REVIEW

Immunogenic and reactogenic efficacy of Covaxin and Covishield: a comparative review

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Abstract
SARS-CoV-2 is an RNA virus that was identified for the first time in December 2019 in Wuhan, China. The World Health Organization (WHO) labeled the novel coronavirus (COVID-19) outbreak a worldwide pandemic on March 11, 2020, due to its widespread infectivity pattern. Because of the catastrophic COVID-19 outbreak, the development of safe and efficient vaccinations has become a key priority in every health sector throughout the globe. On the 13th of January 2021, the vaccination campaign against SARS-CoV-2 was launched in India and started the administration of two types of vaccines known as Covaxin and Covishield. Covishield is an adenovirus vector-based vaccine, and Covaxin was developed by a traditional method of vaccine formulation, which is composed of adjuvanted inactivated viral particles. Each vaccine's utility or efficiency is determined by its formulation, adjuvants, and mode of action. The efficacy of the vaccination depends on numeral properties like generation antibodies, memory cells, and cell-mediated immunity. According to the third-phase experiment, Covishield showed effectiveness of nearly 90%, whereas Covaxin has an effectiveness of about 80%. Both vaccination formulations in India have so far demonstrated satisfactory efficacy against numerous mutant variants of SARS-CoV-2. The efficacy of Covishield may be diminished if the structure of spike (S) protein changes dramatically in the future. In this situation, Covaxin might be still effective for such variants owing to its ability to produce multiple antibodies against various epitopes. This study reviews the comparative immunogenic and therapeutic efficacy of Covaxin and Covishield and also discussed the probable vaccination challenges in upcoming days.

Keywords COVID-19 · Immune response · Vaccine · Covaxin · Covishield

Abbreviations

ARDS	Acute respiratory distress syndrome
CAR	Coxsackievirus and adenovirus receptor
CLRs	C-type lectin-like receptors
CXCL	Chemokine (C-X-C motif) ligand
DAMPs	Damage-associated molecular patterns
DCGI	Drugs Controller General of India
GM-CSF	Granulocyte-macrophage colony-stimulating factor
LAV	Live attenuated vaccine
MAMPs	Microbe-associated molecular pattern
MASP-2	Mannan-binding lectin-associated serin protease-2
MCP-1	Monocyte chemoattractant protein-1
MERS	Middle East respiratory syndrome
MIP 1α	Macrophage inflammatory protein 1-α
MyD88	Myeloid differentiation factor 88
NIV	National Institute of Virology
NLR	NOD-like receptor
NOD	Nucleotide-binding oligomerization domain
PAMPs	Pathogen-associated molecular patterns
PD1	Programmed cell death protein 1
PRRs	Pattern recognition receptors
RBD	Receptor-binding domain
RLR	RIG-1-like receptor
SARS	Severe acute respiratory syndrome
SII	Serum Institute of India
TCRs	Toll-like receptors
TGFβ	Transforming growth factor β
TIR	Toll/interleukin-1 receptor
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α

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Introduction

Coronavirus is an RNA virus belongs to the big family of Coronaviridae (order: Nidovirales), responsible for severe sickness in both humans and animals [1]. There are seven types of coronavirus that have been discovered and are responsible for producing illnesses in people worldwide, while the most prevalent human coronaviruses among them are 229E, NL63, OC43, and HKU1 [2]. Three zoonotic coronaviruses (CoV) have been identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome CoV (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The WHO termed the SARS-CoV-2 clinical syndrome COVID-19 on February 11, 2020 (short form of coronavirus disease-19) [2]. This virus affects the lower respiratory tracts of humans, resulting in inflammatory pneumonia [3]. These viruses can easily be transmitted by symptomatic, asymptomatic, and presymptomatic peoples, mainly through respiratory droplets when they come into close contact with each other [4]. Given the severity of the condition, COVID-19 was declared a pandemic by WHO on March 11, 2020. [5]. In India, in the month of September 2020, the first wave of the SARS-CoV-2 infection rate reached its maximum spike and gradually declined over time. In March 2021, again, new cases of infection started, and as of 17 December 2021, a total number of 271,963,258 confirmed cases, a total of 5,331,019 deaths were reported and 8,337,664,456 vaccine doses have been administered as recorded by WHO [6]. Both the innate and adaptive immune responses to the SARS-CoV-2 virus have evolved rapidly. In innate immunity responses, the cytokine, interleukin-6 (IL-6), and complement system work against the virus, and in adaptive immunity, the monoclonal antibody is focused against the S proteins of the virus along with massive $CD4^+/CD8^+$ T cell, natural killer (NK) cell, memory B cell, and follicular T cell responses have been pragmatic within exposed persons [7]. SARS-CoV-2, having a crown-like appearance and a diameter of 60–140 nm can form a binding interface with the N-terminal end of the ACE2 receptor with higher affinity. After binding, an enzyme, Furin, found in the host cell, helps these viruses enter the respiratory tract after 4 to 5 days. [8]. ACE2 plays a physiological role in blood pressure regulation; metabolize angiotensin II (vasoconstrictor) to form angiotensin 1–7 (vasodilator). ACE2 is extensively disseminated in the cells of the mucosal surfaces of the nose and lungs, which makes the progression of infection in the respiratory tract easier. In addition to the respiratory tract, ACE2 is found on cells throughout the body, such as the endothelium, the cardiovascular system, the gastrointestinal system, and the

kidneys. These organs can be infected by viruses, making them prone to infection. [9]. There is currently no specific COVID-19 responsive drug commercially available for the treatment of COVID-19-associated diseases. Certain medicines, like antiviral/retroviral drugs and some kinds of steroids, are being used to reduce swelling and inflammation of the lungs and other parts of the body. In India, treatment with remdesivir and favipiravir has been found to speed up recovery in some patients; while lopinavir/ritonavir has not been shown to be effective in treating severe patients. The early viral negative conversion was seen with triple therapy. Ribavirin, lopinavir, and interferon-1β are used in triple therapy [10]. Arbidol inhibits the "S" protein/ACE2 interaction in various patients with SARS-CoV-2 infection, resulting in improved therapeutic efficacy [11]. But after a certain period of time, contradictory results of various popular antiretroviral drugs were observed, which dramatically limits their wide application in the management of COVID-19. In the first phase of the initiative, India began providing free COVID-19 vaccinations and aimed to vaccinate its 30 million healthcare and frontline workers on January 16, 2021. In this phase, Covishield (Oxford-AstraZeneca vaccine, the name designated by India) and Covaxin (Bharat Biotech, India, an indigenous vaccine) were approved under restricted emergency use [12]. Both vaccines function by stimulating the immune system in the same way against the S protein of SARS-CoV-2, and both need two doses to achieve effective seroprotection. Nonreplicating adenovirus is used in Covishield to express SARS-CoV-2 S protein towards the antigen-presenting cells of the host, while Covaxin uses SARS-CoV-2, which has been inactivated and taken from an asymptomatic patient and mixed with alum-adjuvant for better antibody response. In both types of vaccination, stimulation of immunogen produces significant cell-mediated and humoral immune responses [13]. The Drug Controller General of India (DCGI) recently approved Sputnik V, a third coronavirus vaccine, for use against the second wave of SARS-CoV-2 illnesses, alongside two previous vaccines. It is originally produced by the Gamaleya Research Institute (GRI) of Russia, acts similar to Covishield, and gives around 92% protection. Two types of nonreplicating (E1 gene removed) human adenoviruses, Ad26 (serotype 26) and Ad5 (serotype 5), were employed to produce the gene that encodes the entire S protein of SARS-CoV-2 (serotype 5) [14]. In the general public, as well as in the scientific community, there are many doubts, misunderstandings, and misinterpretations about which vaccine is the better of the two. There is also lots of information about the composition, therapeutic efficacy, and adverse effects of the two vaccine formulations on the web. Some review reports based on the types of vaccines available against SARS-CoV-2 are also accessible. However,

Fig. 1 The core structural proteins of SARS-CoV-2. Spike (S), envelope (E), membrane (M), and nucleocapsid (N) are the four major structural proteins found in the virus (N). The lipid bilayer envelope contains the S, E, and M proteins, while the N protein encases the virus RNA genome
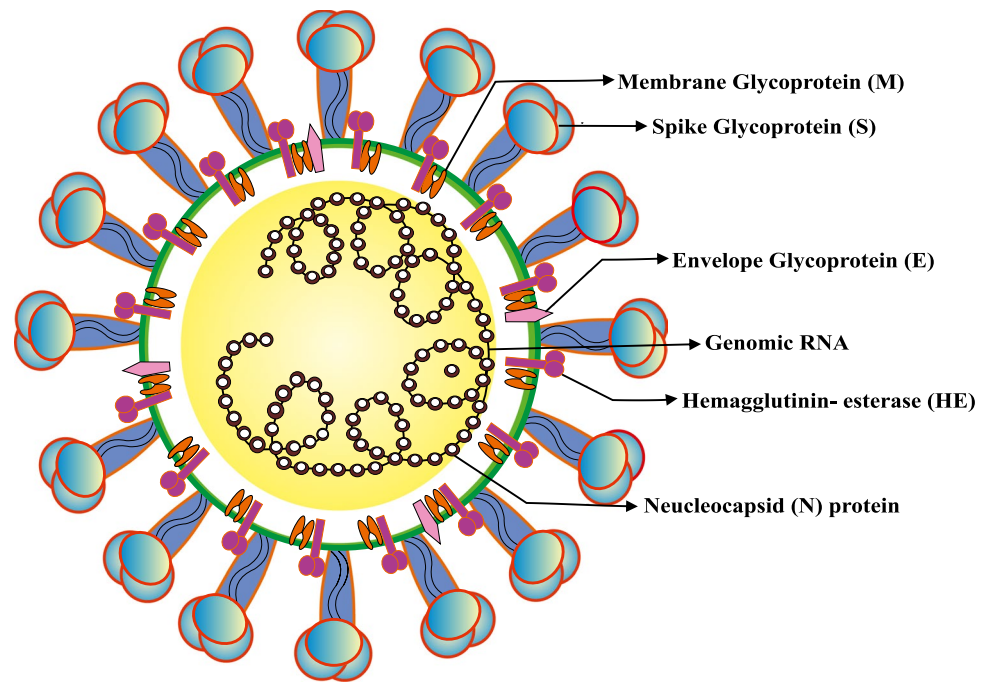
no review article has included a rigorous comparison of the immunologic and therapeutic efficacy of Covaxin and Covishield. So, in this review, an attempt has been made to provide detailed information about the efficacy of those two vaccine formulations in a comparative manner.

