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REVIEW ARTICLE

Current clinical status of new COVID-19 vaccines and immunotherapy

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Abstract

COVID-19, caused by SARS-CoV-2, is a positive-strand RNA belonging to *Coronaviridae* family, along with MERS and SARS. Since its first report in 2019 in Wuhan, China, it has affected over 530 million people and led to 6.3 million deaths worldwide until June 2022. Despite eleven vaccines being used worldwide already, new variants are of concern. Therefore, the governing bodies are re-evaluating the strategies for achieving universal vaccination. Initially, the WHO expected that vaccines showing around 50–80% efficacy would develop in 1–2 years. However, US-FDA announced emergency approval of the two m-RNA vaccines within 11 months of vaccine development, which enabled early vaccination for healthcare workers in many countries. Later, in January 2021, 63 vaccine candidates were under human clinical trials and 172 under preclinical development. Currently, the number of such clinical studies is still increasing. In this review, we have summarized the updates on the clinical status of the COVID-19 and the available treatments. Additionally, COVID-19 had created negative impacts on world's economy; affected agriculture, industries, and tourism service sectors; and majorly affected low-income countries. The review discusses the clinical outcomes, latest statistics, socio-economic impacts of pandemic and treatment approaches against SARS-CoV-2, and strategies against the new variant of concern. The review will help understand the current status of vaccines and other therapies while also providing insights about upcoming vaccines and therapies for COVID-19 management.

Keywords COVID-19 therapies · SARS-CoV-2 · Vaccine · Clinical trial · Nano vaccine · Immunotherapy · Children vaccine · Antiviral drugs

Abbreviations

ACE-2	*Angiotensin-converting enzyme 2*
AD-5	*Adenovirus type-5*
ARDS	Acute respiratory distress syndrome
APC	Antigen-presenting cell
COVID-19	Coronavirus disease of 2019
DCGI	Drug Controller General of India
EMA	European Medical Agency
ER	Endoplasmic reticulum
EUAs	Emergency use authorizations
LNPs	Lipid nanoparticles
MERS	Middle East respiratory syndrome
RBD	Receptor-binding domain
TMPRSS2	Transmembrane protease serine 2
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
US-FDA	United States Food and Drug Administration
WHO	World Health Organization
CD	Cluster of differentiation
MHC	Major histocompatibility complex
VLP	Virus-like particle

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NIAID	National Institute of Allergy and Infectious Diseases
GAVI	Global Alliance for Vaccines and Immunisation

Introduction

The ongoing SARS-CoV-2 pandemic caused havoc to public health infrastructure, with no approved therapy, affecting millions around the globe. The outbreak was first reported on the 31st of December 2019 to the WHO (Zhao et al. 2021). The coronavirus was designated as "2019-nCoV" by the WHO on 12th of January 2020 and then termed SARS-CoV-2. In January 2020, the WHO declared it a public health emergency, and in March 2020, it was declared a global pandemic as the number of infections continued to spread (Majumder and Minko 2021). Global efforts were made first to break this transmission chain by imposing strict lockdowns, which also helped reduce the burden on healthcare infrastructure. The multiple agents of broad therapeutic benefit and symptomatic relief were used initially to manage severe infection cases and compromised patients. While the lockdowns and early treatment approaches were in place, a vast majority were still susceptible to infection. Lack of preparedness and poor healthcare infrastructure in low-income countries caused a socio-economic disbalance, leaving huge population stranded. Vaccination on a mass level and in a controlled manner was the best option to protect the population against the ill effects of severe infection. Therefore, a search for vaccination strategies began. Established and novel strategies were scrutinized with early sequencing reports of the COVID-19. Among this was the emergency use authorizations (EUAs) of lipid nanoparticle-assisted m-RNA-based vaccines by US-FDA, including Pfizer and Elasomeran,m-RNA 1273/Spikevax/Moderna vaccines (Mathieu et al. 2021). Other players aimed at conventional technology containing live/inactivated viruses including AstraZeneca (UK), Covilo/BBIBP-CorV/Sinopharm (China), Ad26.COV.S/Janssen/Jcovden (USA), and Bharat biotech (India) (Mohapatra and Mishra 2021). Novel and efficient strategies are being explored, and some are already seeking emergency approval. Despite prompt action by authorities, attaining mass immunization was limited by bottlenecks in manufacturing, supply chain, and regulatory approvals. The early COVID-19 vaccines required ultracold storage conditions, which was another hurdle and setback to global vaccination. While supply chain disruptions, failures to meet the expected delivery timelines, or vaccine nationalism were preventing the global supply of vaccines (Forman et al. 2021; Karthika et al. 2021). Access to credible information, highlighting limitations and persuasive opinions, is crucial to overcome the above mentioned concerns. This review highlights the potential research direction and summarizes clinical outcomes to advance understanding and business potential.

