate a strong immune response; it is suggested that the IM vaccination antigen is expressed in muscle cells, then moves to antigen presenting cells (APC), representing a cross priming mode of potentiality to prominent $CD8^+$ T cells	Imperial College London	Phase 1 ISRCTN17072692	Vaccine being developed for treatment of SARS-CoV-2	137
39	RNA	RNA based vaccine	SARS-CoV-2 mRNA vaccine	—	Shulan (Hangzhou) Hospital and CDC at Guangxi Zhuang Autonomous Region	Phase 1	Vaccine being developed for treatment of SARS-CoV-2	138
40	VLP	Virus-like particle	Coronavirus-like particle COVID-19 (CoVLP)	Provides immunity by generating a harmless spike protein member, reduces severe infection effects	Medicago Inc.	Phase 2/3	Vaccine being developed for treatment of similar viruses	139
41	VVr + APC	Viral vector (replicating) + APC	COVID-19/aAPC vaccine produced from a variation of lentivirus with immune modulatory genes and viral minigenes to the aAPCs	Artificial antigen-pathogen-specific vaccine, which uses the spike protein binding to the ACE2 receptor; the vaccine utilizes the modified minigenes to direct viral proteins, vary aAPC, and trigger T-cells	Shenzhen Genoimmune Medical Institute	Phase 1 NCT04299724	Vaccine being developed for treatment of SARS-CoV-2	140

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
42	VVnr + APC	Viral vector (non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors transmitting COVID-19 minigene SMENP and immune modulatory genes. Cytotoxic T lymphocytes (CTLs) are activated by LV-DC offering COVID-19 specific antigens.	Vaccine directed with antigen-specific CTLs	Same medical institute	Phase 1/2 NCT04276896	Vaccine being developed for treatment of similar viruses	141
43	PS	Protein subunit	AdimrSC-2f (recombinant RBD ± aluminium)	—	Adimmune Corporation	Phase 1 NCT04522089	Vaccine being developed for treatment of SARS-CoV-2	142
44	DNA	DNA based vaccine	Covigenix VAX-001	Induces neutralizing antibody levels and stable T helper cell immunity	Entos Pharmaceuticals Inc.	Phase 1 NCT04591184	Vaccine being developed for treatment of SARS-CoV-2	143
45	DNA	DNA based vaccine	CORVax	CORVax12 initiates a coordinated vaccine response, able to expose the innate adaptive humoral and cellular arms. These cellular immune responses have the potential to generate a strong antiviral response	Providence Health & Services	Phase 1 NCT04627675	Vaccine being developed for treatment of similar viruses	144
46	RNA	RNA based vaccine	ChulaCov19 mRNA vaccine	The mRNA based vaccine encodes a protein antigen, while RNA is considered to be unstable; the design and development of this novel vaccine is improving its constancy and protein translation efficacy, so it efficiently enhances immune response	Chulalongkorn University	Phase 1 NCT04566276	Vaccine being developed for treatment of similar viruses	145