Epidemiology of COVID-19

Coronavirus (CoV) is named after the Latin word corona, which means "crown". This virus has several crown-shaped spike patterns on its surface [15]. It rapidly infects the human respiratory tract, causing mild to severe respiratory distress syndrome. CoV was discovered for the first time in the 1960s. The last significant coronavirus epidemics were SARS (severe acute respiratory syndrome) driven by SARS-CoV in 2002–2003 and MERS (Middle East respiratory syndrome) caused by MERS-CoV in 2012. [16]. Following a pneumonia outbreak in Wuhan, China, in December 2019 and considering its infectivity pattern, the WHO renamed it the novel coronavirus-19 (nCOVID-19) [3]. The size of SARS-CoV-2 virus particles is 29.9 kb, with spikes. The diameter of the spike is 60–140 nm, and the length is 9–12 nm, which are found on and are made up of four nano-structural proteins (NSPs) [17]. Spike (S) glycoprotein, tiny envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) glycoprotein are the four types of glycoproteins found in the viral body, and they are the main structural proteins of this virus [18] (Fig. 1). Among all known RNA viruses, coronavirus has the largest genome (26.4–31.7 kb) [19]. The "S" protein aids in the virus' binding to the host

cell, allowing it to enter the cell [20]. The M protein, which has three transmembrane domains, helps the virus bend and become spherical, as well as maintain the virus' basic structure [21]. The viral assembly and release are aided by the E protein [22]. It is an RNA virus with a positive strand. When they bind to cellular receptors and enter the host cell, the viral essential protein is produced due to RNA translation, which is required for viral replication. The new viral particle will be released from the host cell and infect additional host cells [23]. The human ACE2 receptor is activated by the spike of this virus, which binds to it via its receptor and receptor-binding domain (RBD). Using biochemical and pseudovirus entry, the binding of receptor and protease activation of the SARS-CoV-2 S protein was studied [24].

Natural immunity against COVID-19

During infection, the structural protein S of SARS-CoV-2 interacts with the host cell's target receptor ACE2. S1 and S2 are two subunits of glycoprotein S. S1 contains a receptor-binding domain, while S2 mediates viral-host cell fusion [25]. T and B cells activate and mediate adaptive immunity, which collectively become effective against the coronavirus [26]. Cytotoxic T cells and NK cells are both required for immune responses to viruses. In comparison to a healthy person, a COVID-19 patient has low lymphocyte and high neutrophil count, with the number of CD8 + and NK cells, in particular, being reduced [27] (Fig. 2). The pathogen is recognized by macrophages, dendritic cells, and monocytes after it enters the body, owing to pattern recognition
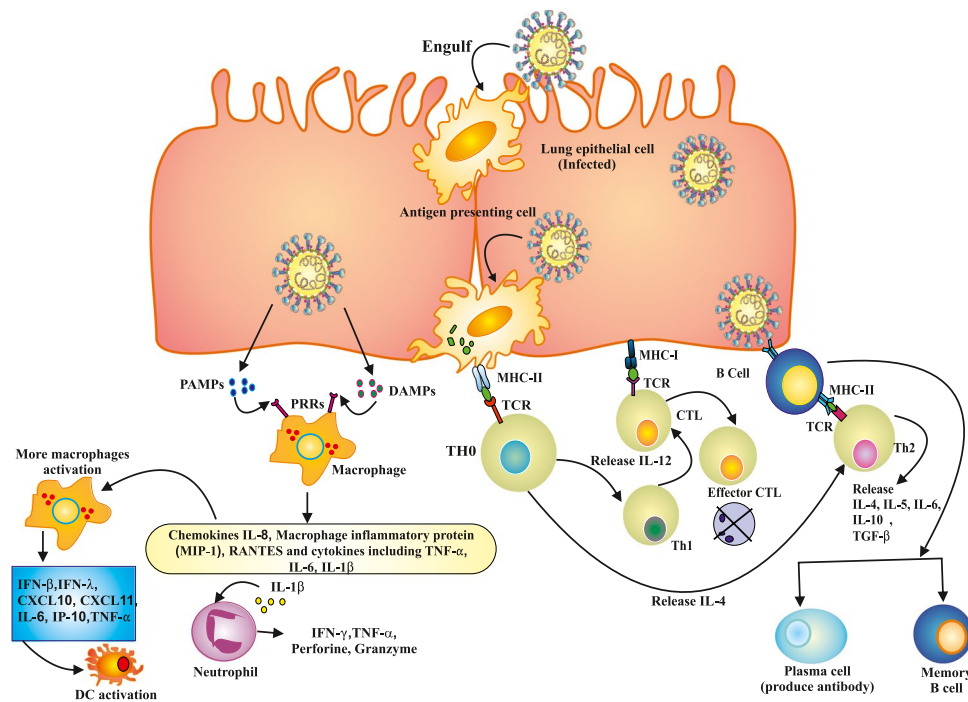
Fig. 2 Summarization of various immune responses against COVID-19. PRRs identify PAMPs and DAMPs in the innate immune response, causes macrophage activation and the release of inflammatory cytokines. T and B cells are also activated, and differentiation is aided. T cells come in a variety of subtypes that release cytokines. IL-1β activates neutrophils, causing them to produce IFN-γ, TNF-α, perforin, granzymes, as well as activates DCs. Infected epithelial cells may give virus antigens to naïve T cells (TH0), which then release IL-12 and differentiate into TH1 (CD4 + T cells) and TH2 (CD8 + T cells). Apoptosis occurs when NK cells become cytotoxic to virus-infected epithelial cells. DCs and macrophages use the MHC-TCR interaction to present viral antigen to CD4 + T cells. Memory T cells are developed, and they may confer protection against reinfection with the same viral strain for a period of time that has yet to be determined. The activated B cell also acts as an APC, presenting the antigen to the TH2 cell via MHC-II and TCR interaction. The TH2 cell then generates IL-4, IL-5, IL-6, IL-10, and TGF-β, while the B cell differentiates into plasma cells and memory B cells, which produce anti-SARS-CoV-2 specific IgM, IgA, and IgG antibodies

receptors (PRRs), which recognize the microbe-associated molecular pattern (MAMPs) [25]. After infection, the incubation period has been estimated in symptomatic patients approximately 5 days of symptom onset. Approximately 97.5% of patients then develop symptoms such as fever, dry cough (less common), difficulty breathing, headache, dizziness, diarrhea, nausea, loss of taste (dysgeusia), muscle joint discomfort, and loss of smell (anosmia) within 11.5 days [4]. The viral loads in mouth swabs and sputum specimens reached their maximum level at 5 to 6 days following the onset of symptoms, ranging from 10^4 to 10^7 copies per milliliter of fluid [28]. Then, an infected person, as well as an asymptomatic patient, can develop acute respiratory distress syndrome (ARDS), which occurs within 7 days after the inception of symptoms and a decline in oxygen levels [29].

Innate immune response

Epithelial cells and hyperactive macrophages are activated by the virus' innate immune response. When these cells are infected, they interact with damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) via PRRs like Toll-like receptor (TLR), C-type lectin-like receptors (CLRs), NOD-like receptors (NLR), RIG-1-like receptors (RLR), and free molecule receptors in the cytoplasm, for instance, Cgas, IFI 16, STING, DAI, etc., on the immune cell, which activate the inflammasome and release pro-inflammatory and inflammatory mediators [30]. In the immune system, myeloid-derived cells such as macrophages and monocytes play a crucial role. TLRs are found in macrophages that identify the nucleic acid pattern (ssRNA) of invading viruses. TLR4, TLR7, TLR8, and TLR9 are among these TLRs, but no specific TLRs involved in SARS-COV-2 pathogenesis have yet been identified [31]. TLRs attach to viruses, which can activate the NF-κB and MAPK signaling pathways, to clean the virus and produce antiviral responses. TLRs also begin the processes of phagocytosis, cytokine release, and several other mediators in order to augment the local anti-inflammatory processes as part of immune control [32] (Fig. 2).

Pattern recognition receptors (PRRs)

PAMPs are microbial structures that can be detected by PRRs in the innate immune system, such as TLRs and RIG-I like receptors, NLR, and others, triggering downstream signaling cascades that finally prompt an efficient antimicrobial response [33]. The type I and III interferon and several other chemokines can be produced more efficiently when the signaling pathways are targeted by the ligand-binding activity, which is notably targeted the various transcription factor (AP-1, IRF3, and NF-κB). These chemokines stimulate the recruitment of more innate immunity responsive cells (polymorphonuclear leukocytes, monocytes, NK cells, and DCs), which in turn stimulate the production of chemokines (MIG, IP-10, and MCP-1) to further promote the recruitment of lymphocytes to the site of infection, which is provided by DCs. [34, 35]. These cytokines act on nearby cells in a paracrine manner through the IFN-α/β receptor (IFNAR) and cause the production of interferon-stimulated genes (ISGs). IFNAR mediates the activation of the Jak/STAT pathway, which leads to the attachment of STAT1 homodimers and STAT1/2 heterodimers to the promoter region of ISGs, which is triggered by interferon-stimulated gene expression. [34].

PAMPs and TLRs

TLRs recognize PAMPs in the cell membrane, endosomes, lysosomes, endocytosomes, and other locations [33]. TLRs activate a variety of adaptor proteins (TRAM, TIRAP, MyD88, and TRIP), which cause a variety of biological responses, all of which share the Toll/interleukin-1 receptor (TIR) structure [36]. Except for TLR3, all TLRs act as adaptor proteins for MyD88 (myeloid differentiation factor 88), which activates the NF-κB and MAPKs pathways and results in the generation of pro-inflammatory molecules [37]. TRIF binds to TLR3 and TLR4 and supports an alternate pathway for the generation of inflammatory cytokines and IFN-1 genes by activating IRF3, NF-κB, and MAPKs [36]. With the help of TLR-7/8, the virus activates monocytes or macrophages, stimulating IFN-I responses [38]. In activated inflammatory macrophages, CCL2, CCL3, CCL20, CXCL1, CXCL3, CXCL10, IL1, IL8, and TNF levels are all increased [39] (Fig. 2).