The global vaccine market is expected to grow at 10.7% compound annual growth rate and reach $109.87 by 2027. In a new year resolution, the WHO had made strategies to achieve global COVID-19 vaccination of 70% of the world's population by mid-2022. This will increase the immunity globally among the individual's employing equity, quality, integration, and inclusivity as the main principles. As of March 2022, the goal was shifted to a new deadline: fall of 2022 as only 57 countries have been vaccinated until May 2022 and most of them were high-income countries (Nurith 2022a).

The major steps to reduce the severity of disease include vaccination of all the older adults and health workers, vaccination of full adult age group in each country, extensive vaccination of adolescents to reduce the disease burden with risk of emerging variants, and reducing viral transmission (WHO 2022). The advent of mutations in SARS-CoV-2 such as the alpha variant (B.1.1.7) showed increased transmissibility and infectivity. In contrast, other variants, such as beta (B1.351) and gamma (P.1) were less sensitive towards neutralization by infection-induced antibodies and vaccines. The delta variant contains mutations in the spike protein different from the prior variants and has a higher share of mortality (Lopez Bernal et al. 2021).

With new emerging variants shaking the healthcare infrastructure, scientists are pushing the limits too (Ikegame et al. 2021). Global alliances like Global Alliance for Vaccines and Immunisation (GAVI) are promoting public–private partnerships to supply aid to low-income countries. In June, GAVI and other partners launched a global alliance COVAX to ensure that people in all corners of the world get access to the vaccines regardless of their wealth. On June 4 2021, GAVI launched COVAX-AMC, which is an advanced market commitment. It is an innovative financing alliance to support low- and middle-income countries. Like GAVI, Wellcome Trust also improves health by funding research and building global partnerships (Bhatia 2021).

With the uncontrolled scenario of emerging variants and no specific approved treatment against the SARS-CoV-2, demand for an effective treatment approach has been the priority. This review discusses the current therapeutic approaches against SARS-CoV-2 and summarizes the clinical status of different vaccines for COVID-19 infection. The review highlights the potential problems associated with the manufacturing, efficacy, and safety concerns of existing therapeutic approaches. This includes the need for an ultracold chain and supply of vaccines to middle- and low-income countries, suggesting non-invasive methods of administration and addressing the

scalability concerns with workable solutions to achieve ambitious goal set by the WHO.

Modes of transmission of SARS-CoV-2

The principle mode of transmission of infection caused by SARS-CoV-2 is majorly by exposure to the respiratory fluids containing the infectious virus. The initial sign of the COVID-19 infection mainly includes shortness of breath, coughing, and fever (Karia et al. 2020), but in later stages, it could cause pneumonia, damage the kidney, and then cause unexpected death. During the start of pandemic, it was declared that the virus is zoonotic and animal to human transmission had occurred. Later, several reported suggested that bats were the reservoir for the virus, and various other animals were also linked to COVID-19 origin (MacKenzie and Smith 2020). However, the correct origin has been established yet. Many reports shows that the exposure to the infectious virus occurs majorly by inhaling very fine respiratory droplets, deposition of infectious respiratory droplets onto the mucus membrane in the nose, mouth, or even eye; and touching inanimate surfaces contaminated with the virus. The potential modes of virus transmission are summarized below.

i. Horizontal transmission: It includes direct contact transmission and droplet transmission.