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
47	DNA	DNA based vaccine	bacTRL-Spike	Symvivo's bacTRL gene therapy platform associates an advanced gene-expression plasmid with a probiotic bacterium to resolve restrictions and distribute the DNA vaccine directly to the gut. The bacterium triggers the immune response	Symvivo Corporation	Phase 1 NCT04334980	Vaccine being developed for treatment of similar viruses	146
48	VVnr	Viral vector (non-replicating)	hAd5-S-Fusion + N-ETSD vaccine	A viral spike protein. Virus enters the host cells through the ACE2 receptor with a fusion linker, S is antigenic, and generates an efficient immune response	ImmunityBio, Inc.	Phase 1 NCT04591717, NCT04710303, NCT04732468	Vaccine being developed for treatment of similar viruses	147
49	VVnr	Viral vector (non-replicating)	COH04S1 (MVA-SARS-2-S)	Vaccine holds the SARS-CoV-2 spike and nucleocapsid proteins inserted into the MVA platform that can replicate DNA within cells. Thus it generates novel CoV protein expression to trigger host immunity against the virus	City of Hope National Medical Center	Phase 1 NCT04639466	Vaccine in development	148
50	VVr	Viral vector (replicating)	rVSV-SARS-CoV-2-S vaccine	rVSV-ΔG-spike stimulated a safe, efficient and adequate neutralizing antibody. Vaccination leads to lower morbidity, protects lungs, and provides fast viral clearance	IIBR, Israel	Phase 1/2 NCT04608305	Vaccine in development	149
51	VVr + APC	Viral vector (replicating) + APC	Dendritic cell vaccine AV-COVID-19: contains autologous dendritic cells load with antigens from SARS-CoV-2, with/without GM-CSF	Produced from isolated peripheral blood monocytes from patients. Monocytes are then distinguished into dendritic cells with GM-CSF and IL=4	Aivita Biomedical, Inc.	Phase 1/2 NCT04690387 NCT04386252	Vaccine in development	150

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
52	LAV	Live attenuated virus	COVI-VAC	Codagenix's synthetic attenuated virus engineering (SAVE) platform utilizes synthetic biology to re-code the virus genes into the vaccine. Since this design involves distributing a benign, live attenuated version of SARS-CoV-2 it may stimulate a strong and enduring immune response	Codagenix/Serum Institute of India	Phase 1 NCT04619628	Vaccine in development	151
53	PS	Protein subunit	CIGB-669 (RBD + AgnHB)	Stimulates the generation of antibodies that enable a strong immune response to the pathogen	CIGB	Phase 1/2 RPCEC00000345	Vaccine in development	130
54	PS	Protein subunit	CIGB-66 (RBD + aluminium hydroxide)	Stimulates the generation of antibodies that boost the targeted immune response to the virus	CIGB	Phase 1/2 RPCEC00000346	Vaccine in development	130
55	IV	Inactivated virus	VLA2001	Vero-cell supported the refined inactivated candidate, based on Valneva's JE vaccine, uses the spike protein normal structural array with CpG 1018 and can stimulate an immune response with a high titer of neutralizing antibodies	Valneva, NIHR, United Kingdom	Phase 1/2 NCT04671017	Vaccine in development	130
56	PS	Protein subunit	BECOV2	Candidate based on inactivated SARS-CoV-2 virus components	Biological E Limited	Phase 1/2 CTRI/2020/11/029032	Vaccine in development	130
57	VVr	Viral vector (replicating)	AdCLD-CoV19	Immunotherapeutic vaccine based on cells	Cellid Co., Ltd.	Phase 1/2 NCT04666012	Vaccine in development	152
58	DNA	DNA based vaccine	GLS-5310	Nucleic acid-based vaccine platform	GeneOne Life Science, Inc.	Phase 1/2 NCT04673149	Vaccine in development	152

Table 4 (*Contd.*)

ID	Vaccine division acronym	Vaccine sector description	Vaccine category and composition	Characteristic nature of vaccination	Producers	Clinical phases	Vaccine utility for other viruses	Ref.
59	PS	Protein subunit	Recombinant SARS-CoV-2 spike protein, aluminum adjuvanted	Protein subunit containing the recombinant SARS-CoV-2 S1 domain of the spike protein, also integrates either CoVaccine HT™ or alhydrogel. CoVaccine HT™, a single dose stimulated high titers of antigen-binding IgG. This accelerates the affinity maturation and switching of class to higher values, enhancing cell-induced immunity and virus antibodies	Nanogen Pharmaceutical Biotechnology	Phase 1/2 NCT04683484	Vaccine in development	153
60	PS	Protein subunit	Recombinant protein vaccine S-268019 (based on Baculovirus expression vector system)	Vaccine is based on recombinant protein units together with GSK; development of mRNA vaccine by Sanofi, in collaboration with Translate Bio. Preclinical data revealed that the two immunizations of the mRNA based vaccine stimulated high neutralizing antibody levels equal to those produced in infected humans	Shionogi	Phase 1/2 jRCT2051200092	Vaccine in development	130

[a] Globally, vaccine producers have the ability to achieve rapid development of highly efficient, safe – minimum toxicity – vaccines.