RIG-1-like receptors (RLRs)

RLRs recognize the nucleic acid of RNA viruses and can be utilized to program the adaptive immune response via a cross talk with the innate immune system's parallel arms [40]. RIG-1 recognizes triphosphine RNA at the 5′ end of viral nucleocapsid proteins, as well as double-stranded RNA containing basic acid [41]. Ultimately, it stimulates some downstream intracellular pathways to produce cytokines, chemokines, and chemotactic factors for effective antiviral action, in addition to MDA5 and LGP2 [40].

NOD-like receptors (NLR)

NOD-like receptors (NLRs) are cytoplasmic receptors that aid in the innate immune response by detecting PAMPs and DAMPs [42]. In response to PAMPs identification, these receptors can trigger the expression of pro-inflammatory cytokines; they are also required for reproduction and embryo regeneration, regulation of apoptosis, and participation in acquired immune system reactions. NLRs are mostly expressed in macrophages, DCs, and lymphocytes, but they have also been recognized in nonimmune cells like epithelial cells [43].

Innate immune response through specialized cells

DCs, one of the professional antigen presenting cells (APCs), play a critical role in adaptive and innate immune responses [44]. DCs are classified into two types: plasmacytoid DC (pDCs) and conventional DC [45]. These cells include the generation of immune-increasing cytokines like IL-12 and IFN-I and also the mobilization of innate lymphocytes. Despite the fact that DCs have phagocytic properties, limited particle absorption potency and their phagocytic ability are not known to contribute to microbial minimization or death; their phagocytic ability is effective for antigen presentation and processing on MHC I and II [46]. pDCs boost the production of IFN-I to remove viruses from circulation through the macrophages and also to preserve the integrity of pDCs for the priming of adaptive immunological responses [47]. NK cells, also known as cytotoxic cells, provide virus immunity by recognizing pathogens using natural cytotoxic receptors (NCRs) such as NKp46 and NKp44 [48]. NK cells are yet another important component of innate immunity. It was quickly discovered that the overall number of NK cells in COVID-19 patients is significantly reduced [49]. NKG2A expression on NK cells was dramatically enhanced in individuals infected with SARS-CoV-2 [50]. It binds to a nonclassical HLA class I molecule with negligible polymorphism (HLA-E). NKG2A transduces inhibitory signaling through two inhibitory immune-receptor tyrosine-based inhibition motifs after being ligated by peptide-loaded HLA-E, reducing NK cytokine production and cytotoxicity [51]. The killing of bacteria by neutrophils via phagocytosis and degranulation promotes the first-line defense of innate immunity [52]. To improve the severity of COVID-19, this cell forms neutrophil extracellular traps (NETs). CXCR2 is higher in neutrophils, and the type I IFN response is delayed [53]. The complement system is also engaged in innate immune response, which is a mechanism

that does not require the use of antibodies (lectin pathway). The mannose-binding lectin-associated serine protease 2 (MASP-2) is involved in this mechanism, which causes the complement system to be questioned [54]. MASP-2 activation by SARS-CoV-2 causes the complement system to become hyperactive, causing damage to the infected tissue [55] (Fig. 2).

Adaptive immune response

Cell-mediated immunity

Severe lymphopenia was observed in non-survivor COVID-19 patients. Despite having normal or high total B lymphocyte counts, up to 80% of SARS patients in the hospital had severe leukopenia and a decrease in CD4 and CD8 T cells [50, 56]. Internalized by phagocytic cells like macrophages and DCs, the virus is digested and peptide fragments known as antigens (epitopes) are represented by MHC II on the surface of this cell by specific CD4+/helper T cells [57]. The CD4+cells then secrete IL-2 and IFN-γ, which activate many macrophages and increase B-cell proliferation, allowing antigen-specific antibodies to be produced [58](Fig. 2). Then, the antibody forms a coat around the bacteria, and they become easier to phagocytosis. In addition to phagocytosis, the innate immunity, cells recognize the pathogen by PRRs and trigger inflammation signaling and begin cytokine production, such as TNF, IL-1 and IL-12 [59]. When a virus infects a cell, certain cells promote the release of type I IFN-α and IFN-β, which induces antiviral resistance and activates NK cells [60]. The immune system generates memory cells to provide defense against reinfection. The memory CD8+and CD4+T cells and B cells remained in a resting condition during reinfection but became active and quickly eliminated the source of antigen. Vaccine strategy is largely based on immunological memory [61]. When normal cells become infected by a virus, the number of MHC-I decreases, then, the infected respiratory epithelial represent the viral epitopic part through MHC-I to the CD8+cytotoxic T cell. When a viral epitope interacts with a CD8+cytotoxic T cell, the T cell produces perforin and granzyme, which kills the virally infected cell [62] (Fig. 2).

Humoral immunity

The humoral immune response is a neutralizing mechanism by which it prevents viral infection. The host humoral response to SARS-CoV-2 (IgA, IgM, and IgG) was studied using an ELISA-based test based on the recombinant viral nucleocapsid protein. The post-symptomatic onset (PSO) of IgM is observed within 5 days, IgA between 3 and 6 days and IgG of 14 days [63, 64]. IgA and IgG antibodies against S protein subunit 1 of SARS-CoV-2 were measured in the serum of infected people [65]. After roughly 28 days, IgM and IgA levels drop, whereas IgG amounts reach their peak after around 49 days [66]. Along with neutralization, these antibodies also can perform antiviral protection through other mechanisms, including antibody-dependent cell cytotoxicity (ADCC), antibody-dependent phagocytosis (ADCP), etc. The ADCC is a result of FcγRIIIa cross-linking in NK cells, and ADCP is mediated by professional phagocytes (monocytes, macrophages, neutrophils, and eosinophils), which are attached to the antibody-covered virus via special Fc receptor, and IgM and IgG also activate the complement system [67]. Long-term memory T cell and B cell work against SARS-CoV-2 the same as adaptive immune responses. During subsequent infection, T cells aid in the destruction of infected cells. Without the presence of any antigens, case investigations in recovered SARS patients revealed that both CD4+and CD8+memory T cells were effective in inducing immunological responses from 3 months to 6 years [68]. After the acute phase of infection, the antibody level declines because most of the plasmoblasts are induced during the first week after a short-lived infection. Smaller number of long-lived plasma cells maintain the serological memory. The long-lived plasma cell is found in the bone marrow and secretes antibodies when there is no antigen present to recognize. The pool of long-lived memory B cells generates this response [68]. During the first week after infection with SARS-CoV-2, T cells become activated, and virus-specific memory is generated in the body. CD4+and CD8+T cells reach their peak level in 2 weeks but remain low for 100 days or more. SARS-CoV-2 memory CD4+T cells were detected in up to 100% of COVID-19 patients, while CD8+T cells were observed in roughly 70% [69] (Fig. 2).

Infection mechanism of SARS-CoV-2

Despite the fact that SARS-CoV-2 is assumed to primarily infect respiratory epithelial cells, a recent study revealed that it could also affect T lymphocytes, spleen, and lymph nodes. [70]. The infection is mediated through the ACE2 receptor in the same way as SARS and the receptor-binding motif (RBM), which is a part of the RBD of SARS-CoV-2 that establishes contact with that receptor [71]. ACE2 is largely expressed on type II alveolar epithelial cells, but it is also identified on the surface of epithelial cells from the nasal and oral mucosa, in addition to the nasopharynx, implying that SARS-CoV-2 is primarily concentrated on the lungs. This ACE2 is highly expressed in enterocytes of the small intestine, notably in the ileum, as well as heart, kidney (proximal tube), and bladder urothelial cells [72, 73]. The entry of the first virus may be strongly dependent on TMPRSS2 expression because even small quantities of ACE2 can support
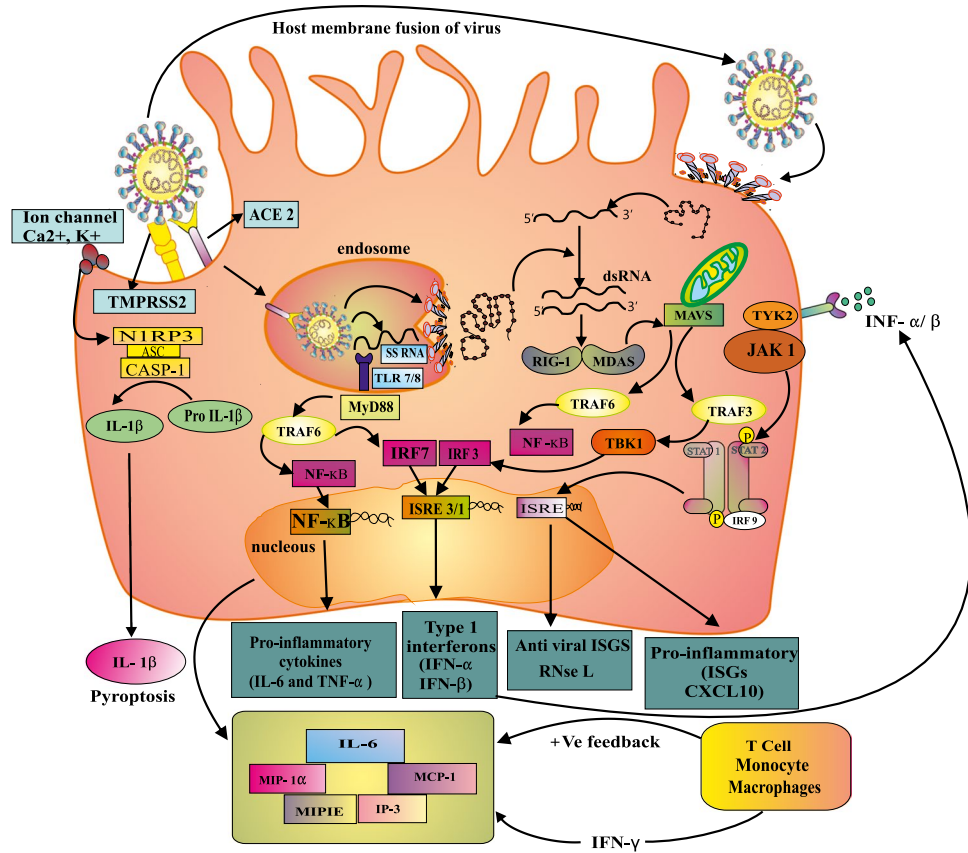
Fig. 3 Infection mechanism of COVID-19. When alveolar epithelium cells are invaded by SARS-CoV-2, the cells express the surface receptors ACE 2 and TMPRSS2, and the virus is recognized by innate immune receptors such as the endosomal RNA sensors TLR7/8, RIG-I, and MDA5. This TLR7/8 can detect viral RNA species created during viral replication, such as viral genomic RNA and dsRNA. While RIG-I and MDA5 are responsible for sensing cytoplasmic viral RNAs such as 5′-3' RNA or dsRNA. This causes NF-κB and IRF3/7 to become activated, resulting in the generation of proinflammatory cytokines and type I interferons, respectively. Type I interferons are important in restricting viral multiplication, and their effect is exacer-

bated by the production of ISGs like RNAse L. IL-6, IP-10, MIP-1α, MIPIE and MCP1 are the major pro-inflammatory cytokines and chemokines. These proteins draw monocytes, macrophages, and T cells to the infection site, causing further inflammation and triggering a pro-inflammatory feedback loop. In the case of a faulty immune response (left side), this can lead to increase inflammatory immune cell trafficking in the lungs, generating an overproduction of pro-inflammatory cytokines, and eventually causing lung damage. The cytokine storm that results spreads to other organs, causing multi-organ damage