- Direct contact transmission: The direct contact transmission occurs during the direct contact with the virus-contaminated surfaces or objects. Fomites are suspected to be the major source of infection. Also, the healthcare workers handling the SARS-CoV-2-infected patients bear major risk of being infected and spreading the disease.
- Droplet transmission: Droplet formation and its transmission through air is the major and most common route of transmission of infectious virus. The infection easily spread by coughing and sneezing from an infected patient (Karia et al. 2020). It involves inhalation of the "droplet nuclei" or aerosols generally smaller than 5 μm and at a distance of 1–2 m away from the infected person (Wang et al. 2021a)**.** As the droplets transmit from warm to moist environments, they evaporate, forming residual particles which are referred to as aerosols or droplet nucleus. These aerosols could contain active pathogen up to 6 days with 50% relative humidity and at 20 °C (Kirubananthan et al. 2021).

ii. Gastro-intestinal tract transmission: GIT may be another potent source of virus transmission, including the fecal-oral transmission from the excreta of infected patients. Some studies have reported SARS-CoV-2-positive family cluster, an asymptomatic case where the anal swabs taken show persistently positive for COVID-19. The fecal-oral transmission has been reported due to the existence of viral RNA in the fecal specimen (Wang et al. 2021b). Prolonged RNA shedding has been observed in excreta of some recovered cases. This may be attributed to faster respiratory clearance of virus in about 2 weeks while slower clearance from GIT, which can take over 4 weeks (Hindson 2020).

iii. Vertical transmission: Pregnant women are found to be more susceptible to the viral infections due to anatomic and immunologic alterations. The impact of virus on placenta and potential vertical transmission is possibly related to high maternal-fetal inflammatory state (Wang et al. 2021b).

iv. Ocular transmission: Ocular surface may be an entry point for the SARS-CoV-2 virus and also serves as a reservoir for the virus. In some patients with moderate to severe COVID-19, tear fluid collected using conjunctival swab was found positive for SARS-CoV-2 RNA (Kitazawa et al. 2021). However, the link between SARS-CoV-2 ocular entery and infection onset in not clearly understood. Certain experiments showed that tears and eye secretions drain into the respiratory tract or are swallowed into the digestive system (Qu et al. 2021).

v. Fomite transmission: Fomites include inanimate objects including plastics, copper, stainless steel surfaces, gloves, and sponges. These surrounding surfaces may get contaminated upon droplet emission from the infected individuals. Viral viability of these fomites depends on environmental conditions and viral load (Lewis 2021a)**.** Sustainable environment plays a major role in reducing the risk of factors associated with preventing the pandemic. Reports show that the polluted cities should not exceed 48 days per year of high level of air pollution (Coccia 2022a). The reduction in quality of air and other factors associated could accelerate the damage to the public health and promote transmission of COVID-19. Environmental policies should aim at the main source of air pollution and improve the ventilation in order to reduce the dispersion of particulate matter.

Risk factors accelerating the diffusion of virus into the environment

There are several factors involved in the virus's transmission including the air-borne, fecal–oral, fomite transmission, and other environmental factors associated with the spread of SARS-CoV-2 virus (Azuma et al. 2020). However, some findings have shown that environmental factors like

humidity, temperature, and climate change also affects the virus transmission.

a. Temperature and humidity

Low temperatures and low humid conditions have found to increase the COVID-19 infections (Ma et al. 2020). The viability of SARS-CoV-2 also depends upon the humidity and temperature. It was found that increasing temperature will decrease the viability of SARS-CoV-2. Most of the viruses, including influenza virus, human coronavirus, measles virus, and rubella virus, remains infective in low humid conditions (20–30%). Data from 166 countries report that upon 1°C increase in temperature and 1% increase in relative humidity showed 3.08% and 0.85% decrease in daily cases (Wu et al. 2020).

b. Sunlight

Studies have shown that UV-radiation inactivates the SARS-CoV-2 in the bulk culture medium. The SARS-CoV-2 aerosol from the artificial saliva was used in this study and found that sunlight inactivates the virus by damaging the genetic material (Biryukov et al. 2021).

iii. Climate change

Climatic change has become a global public health concern due to the impact on viral respiratory infections. Over the past century, the average global temperature has been found to increase by 0.8 °C. The ambient temperature, humidity, precipitation, and other climatic conditions are associated with the reproduction, survival and abundance of vectors, and immune responses (Zhan et al. 2020; Coccia 2021a).