In order to determine the similarities and differences between previously available vaccines and COVID-19 vaccines, the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis is provided as one more example; it confers a wide range of immunity against other infections, and it also may minimize the intensity of COVID-19. Moreover one epidemiological analyses provided universal connections between the vaccinations of BCG and COVID-19 mortality: the suggestion of BCG vaccination results on COVID-19 fatality are dominated by socio-economical and demographical variations between countries. In the wake of reducing the manifold distracting factors, many substantial connections between the BCG vaccination and decreased COVID-19 fatalities were perceived. Obviously this investigation emphasizes the necessity for an intrinsic mechanism of studies supporting BCG vaccination effects on COVID-19, and also for clinical evaluation to control the COVID-19 pandemic.[99b]

COVID-19 is a serious respiratory related disease, so the scientific and medicinal community are working hard across the globe to develop a vaccine. Presently, around sixty vaccine candidates are on trial in many countries. Now, nearing twenty candidate vaccines are in phase 3 clinical trials. Gratifyingly, seven vaccines have been approved in many countries.

Conclusions

Globally, as of January 2021, there have been around 88 million COVID-19 cases, including nearly 1.9 million fatalities, WHO have registered (see WHO Covid-19 case report).[99d] These numbers are expected to increase further, so there is an

emergency requirement to produce vaccines to protect people. Several candidates vaccines are being developed which are in pre-clinical and clinical trials. The mechanism of action of these candidates varies significantly, as better knowledge becomes available[154a] about this virus, researchers can adapt their design so if one candidate shows low efficacy, another one may be more active.

Similarly, different demographics may necessitate the need for designing vaccines with different mechanisms of action. The time required for the various stages of clinical trials needs to be shortened (without compromising on the ethics and safety) to achieve the desired goal in a short period of time.[154b] Finally, manufacturing such large quantities of the vaccine or vaccines, quickly (without compromising on the quality, purity and efficacy) and distributing them to all parts of the world is another problem which the present planners have not faced before. This requires sufficient manufacturing capacity, availability of raw materials, logistics and several other factors. Also, as all resources are diverted towards SARS-CoV-2, epidemiologists and public health organizations should not lose track of their fight against other viruses.[155]

The current assemblage of vaccine developers[156a] may reward researchers with increased capability, as numerous basic, transformational and preclinical statistical data have become available during coronavirus exploration. These factors combine together as a substantial promising source for rapid vaccine development.[156b]

Since, December 2020, some new vaccines have emerged and also have been approved by certain national regulatory authorities for use against COVID-19. Amongst these, as per the universal expectations of the WHO EUL/PQ assessment, the Pfizer vaccine and some other candidates have been approved. More studies on vaccine aspirant efficacy and safety results,[157] including on the Moderna and AstraZeneca vaccine, therein have been widely reported, and AstraZeneca have published their results in well reputed journals. Thus we are eagerly expecting more potential COVID-19 vaccine candidates will be offered to governing authorities for approval in the coming years. Gratifyingly, the growth of many efficient COVID-19 vaccine aspirants under clinical trials is fascinating. When the vaccine candidates are proven to be benign and efficient, they need to be acknowledged by the governing authorities, produced to the necessary standard, and distributed. WHO is collaborating all over the world to assist with the roles in this process, which includes facilitating reasonable access to safe and effective COVID-19 vaccines for everyone.

Author contributions

KD and SA equally contributed to the collection of data and developed the entire manuscript. MD corrected the manuscript. SG and ST assisted in drafting.

Conflicts of interest

We have no conflicts of interest.

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