SARS-CoV-2 entry if TMPRSS2 is present [74]. RNA is injected within the host cell by viruses, which is translated into viral replicase polyproteins, which then cleave into NSPs of individuals and form RNA-dependent RNA polymerase [75]. Enzyme replicase requires a full-length positive-strand RNA genome as a template in order to create full-length negative-strand RNA copies of the viral genome. During transcription, the RNA polymerase enzyme transforms subgenomic mRNA to viral protein (S, E, N, and M). The viral protein and genome RNA are formed into virions in the Golgi and endoplasmic reticulum, which then migrate into ERGIC (ER-Golgi-intermediated compartment) and exit the cell via vesicles [76, 77] (Fig. 3).

PAMPs and DAMPs

Alveolar epithelial cells and alveolar macrophages identify and release PAMPs (viral RNA), and DAMPs (ASC oligomers, DNA, and ATP) via a number of PRRs [78]. This detection process affects the activation of intracellular signaling pathways, which is able to produce IFN-I, GM-CSF, TNF, IL-1, IL-6, IL-8, and also many other pro-inflammatory cytokines, which systematically employ activated leukocytes within the lungs and amplify microvascular permeability [79]. The RLRs include RIG-I and melanoma differentiation-associated gene 5 (MDA-5), TLR 3, 7, and 8 that trigger IFN pathways and the production signaling of cytokines. When PRRS recognizes a viral particle, it acts downstream via the TANK-binding kinase-1 (TBK1) and inhibitor-κB kinases (IKKs), which activate IRF-3, IRF-7,

and the nuclear factor of the kappa light chain enhancer in activated B cells. This entire cascade promotes the nuclear translocation process. The activation of these proteins promotes the type I IFNs and IFN-stimulated genes; many of them have antiviral properties; on the other hand, the pro-inflammatory mediators, such as chemokines, cytokines, and antimicrobial peptides, they all are important for the trigger immune response (innate and adaptive) in the host. Moreover, the synthesis of IL-18, IL-1, and inflammasomes is triggered by the missing in melanoma 2 (AIM2)-like receptors and NLRs, resulting in pyroptosis [80].

Downregulation of antiviral cytokines

The antiviral is based on IFN-I (particularly IFN-β and IFN-α), and type III IFNs serve as a basic component of innate immune response and facilitate the development of adaptive immune response against viral infection [81]. This infection promotes low levels of antiviral cytokines IFN-α/β. This virus suppresses IFN synthesis by covering viral RNA from cellular components in the host cell [82]. SARS-CoV nsp-1 (nanostructural protein 1) suppresses the immune response along with the generation of IFNs (IFN-I). nsp demonstrates an elevated expression of IFN-I [83]. Activation of IFN-I also minimize the expression of viral proteins such as nsp1, nsp7, and nsp15, as well as ORFs such as ORF3B, ORF6, and ORF9b [84]. IFR3, which promotes IFN production, is activated by IFN gene signaling, which is disrupted by the virus' ability to prevent IFN production [85]. Transmembrane inhibitor 1(TM1), which binds to RIG-1, TANK-binding kinase-1, TNF receptor-associated factor-3 (TRAF-3) and inhibits M protein production (TBK-1). After binding these molecules to M protein, it prevents them from binding to any other downstream effectors to prevent IFN-1 induction [86]. SARS-CoV-2 produces the abnormal level of the following cytokines and chemokines such as GM-CSF, M-CSF, G-CSF, MCP-1, MIP 1-α, IFN-γ, TNF-α, IP-10, hepatocyte growth factor (HGF), IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, and vascular endothelial growth factor (VEGF) [87]. The abnormal production of these cytokines and chemokines pulls immune cells from the bloodstream, particularly monocytes and T lymphocytes. But they are not able to pull neutrophils into the infected site. An elevated level of neutrophil–lymphocyte ratio and lymphopenia were observed approximately in 80% of COVID-19 patients, and this observation could be the scientific explanation of pulmonary recruitment of immune cells from the bloodstream [78]. The dysregulation of innate immunity is caused by the elevated production of TNFα, IL-6, and a low amount of type I and III IFNs in people who are affected by COVID-19 [87].

Cytokine storm

COVID-19-associated lung pathogenesis is common during manifestation. The infection and overproduction of pro-inflammatory cytokines, which are referred to as 'cytokine storm', are mainly responsible for this [88]. In COVID-19, the cytokine storm is characterized by elevated levels of expression of IFN-γ, IL-1, IL-6, IL-8, IL-12, TGF-β, and also the upregulation of CXCL9, CXCL10, etc. In addition, plasma levels of IL-2, IL-7, IL-10, GM-CSF, MIP1-α, TNF-α, and MCP-1 were also raised in patients suffering from SARS-CoV-2 infection [89]. The cytokine storm follows the angiotensin 2 (AngII) pathways, and IL-6 has been found to be the central mediator in this event [90]. GM-CSF activates inflammatory monocytes (CD14$^+$ CD16$^+$), causing them to generate significant amounts of IL-6, TNF-α, and other pro-inflammatory cytokines [91]. Poor IFN induction could be a significant cytokine amplifier, Fc and Toll-like receptors, etc. may lead to an imbalanced inflammatory response [92]. The IL-6-sIL-6R complex is generated when IL-6 bind to the sIL-6R through gp130, and in the case of nonimmune cells, it can activate the signaling cascade and act as the activator of STAT3 [90]. The acquired immune system and innate immune system both have pleiotropic effects when cis signaling (classical signaling) is activated, which can play an important role in cytokine release syndrome [93]. The cytokine storm impacts negatively on the body, which is responsible for the ARDS, several organ malfunctions, and death [94]. A cytokine storm causes an uncontrolled influx of immune cells into the lungs, particularly monocytes and neutrophils. IL-1, IL-6, TNF-α, CCL2, CCL7, and CCL12 are among the inflammatory cytokines and chemokines secreted by these cells, which contribute to the severity of the condition. IL-1 has previously been shown to trigger pyroptosis, which is defined as non-programmed cell death in response to pathogenic infection [95]. Due to the increased release of harmful chemicals, such as proteases and reactive oxygen species (ROS), uncontrolled cell infiltrations cause serious lung injury, including pneumocyte desquamation, alveolar injury, hyaline membrane development, and pulmonary edema, all of which are early indications of ARDS [96].

Disturbance in complement activation

COVID-19 people have excessive coagulation, which leads to more thrombosis and a poor clinical outcome [97]. Complement activation is a key factor in the host intermediary of SARS-CoV-2-mediated illness because it controls a systemic pro-inflammatory response to it [98]. The levels of complement components like soluble C5b-9 and C5a in plasma of the severely ill patient increased notably [99]. The virus' N protein and MASP-2 interact to initiate the lectin

pathway, and this interaction also causes abnormal complement activation [98]. The complement system uses pattern recognition molecules from the canonical classical and lectin pathways (CP and LP) to detect invading infections along with environmental or self-derived antigens. A sequence of proteolytic activities results in pathway-specific canonical C3 convertase cleaving C3 into the anaphylatoxin (AT) C3a and the opsonin (C3b). The foundation for the C5 convertase that cleaves C5 into the AT C5a and C5b is formed by the C3 convertase. Apart from CP and LP activation, any nucleophilic attack on the thioester in C3 could activate it directly, resulting in the activation of the so-called alternative route (AP) and the synthesis of substantial amounts of C3a and C5a [100]. When complement hyperactivation was revealed in SARS-CoV-2 infected patients, anti-C5a monoclonal antibodies were injected into them, which led to a suppressive effect [101].

Dysregulation of immune cells

SARS-CoV-2 engages monocytes/macrophages through TLR7 and TLR8, which can produce type I IFN responses along with cytokine production. These collective immune responses gave inhibitory outcomes towards viral infection [38]. The activities of monocytes and macrophages are dysregulated by SARS-CoV-2 causing lung damage and respiratory disorders, including ARDS [102]. During the early stages of infection, the number of CD14 + monocytes and CD14 + IL-1 + monocytes are increased in the blood circulation of infected patients [103]. Macrophages play an important role in the induction of cytokine storms. In COVID-19 patients, IL-1 and IL-6 from circulating monocytes and macrophages cause macrophage activation syndrome (MAS), which leads to severe respiratory failure [104]. The number of CD4 + and CD 8 + T lymphocytes also decreased. In the patient's body, the delayed IFN responses can lead to enhanced pro-inflammatory cytokine responses, altering the dynamics of antigen presentation and cytokine generation in innate immune cells and perhaps contributing to T cell response dysregulation [105]. SARS-CoV-2 similarly avoids the host immune system via reducing the number of NK cells. From the 16th day after the onset of the disease, the number of NK cells begins to decline. The deficiency of this cell is responsible for the number of viral infections and viruses protect themselves by enhancing their own survival mechanism [106]. As similar to the NK cells, T and B cells also showed gene signatory modification, which is linked with the high IFN-based immune responses and also to the activation of the apoptotic signaling cascade in the infected patient. According to the prior research, the responsible genes for B cell activation were found lower in the severely infected group as compared to the moderate group, these may be

associated with the delayed humoral response contributed to the disease severity [107]. Infection of DCs with SARS-CoV-2 led to the inhibition of MHC-I expression on DCs, delaying the development of IFN-α [108]. This virus causes DCs to produce too many chemokines, which causes DCs to migrate to lymph nodes, while increased TRAIL expression causes lymphocytes to apoptosis when they come into contact with DCs. Due to the DC-associated death of T cells, the virus-specific adaptive immune response is declined. SARS infection slowed DC activation and migration to draining lymph nodes, resulting in a poor adaptive T cell response [109].

Overview of COVID-19 vaccines

The alarming SARS-CoV-2 outbreak necessitated a rapid response and vaccine development in an unprecedented time frame, and vaccine development was initiated [110]. The S protein of the SARS-CoV-2 virus has been used for the production of several COVID-19 vaccines. Over 214 numbers of unique vaccines were developed against SARS-CoV-2 by various pharmaceutical companies and academic institutes as of December 10, 2020, using different vaccine platforms such as recombinant viral-vectored vaccines, live attenuated viruses, protein subunit vaccines, inactivated vaccines, nucleic acid-based vaccinations, and virus-like particles [111]. The novel vaccination must pass three steps before being approved: There are three stages in the research process: exploratory, preclinical, and clinical (phase 1, phase 2, and phase 3) [112]. Moderna's mRNA-1273, Ad5-nCoV (CanSino BIO), ChAdOx1 (University of Oxford), AstraZeneca's AZD1222 and Pfizer, and BioNTech's BNT162 are currently in phase 3 clinical trials [113].

Inactivated vaccine

In an inactivated vaccination, the virulence properties of live viruses are reduced by heat, UV rays and chemical treatment (formaldehyde or propiolactone). The pathogen in this vaccine remains in a dormant state. Although this deadly virus cannot cause disease, it can trigger an immune response in the event of a future infection. The inactivation form of the organism creates a secure vaccine, especially for immunocompromised individuals. Moreover, these COVID-19 vaccines showed a lower immune response as compared to the live vaccines, and they also may need many booster doses. These inactivated vaccines take a large amount of time to make, since the virus must first be cultivated in the laboratory before being inactivated [114, 115]. In addition, in

the host body, the vaccine is unable to initiate a replicating process. It is less dangerous than a live attenuated vaccination (LAVs). Adjuvant in vaccine formulations is required to improve vaccination efficacy [116]. CoronaVac (Sinovac), Sinopharm, BBIBP-CorV, and Covaxin are the inactivated vaccines [117].

Live attenuated vaccine

LAV is the most traditional technique. A live attenuated vaccine is created by a live virus until it weakens as it transits through an animal or human cell, rendering the genome incapable of producing disease. This virus may multiply and replicate like a normal infection, resulting in a powerful immunological response from T and B cells. However, there is a slight risk that the mutation will revert to virulence and cause diseases [118]. Medicago Inc. and Codagenix are live attenuated vaccines. It is an influenza virus vaccine that is developed to utter the RBD domain in the SARS-CoV-2 S protein. This vaccine has the ability to induce TLRs (TLR 3, TLR 7/8, and TLR 9), which interact with B cells to generate an immune response [119].

Protein subunit vaccine

Long-lasting immune responses require recombinant antigenic proteins mediated sub-unit vaccines. SARS-CoV RBD (sRBD) holds antigenic epitopes, which elicit the neutralization process of antibodies as well as T cell responses [117]. RBD vaccinations were more immunogenic than full-length S protein vaccines. In the area beyond the RBD of the full-length S protein, super-antigens are present there. As a result, the RBD-based sub-unit vaccine may be the most suitable and secure way to make the COVID vaccine [120]. Sub-unit proteins are a considerably safer option, although their efficiency is limited. Adjuvanted systems have already been shown to efficiently improve the immunogenicity potency of these sub-unit vaccines by protecting and improving antigen targeting to professional antigen-presenting cells [121]. Recently, the Chinese Academy of Science developed a subunit vaccine known as Novavax.

Nucleic acid vaccine

The development of COVID-19 vaccines using nucleic acid is a cost-effective strategy. The nucleic acid-coded antigen is significantly used in vaccine development research. After the failure of the initial clinical study, plasmid DNA emerged as a potential platform despite the volatility of mRNA. A new set of clinical trials to make vaccinations against COVID-19 has been sparked by advancements in vaccine delivery. Several research organizations are now working on nucleic acid-based vaccinations [122]. The mRNA-based vaccination is

a new, noninfectious, non-integrating platform that has a lower risk of insertional mutagenesis. Because of its less expensive and high safety issue in animal trials, it is the most promising option [123]. The immunogenic potency of the mRNA can be reduced, and changes can improve the vaccine's stability. The mRNA-1273 is a synthetic viral mRNA vaccine that covers the entire SARS-CoV-2 S protein and simulates natural infection. Synthesized viral mRNA is recognized by the host body, which then translates the viral protein [124]. sRBD and the entire spike are encoded by the BNT162b1/BNT162b2 vaccines, which are codon-optimized mRNA vaccines [125]. In the case of antigen-encoded DNA vaccine, it is potent enough to stimulate the adaptive immune response, and it is the most revolutionary technique for immunization. Similar to the living virus, the transfected cells convey the transgene and allow a gradual supply of transgene-specific proteins. DNA vaccines that target the S, M, and N proteins elicit both humoral and cellular immune responses. Although the DNA-based vaccine platform is temperature stable and can be produced quickly, its efficacy and immunogenicity in humans have yet to be established. The injection of genome integration, vector mutations, and DNA vaccines within the host gene are still challenges [117]. INOVIO Pharmaceuticals has developed INO-4800, a DNA vaccination candidate. It was developed with the intention of improving the S protein sequence of the SARS-CoV-2 virus [126].

Viral vector vaccine

Recombinant DNA technology is used to create viral vector vaccines. Also introduced into the virus is DNA that encodes an antigen from the pathogen [118]. These types of vaccines are able to transfer the genes to the targeted cells in a very precise way. It was also observed that these kinds of vaccines produce a high level of immune response along with the massive gene transduction process. Due to the long half-life and peak level of antigenic protein expression, viral vector vaccines are more effective compared to other types of vaccines. They activate cytotoxic T cells, which kill virus-affected cells. Replicating (vesicular stomatitis virus and measles virus) and nonreplicating vectors (adenoviruses and poxviruses) are the two types of viral vectors. Interestingly, this adenovirus vector is used as the key element in some kinds of vaccine formulations. Due to its unique characteristics (genetically and physically stable), it does not combine with the host DNA. With DCs, entire dividing and nondividing cells can be easily infected by the Ads vector. But adenovirus vectors need high concentrations or doses to produce a satisfactory immune response. Also introduced into the virus is DNA that encodes an antigen from the pathogen. The viral vectors then enter the host cell and express the antigen. Within

the host cell, some viruses can replicate and some fail to do so. In the biotechnology field, the S protein gene of SARS-CoV-2 was encoded into a replicating virus, such as measles or adenovirus. It is a safe virus and is able to induce a strong immune response through T and B cells (such as hepatitis B and HPV) [118, 121]. SARS-CoV-2 is also encoded by nonreplicating measles or adenoviruses with dormant genes. This vaccination is also safe, but long-term immunity requires a booster dose [118]. In this case, chimpanzee adenovirus (ChAdOx1) is used as a vector, which has been engineered to express the S protein of SARS-CoV-2 [13]. The University of Oxford and AstraZeneca are working together to develop AZD1222. This adenovirus has been genetically altered to prevent it from replicating in humans [127].

Immunological efficacy of COVID-19 vaccines currently used in India

Covaxin

With the collaboration of the Indian Council of Medical Research (Indian government-funded biomedical research agency), Bharat Biotech developed the Covaxin, India's first indigenous COVID-19 vaccine [128]. Covaxin gained DCGI permission for human clinical trials in June 2020, and the first phase of the trials was completed by July [129]. Covaxin phase I clinical trials were conducted on 365 healthy volunteers across 12 institutes in India, including the All India Institute of Medical Sciences (AIIMS) in New Delhi, AIIMS Patna, and the Post Graduate Institute (PGI) of Medical Sciences in Rohtak [117]. It is an inactivated vaccine, and it cannot cause serious sickness in the host body. It makes use of a fully infective SARS-CoV-2 viral particle, which is composed of RNA, encased in a protein capsid that has been modified to hinder the viral reproduction process. It is comprised mostly of an entire inactivated SARS-CoV-2 antigen (strain NIV-2020–770), 250-g aluminum hydroxide gel as an adjuvant, 15 g TLR 7/8 agonist (imidazoquinolinone), 2.5 mg TM 2-phenoxyethanol, and phosphate buffer saline to a concentration of 0.5 ml. The vaccine does not require subzero storage or reconstitution, and it is available in multidose vials that are stable at temperatures ranging from 2 to 6 °C [130]. An adjuvant is used to boost up the specific immune response against the particular antigen, which is present in vaccine formulation [131]. In the case of Covaxin, an aluminum hydroxide-based adjuvant is formed to generate a crystalline aluminum oxyhydroxide by the addition of alkali to the solution of aluminum salt [132].

Covishield

Covishield (ChAdOx1-nCOV or AZD1222) is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 S glycoprotein vaccine currently being developed by the Serum Institute of India (SII), Pune, based on the AstraZeneca-Oxford model [133, 134]. The AZD1222 COVID-19 vaccine was licensed by the UK on December 30, 2020, and India on January 2, 2021 [135]. This contains nonreplicating SARS-CoV-2 and adenovirus strains (causative of the common cold) that have been genetically engineered and weakened. According to the interim research, AZD1222 is 70.4% effective against COVID-19 prevention with no significant side [13]. A number of 5×10^{10} ChAdOx1-S (recombinant) virus particles are contained in one dose (0.5 ml). This vaccine also comprises the recipients' magnesium chloride hexahydrate, L-histidine, L-histidine hydrochloride monohydrate, disodium edetate dihydrate, sodium chloride, ethanol, sucrose, polysorbate 80, and water for injection, in addition to ChAdOx1-S (recombinant) [130]. Both vaccines are stored and transferred at 2–8 °C [136, 137]. The immunization regimen of Covaxin and Covishield consists of two doses; in the case of Covaxin, 28 days apart; intramuscular injections are advised, and Covishield (0.5 ml in each dose) should be given 4–6 weeks apart [137].

Immunological response of both vaccines

Immune response of Covaxin

Individuals cannot be infected by inactivated vaccines because they cannot multiply, and the adjuvants are used to boost immunogenicity [138]. One of the most important findings from the phase I/II studies was the evidence of improved humoral and cell-mediated immune responses in Covaxin recipients [139]. Though CD4 + and CD8 + T cell responses were only detected in a subgroup of patients in the phase I study, the cell-mediated immune response was considerably improved in the phase II trial. Covaxin improved T cell memory, as seen by a rise in CD4 +, CD45RO +, and CD27 + T cells, supporting the antigen recall memory response. The adjuvant molecule Covaxin has a Toll-like receptor (TLR 7/8) agonist [140]. TLR7 and TLR8 agonists enhance the Th1 immune response but suppress the TH2 response, which is good for COVID-19 vaccines. Additionally, employing TLR 7/8 agonists as adjuvants may boost CD8 + T cell responses. Antiviral cytokines like TLR 7/8 agonists boost Th1 responses while suppressing Th2 responses, which is good for COVID-19 vaccines. Additionally, employing TLR 7/8 agonists as adjuvants may boost CD8 T cell responses. On days 7 and 14, antiviral cytokines such as IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, and IFN were

Fig. 4 Immune response of Covaxin and Covisheild. Covaxin: the virus is used in its inactive form, but its S protein remained intact. Aluminium-based adjuvant was also used here. Some of the inactivated viruses are captured by APCs inside the host. The coronavirus is processed apart by the antigen-presenting cell and displays some of the fragments on its surface. The fragment could be detected by helper T cell and become activated, which can help recruit other immune cells to respond to the vaccine if the fragment fits into one of its surface proteins. Covisheild: the genetic instruction of the SARS-CoV-2 S protein has infiltrated the adenovirus. In the body, the virus is engulfed in a bubble by the cell, which pulls it within. Once inside, the adenovirus breaks free from the bubble and proceeds to the nucleus and pushes into it. The coronavirus S protein gene may be read by the cell and copied into mRNA, which begins constructing S proteins after it leaves the nucleus. Some of the cell's S proteins make spikes that migrate to the cell's surface and stick out their tips. Some of the proteins are also broken down into pieces by the vaccinated cells, which are present on their surface. The immune system can then recognize these protruding spikes and S protein fragments
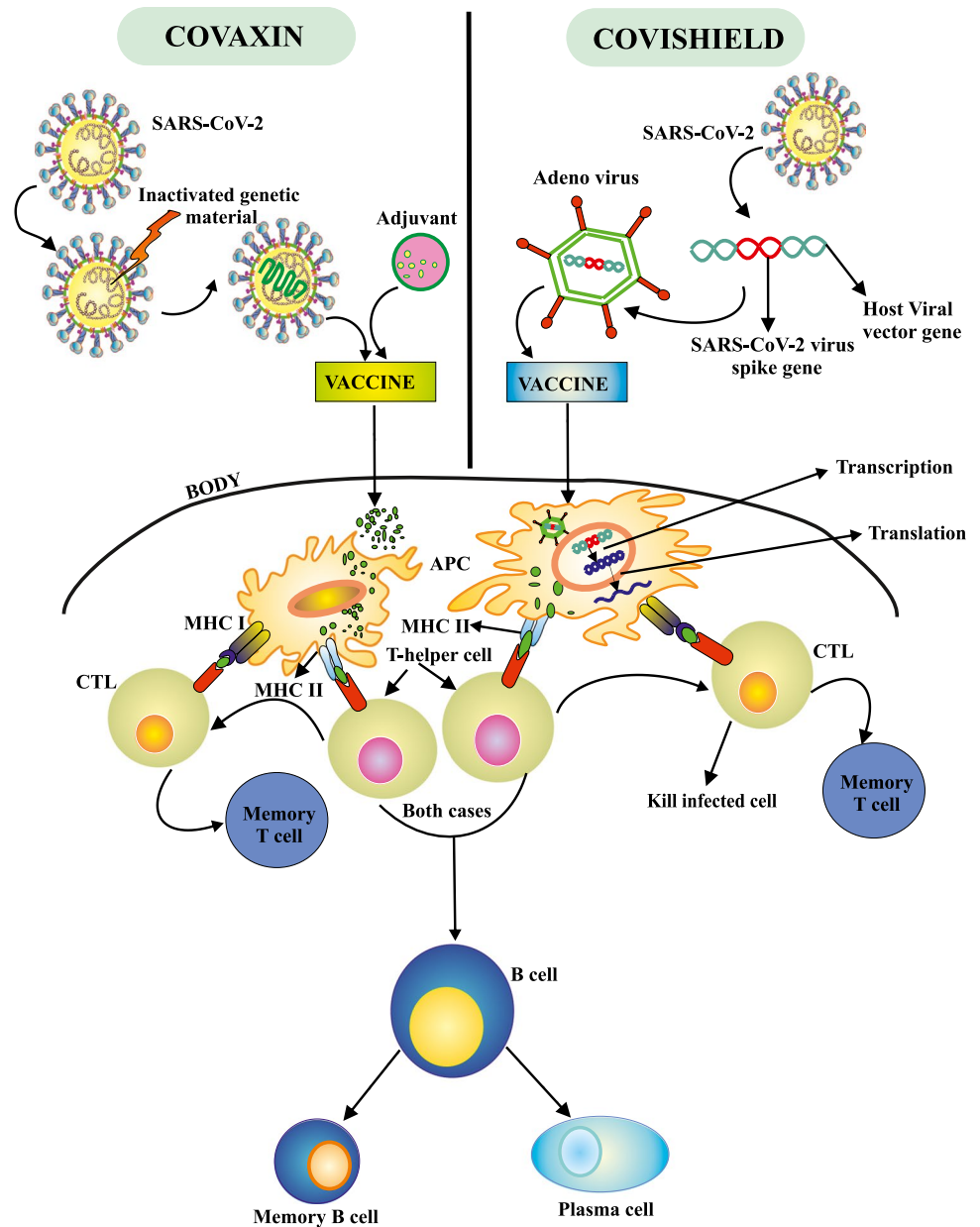
also released, possibly contributing to increased APC activation such as DCs and macrophages. TLR recognition in the innate cell population has also been linked to the generation of early-IFN I, which aids viral clearance and the generation of pro-inflammatory cytokines [141] (Fig. 4).

APCs (DCs, macrophages, neutrophils) pick up the S protein via phagocytosis, and they have the ability to trigger the proliferation and secretion of cytokines by naïve T cells [142]. APCs can break the protein into fragments and present the peptides on the surface through MHC I and MHC II with CD8 + and CD4 + T cells in lymph nodes [143]. Then, interleukin-12 and interleukin-4 are released by the interaction, which differentiates the naïve T cell to T helper cell-1 and T helper cell-2, respectively. T helper cell-1 acts in cell-mediated immunity and releases cytokines, IFN-γ, interleukin-2, and TNF-β, which make these cells particularly effective at preventing intracellular viral infections. T helper-2 cells can identify by secretion of IL-4, IL-5, IL-10, and IL-13 [144]. Helper T cells are important in a variety of immunologic processes, including cytotoxic T cell and macrophage activation, B cell maturation into plasma cells and memory B cells and produce B cell antibodies [145]. Cytotoxic CD8 T cells also secrete the cytokines IFN-γ, TNF-α, and TNF-β, which help the host defend itself in a variety of ways. Some B cells and T cells become memory cells, and they are ready to be reactive when they come into contact with some

antigens [146]. Memory B cell plays a role in long-term immunity [147]. When SARS-CoV-2 enters the body, antibodies stop the viruses from binding to cells or tag them for destruction, and cytotoxic T cells recognize and destroy infected cells. Antibodies also stick to them and target S proteins and prevent the virus to enter cells [108].

Immune response of Covishield

The adenovirus vector ChAdOx1 nCoV-19 adenoviral vector-based vaccine (AZD1222) carries the entire structural surface glycoprotein (S protein) of the SARS-CoV-2. The S protein encoded by ChAdOx1 nCoV-19 has a codon-optimized coding sequence [148]. Human adenovirus, often known as the common cold virus, is the most prevalent nonreplicating viral vector used in the COVID-19 vaccine, i.e., Covishield [149]. ChAdOx1 nCoV-19 generates a widespread and robust T cell response in the host. There was a considerable increase in B cell activation and proliferation, as well as anti-IgA and anti-IgG antibodies, to the SARS-CoV-2 virus after immunization. S proteins were easily recognized in vaccinated people's serum [150]. CD4 + T cells mainly produced Th1 cytokines (IFN-γ, IL-2, and TNF-α/β) instead of Th2 cytokines (IL-5 and IL-13). Importantly, it is shown, using a number of approaches, that immunization with ChAdOx1 nCoV-19 induces mostly a Th1 response [148]. ChAdOx1 nCoV-19 was found to be safe, tolerable, and immunogenic, with paracetamol being found to reduce reactogenicity and tolerability. A single dose of this vaccine can develop both humoral and cellular responses, and a booster dose generates neutralizing antibody titers [150].

In the vaccine, the adenovirus of chimpanzees is used. Some genes (E1 and E3) of this adenovirus are removed by a biotechnological method that makes adenovirus replication incompetent [151]. The gene of RNA of SARS-CoV-2, which synthesizes S protein through the process of reverse transcription from double-stranded DNA, S protein. Then, the DNA gene is inserted into the adenovirus, and the adenovirus is converted into the vector-based DNA vaccine and, after entering into the cell, activates the immune response. Then, adenovirus enters into the host cell and forms an endocytotic vesicle. Extrachromosomal DNA is converted into SARS CoV's S protein mRNA, and it comes out of the nucleus. Next, the mRNA of S protein is translated by using the cellular translation machinery into the S protein [152]. Then, the S protein is processed, and some fragment of S protein (epitope) is displayed by MHC-I on the surface of this host cell. Next, the cytotoxic T cell (CD8 + lymphocyte) interacts with the MHC-I receptor and becomes active. Some S protein particles are picked up by B lymphocytes. APC engulfs the S protein particle and the viral DNA transcribed and translated by the cell machinery and produces S proteins. Some of these S proteins break into small pieces and are represented by the MHC-II on the surface of this cell to the CD4 + T cell. Through these interactions, some chemokines and interleukins are released and activate the growth and proliferation of CD8+ T cells and B cells. When the cytotoxic T cells become active, some of them destroy the vaccine-infected host cell by releasing granzyme and perforin, and some convert them to memory T cells. Then, the B cells are converted into plasma cells and memory B cells. The plasma cell produces antibodies against the S protein. This vaccine is based on highly immunogenic technology and stimulates a strong antibody and cell-mediated immune response, which provides long-term protection [153].

Efficacy of Covaxin and Covishield against mutant variants

WHO has renamed some variants "Variants of Concerns (VOCs)" or "Variants of Interests (VOIs)" because of their potency to notably change the virus' properties. Recently, WHO has designated the dominantly spreading virus variants by Greek alphabets, i.e., Alpha (α) for B.1.1.7 (UK variant), Beta (β) for B.1.351 (South Africa), Gamma (γ) for P.1 (Brazil), Delta (γ) for B.1.617.2 (India), etc. [154]. SARS-CoV-2 Brazil variant, known as B.1.1.28 variant originated in Brazil, COVID-19 South Africa variant, known as the B.1.351 variant outbreak in South Africa, and UK variant, known as B.1.1.7 variant, are around in Delhi and Punjab, also a British variant [155]. A number of cases in the second wave have been gradually increasing in India. SARS-CoV-2 L452R, T478K, E484Q, D614G, and P681R variant cause for a large number of coronavirus cases in Maharashtra. The B.1.36 variant of SARS-CoV-2 cases was found in much higher numbers in Bangalore [156]. The known SARS-CoV-2 mutation in India is the SARS-CoV-2 double mutant strain, a combination of more than 2 COVID-19 variants, found in Punjab, Delhi, and Maharashtra and is classified as a B.1.617 variant, which contains L452R and E484Q variants [157]. SARS-CoV-2 triple mutant strains are also found recently in Maharashtra and Delhi during the second wave, which are more complex based on their severe infectivity pattern [158]. The B.1.617.2 variant has been given the name Delta. Delta, a highly contagious (and probably more severe) SARS-CoV-2 virus strain initially found in India in December 2020, is currently a major source of concern. It subsequently spread quickly throughout that country, as well as throughout Great Britain. The first Delta case in the USA was discovered just a few months ago (in March). Initially, the Delta variant was thought to be a variant of interest. However, due to its rapid spread over the world, the WHO classified this strain as a VOC in May 2021 [159]. Along with the mutations identified in the Beta and Gamma variations, the Delta Plus variant carries extra three

mutations, K417N, V70F, and W258L on the coronavirus S protein. It was found for the first time in South Africa and Brazil, respectively. According to a previous analysis, Beta was associated with higher hospitalization and fatalities during South Africa's first wave of illnesses, whereas Gamma was thought to be highly transmissible at the time. When comparing infectivity and transmission qualities amongst people who were previously infected earlier in the pandemic or who had weak or incomplete vaccination immunity, Delta Plus may have a minor advantage [160]. On November 25, WHO received the first report of the novel SARS-CoV-2 variant, Omicron, from South Africa. According to WHO, the first confirmed B.1.1.529 infection was discovered in a sample obtained on November 9 of this year. The new SARS-CoV-2 variation B.1.1.529, which was discovered in South Africa, was given the name 'Omicron' by WHO on November 26. Omicron has been categorized under 'Variant of Concern,' according to the WHO [161]. A summary of the information on the variants of SARS-CoV-2 has been provided in Table 1.

Comparative therapeutic advantages

In the Covaxin (BBV152), the virus strain (NIV-2020–770) with the Asp614Gly mutation, was isolated and sequenced from the patient who is infected by COVID-19, is used. The vaccine is injected intramuscularly into the deltoid muscle with 0.5 ml/dose volume. Two doses are needed in the gap of 28 days [133]. In this vaccine, the entire virion β-propiolactone-inactivated SARS-COV 2 vaccine is absorbed into the alum. By the 3 phases' trail, it is observed that the efficacy is 81% [140]. This vaccine is also found to be effectively neutralized against the B1.1.7 variant of SARS-CoV-2 [176]. Covishield (AZD1222), the ChAdOxl nCoV-19 vaccine, is made with the help of an adenovirus vector; it carries a full length of this virus, which is inserted the coding sequence of the S protein of SARS-CoV-2. It is also administered in two doses and 0.5 ml, which contain $5 \times (10)^{10}$ viral particles. It is injected intramuscularly into the deltoid muscle, and the second dose is generally given 12 weeks apart after the first dose [148]. The general efficacy of this vaccine is 70% in Brazil and in the UK. In South Africa, the same vaccine showed only 22% efficacy for the new variant 501Y.V2 (B.1.351), which can resist both innate and adaptive immunity [177]. Covaxin is applied only to those people above 18, and Covishield is applied to people over 12 years old. The first dose of Covaxin was administered among 96 health workers, and Covishield was administered in 456 individuals in India. Covishield had a larger responder rate and a higher median increase in anti-spike antibodies than Covaxin (86.8% vs 43.8%), as well as a higher median increase in anti-spike antibodies (61.5 vs 6 AU/ml). Age, sex, and BMI had no effect on the results.

With hypertension, the response rate was lower (65.5 vs 82.3%), and Covishield recipients experienced more side effects than Covaxin recipients (46.7 vs 31.2%). After the first dosage of Covishield, seropositivity rates to anti-spike antibody are higher in Covishield recipients than in Covaxin recipients [133]. Covishield vaccine has completed three trials, Covaxin has completed phase I and phase II studies, and phase-III is enrolled. The two doses of Covishield improve protection with a gap of 12 weeks, and Covaxin is recommended to be taken as a second dose after 4 weeks of the first dose [178]. Mild symptoms occur as a side effect of Covishield vaccine administration. Headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site warmth, injection site pruritus, weariness, malaise, feverishness, and chills are all very prevalent (around 10% of participants). Injection site edema, erythema, and fever are common (1–10% of people). Bharat Biotech also highlighted the hazards and negative effects of Covaxin. These include injection site pain, swelling, redness, itching, stiffness in the upper arm, weakness in the injection arm, body ache, headache, fever, malaise, weakness, rashes, nausea, vomiting, and body ache, headache, fever, malaise, weakness, rashes, nausea, and vomiting [130, 138]. If someone has a severe allergic problem with any ingredient in a vaccine, then he/she should not get the Covishield vaccine. And if anybody shows an allergic reaction after taking the first dose of Covishield, then he/she should not take the second dose of this vaccine. In the case of Covaxin, the same conditions apply, including acute infection and fever, pregnant women, and if someone is on blood thinner [179]. In Covaxin, the entire virion is propiolactone inactivated, imidazoquinoline molecule (Algel-IMDG) is used as TLR 7/8 agonist, but in the case of the Covishield vaccine, the adjuvant is not part of this vaccine formulation [139]. Here, the authors, Singh et al., conducted a study to increase the humoral response in the kinetics of antibody production against SARS-CoV-2 S protein as a result of the first and second doses of both vaccinations, Covishield and Covaxin, until 6 months after the trial was completed. SARS-CoV-2 naïve and SARS-CoV-2 recovered people are both involved in this study. The binding antibody against S protein kinetics after the first dose (day 21 or more till the second dose of vaccine) of two vaccines were reported in this experiment from the continuing coronavirus vaccine-induced antibody titer (COVAT) investigation. According to a survey, there is no significant difference in response rates based on age, sex, BMI, blood group, or other comorbidities, including any of the previously mentioned variables. Females had a greater median antibody titer than males. In the SARS-CoV-2 naïve individual, the median anti-spike antibody titer is higher in the SARS-CoV-2 vaccine-induced naïve individual. Post-vaccination side effects and the median elevation in antibody against SARS-CoV-2 S protein are higher in Covishield

Table 1 Characteristics of different SARS-CoV-2 variants and efficacy of COVID-19 vaccines

Mutant strains of SARS-CoV-2	Pango lineage	First identified	GISAID clade	Site of mutation	Key mutation	Additional amino acid changes observed	Alteration of vaccine effectiveness	Antibody response	Reference
Alpha variant	B.1.1.7	UK, September 2020	GRY	Spike protein	N501Y mutation: enhanced the viral binding potency with ACE2 receptor. H69del/V70del mutation: responsible for S gene targeting failure. P681H mutation: effectively increase the viral cell entry	+ S:484 K + S:452R	The efficacy of the AstraZeneca vaccine's 70% and of the Pfizer vaccine is roughly 90%	High	[162, 163]
Beta variant	B.1.351	South Africa, May 2020	GH/501Y.V2	Spike protein	There are 23 mutations with 17 amino acid changes, but the notable mutations in this variant are K417N, E484K, and N501Y on the spike protein. These mutations are able to increase their binding efficacy to the ACE2 receptor	+ S:L18F	The Pfizer vaccine was 75% effective against any infection caused by the Beta variant after two doses. Novavax clinical trials in the UK revealed 89% efficacy, compared to merely 60% in South Africa, where the Beta strain was prevalent. Similarly, trials of the Johnson & Johnson vaccine in South Africa found lower levels of protection against moderate-to-severe COVID-19 than in the USA	Reduced	[163, 164]

Table 1 (continued)

Mutant strains of SARS-CoV-2	Pango lineage	First identified	GISAID clade	Site of mutation	Key mutation	Additional amino acid changes observed	Alteration of vaccine effectiveness	Antibody response	Reference
Gamma variant	P.1	Brazil, November 2020	GR/501Y.V3	Spike protein	17 numbers of novel amino acid changes were observed, where 10 numbers of mutation in its S protein. The three main alarming mutations are N501Y, E484K, and K417T	+S:681H	After vaccination with Moderna or Pfizer, the variant has been demonstrated to be relatively resistant to neutralisation by convalescent plasma and vaccinee sera. The severity of the loss, however, was minor (3.8 to 4.8-fold)	High	[165]
Delta variant	B.1.617.2	India, October 2020	G/478 K.V1	Spike protein	L452R and P681R mutations were observed in spike protein. Some extra mutations were observed such as Y145H, A222V, etc., in the Delta Plus variant	+S:417 N+S:484 K	mRNA-1273 Vaccine effectiveness against infection with the Delta variant declined from 94.1% (90.5 to 96.3%) 14–60 days after vaccination to 80.0% (70.2 to 86.6%) 151–180 days after vaccination	High	[166, 167]

Table 1 (continued)

Mutant strains of SARS-CoV-2	Pango lineage	First identified	GISAID clade	Site of mutation	Key mutation	Additional amino acid changes observed	Alteration of vaccine effectiveness	Antibody response	Reference
Epsilon variant	B.1.429 B.1.427	Cedars-Sinai Medical Center, California July 2020	CAL.20C	Spike protein	I4205V in ORF1a; D1183Y in ORF1b; L452R; W152C and L452R; these mutations were identified in spike protein	+ S:13I	Neutralizing antibody titers against the B.1.427/B.1.429 variations are reduced (3 to sixfold) as compared to wild-type pseudoviruses, according to an analysis of neutralising antibody responses following spontaneous infection or mRNA vaccination	High	[168, 169]
Lambda variant	C.37	Peru, December 2020	GR/452Q.V1	Spike protein	G75V,T76I, L452Q, F490S, D614G, and T859N amino acid mutations were observed in S protein	—	Lambda variant of interest confers increased infectivity and immune escape from neutralizing antibodies elicited by CoronaVac	High	[170, 171]
Mu variant	B.1.621	Colombia, January 2021	GH	Spike protein	T95I, Y144S, Y145N, R346K, E484K, or the escape mutation, N501Y, D614G, P681H, and D950N were observed	—	Mu variant shows a pronounced resistance to antibodies elicited by natural SARS-CoV-2 infection and by the BNT162b2 mRNA vaccine	High	[172, 173]

Table 1 (continued)

Mutant strains of SARS-CoV-2	Pango lineage	First identified	GISAID clade	Site of mutation	Key mutation	Additional amino acid changes observed	Alteration of vaccine effectiveness	Antibody response	Reference
Omicron variant	B.1.1.529	Multiple countries, November 2021	GRA	Spike protein	A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F; these mutations were observed in spike protein. Many other mutations were located in RBD 319 to 541	+ R346K	Three doses of the Pfizer BioNTech Vaccine potently minimize the Omicron variant. After two significant doses of this vaccine, reduction of titer neutralization was noted	High	[174, 175]

recipients than in Covaxin recipients. In the case of Covaxin, there is an increase in IgG antibodies (peaked by 28 days), and in the case of Covishield, there is an increase in IgG anti-spike antibodies after the second dose. The first dosage of Covishield generates binding antibody immunoreactivity by raising antibodies against the S protein in most individuals 21 days after the first dose, whereas Covaxin shows lower efficacy after the first dose. The structure of this virus' spike glycoprotein and nucleocapsid protein is critical for the development of a vaccine [133]. In India, two vaccines are used, Covaxin and Covishield. These two main types of vaccines are produced by two different mechanisms; Covaxin, which is an inactivated virus vaccine, and Covishield, which is a nonreplicating virus vector vaccine. They induced immune responses and protective mechanisms in various ways [130, 139]. In the body, Covishield can produce 98.1% antibodies, and Covaxin can produce 80% antibodies. A total of 5.5% of people has become infected with the virus after taking Covishield, and 2.2% of people has become infected after taking Covaxin [133]. Multiple doses are required to induce adaptive immunity with these vaccines, which is one of their major drawbacks. Vaccines given with adjuvants cause a significant local reaction, which increases the antigenicity [180]. These vaccines necessitate booster shots as well as a large amount of virus to maintain the immunogenic particle's integrity [181]. The therapeutic effectiveness of Covaxin and Covishield has been given in the comparative form in Table 2.

Upcoming vaccines in India

Sputnik V

Sputnik V, a nonreplicating viral vector vaccine developed by the Gamaleya Research Institute in collaboration with the Russian Federation's Ministry of Health, is now being studied in a phase 3 study in the Russian Federation. On August 11, 2020, Russia granted a license to the anti-SARS-CoV-2 vaccine Sputnik V, which was developed by the Gamaleya Institute in Moscow [179]. It is an adenoviral vector-delivered antigen same as Covishield. It also induces both cellular and humoral immunity after a single immunization, and after double immunization, it gives a double and long-lasting immune response [184]. This is a rAd type 26 and rAd type 5 combination vector vaccination. They both have the full-length SARS-CoV-2 glycoprotein S gene. They are administrated intramuscular and separately with a gap of 21 days. The first and second phase of the trial of this vaccine is done in August 2020 [185].

Biological E vaccine

Biotechnological E vaccine (Corbevax) is a new vaccination in India that is similar to the Novavax vaccine. It will be available in the country by the end of the year. It is a form of protein subunit vaccination that requires two separate doses to be effective. The Bio-E vaccine is a made-in-India vaccine that is projected to have 90% effectiveness against COVID-19 variations and will likely be a game changer in the fight against the pandemic, according to the manufacturer. Novavax will be manufactured in India by the Serum Institute of India, which also manufactures Covishield [186].

ZyCoV-D vaccine

ZyCov-D vaccine is developed by Ahmedabad-based Zydus-Cadila. Zydus Cadila, focused on discovering and developing NCEs, Novel Biologicals, Biosimilars, and Vaccines. Zocovirus-D is a DNA vaccine that is designed to function against the key viral membrane protein that is responsible for the novel coronavirus' entrance into human cells. A plasmid DNA molecule, a small circular, and extrachromosomal bacterial DNA molecule that is employed in genetic engineering serve as the foundation for this technology. Additionally, the vaccine will be the first COVID-19 vaccine in India to have been tested in an adolescent population in the 12–18 years age bracket, which will be a significant benefit for the country. In addition, ZyCoV-D is a three-dose, intradermal vaccine [187].

Nasal spray vaccine

COVID-19 nasal vaccine BBV154 is developed by Bharat Biotech based in Hyderabad, India. Syringes are not used to administer other vaccines. In the area where they are immediately taking from the nose, COVID-19 nasal immunizations are more effective than syringe-based vaccines. Vaccination with BBV154 is administered intravenously and results in a broad immune response that includes neutralizing IgG, mucosal IgA, and T cell responses. Immune responses at the injection site (in the mucosa of the nose) are crucial for preventing both COVID-19 infection and transmission [188].

Future perspectives

Covishield is a type of vaccine that provokes antibodies against the S protein of the coronavirus. The immunological stimulation is better as it consists of a single epitope. As there is no significant mutation-related alteration in the S protein epitopic structure, Covishield is still widely effective against all mutant variants of COVID-19, including the

Table 2 Summary of the comparative therapeutic advantages of Covaxin and Covishield

Properties	Covaxin	Covishield
Developed by	Bharat Biotech, Hyderabad, and ICMR	Based on the AstraZeneca-Oxford model, Serum Institute of India
Types	Inactivated virus vaccine	Nonreplicating viral vector vaccine
Composition	It consists primarily of the entire inactivated SARS-CoV-2 antigen (strain NIV-2020–770) and a 250-g aluminium hydroxide gel adjuvant [140]	Covishield (AZD1222), the ChAdOxl nCoV-19 vaccine is formulized by the adenovirus vector, and it carries an entire length of virus, which is inserted the coding sequence of the spike protein of SARS-CoV-2 [148]
Efficacy rate	Covaxin has been found 78–80% effective	Covishield can be up to 90% effective
Antibody response	After the second dose of Covaxin, the level of IgG anti-spike antibody increased. Covaxin has lower efficacies after the first dose than Covishield. Covaxin can produce 80% antibodies in the body [133]	Single dose of Covishield, the number of IgG antibodies increased (peaking after 28 days). Covishield produces binding antibody immunoreactivity by increasing antibodies against the spike protein in most people 21 days after the first dose. Covishield can produce 98.1% antibodies [133]
Side effects	Localized side effects of Covaxin include pain and swelling at the injection site, whereas widespread side effects include upper arm stiffness, fever, fatigue, weakness, headache, nausea, vomiting, body discomfort, and rashes [182]	Localized effects include pain and tenderness, warmth, redness, swelling, or brushing at the injection site, and generalized effects include headache, fatigue, myalgia (muscle pain), malaise (generalized weakness), pyrexia (fever), chills, arthralgia (joint pain), nausea, and in rare cases, neurological complications [171]
Post-vaccination side effect	Lower than Covishield [133]	Higher in the case of Covishield [133]
Limitation	A person having acute illness and fever, pregnant women, and people who are on blood thinners should not take this vaccine [183]	If a person has a severe allergic reaction to any vaccine ingredient, he or she should not receive Covishield vaccination, and if a person has an allergic reaction after receiving the first dose of Covishield, he or she should not receive the second dose of this vaccine
Level the titer of antibodies	51 AU/ml	115 AU/ml
Doses	2-dose gap intervals 28 days or 4 weeks [133]	2 doses gap in 12 weeks [148]
Infected after vaccination	Approx. 2.2% [130]	Approx. 5.5% [130]

Delta strain in India. On the other hand, Covaxin can develop antibodies against several epitopes, which are mostly similar to natural COVID-19 infections. But the overall effectiveness of this vaccine is lower than the Covishield. However, if the epitopic structure of spike protein is altered significantly in the future owing to spontaneous mutation, the Covishield may not function correctly. Therefore, immunization with one dosage of Covaxin and another dose of Covishield, or vice versa, may provide superior effectiveness. If a vaccine is developed based on the virus' conserved sequence, it will be more effective than others. Even if many new variants or mutant strains are discovered, the efficacy rate of those vaccines will not be reduced. But it needs more experimental trials and should meet the entire desired standard for a successful vaccine formulation.

Conclusion

Since the emergence of SARS-CoV in 2002 and its propagation throughout 32 nations and areas, the globe has seen the outbreak of MERS-CoV and now the COVID-19. CoVs pose a constant threat to human health since they appear on a regular and unpredictable basis, spread quickly, and cause deadly infectious diseases. The first case of SARS-CoV-2 in India was reported in Kerala on 27 January 2020. There is currently no specific COVID-19 responsive drug commercially available for the treatment of SARS-CoV-2 infection. Some medicines and therapies like antiviral/retroviral drugs and certain kinds of steroids are being used to reduce swelling and inflammation of the lungs and other parts of the body. There are many mutant strains that have been detected in India, but still, the Covaxin and Covishield work against them. To date, in India, the effectiveness of Covishield is much higher than Covaxin. In Covishield, only the S protein work as a single epitope, so the immunogenicity and antigenicity are more. Because Covaxin contains the entire SARS-CoV-2 virus in an inactivated form, the body generates antibodies against various epitopes. Several studies reported that there is reduced efficacy of both vaccines against the Delta variant (B.1.617.2). Following Delta, the Omicron variant of SARS-CoV-2 (classified as B.1.1.529 by WHO) has recently emerged as another global menace, and investigations are being conducted to search out the efficacy of existing COVID-19 vaccines against it. Finally, the present review covers detailed insights into the immunological and therapeutic efficacy of two widely administered vaccines in India, which will enrich the knowledge in the field of concern.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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