Socio-economic, environmental, and health implications of the pandemic

The COVID-19 pandemic had created not only a global health crisis but triggered a socio-economic crisis. Early measures to contain the spread of COVID-19 included strict movement controls on short notice, longer quarantine for travelers, and circuit breakers. As a result, some implications were neglected, giving major blows to small-scale business in a short while. The second-degree impact is being felt throughout the service and manufacturing sectors, which is further leading to global chaos. Reduction in industrial output was felt positively in terms of pollution and improving urban sustainability (Akter et al. 2021). However, a new great challenge is the management of enormously large amount of infectious medical waste generated from COVID-19 infections.

It was reported that before the pandemic hit, the average quantity of biomedical waste produced was 0.5 kg/bed/day, which increased to 3.4 kg/bed/day during the pandemic (Mondal et al. 2022). Improper handling and disposal of contaminated waste could cause the unintentional spread of the infectious virus. Encouraging home isolation and home recovery programs helped tremendously in reducing the patient load on healthcare system, while cutting the biomedical waste generation from hospitals. Other measures include autoclaves or mobile incinerators to neutralize excessive biomedical waste. Moreover, globally high inequitable distribution of vaccines persisted. The strict storage conditions and vaccine hesitancy led to wastage of vaccines. In high-income countries, over 2.3 billion doses have been administered and bought over 7 billion doses, while in low-income countries, 15% of the population has been administered with the vaccine (Lazarus et al. 2022b). The strict conditions that all doses in a vial must be used within few days after opening a vial, led to wastage in case of insufficient or no immediate demands. Further, vaccine integrity during the supply chain is a major concern due to non-compliance in maintaining cold chain storage conditions, which cause huge vaccine waste. GAVI alliance had recommended a maximum 25% wastage rate in the first year, 15% reduction in vaccine waste by third year. So, regulatory authorities and vaccine developers should work to upgrade supply chain and wave off patent protection so that vaccines are accessible to even the low-income countries.

Although COVID-19 pandemic created a negative impact globally, yet the improvement in quality of air and water are the major silver linings. Certain satellite images show 20–30% reduction in major environment pollutants (Mofijur et al. 2021). NO_2 and NO gases are produced as a result of burning fossil fuels and coals. As per WHO, these gases are typical air contaminants that corrode lungs, respiratory problems and aggravate asthma. According to European Space Agency, the average level of NO_2 had reduced by 40% between March and April 2020. In some countries, particulate matter emission has also reduced during the pandemic. Particularly the particulate matter of diameter 2.5 μm or less had found to cause severe health problems and also a threat to environment (Irfan et al. 2021).

Although the source of infection is environmental, cases of black and yellow fungus associated with COVID-19 infection have been reported (Song et al. 2020). This could be due to the airborne spores of fungi that enter the body through inhalation or through open wounds. Healthy people generally clear these spores from their bodies, but immunocompromised individuals or patients associated with comorbidities are the prime targets for nosocomial infections (Singh et al. 2022). Some studies also mention that (Quinn and Bell 2022) people who have recovered from the

infection are likely to have negative impacts on their quality of life, reduction in functional abilities, and a shortened life expectancy. The need for the hour demands new health policies and strategies to address such long-term sufferings, and its long and deadly tail should never be ignored.

COVID-19 therapeutic approaches

Conventional drug discovery was based on the hit and trial approach, which gives extremely low throughout. Repurposing existing drugs is one such strategy to overcome the setback (Luo et al. 2021). Despite promising therapeutic benefits by drugs including Remdesivir, Chloroquine, and Lopinavir, increased cases with serious side effects are being reported. The early vaccine development against SARS-CoV-2 included live attenuated or inactivated virus vaccine, nucleic acid-based, viral vector, protein subunit, and virus-like particle (Vivekanandhan et al. 2021). Other curative approaches being employed to manage the infection include immunotherapy, use of steroids, and convalescent plasma therapy, which are described below.

Antiviral drugs

With no specific antiviral treatment available and less efficient conventional drug discovery approach, repurposing the existing drugs might be a better choice to tackle the ongoing pandemic (Luo et al. 2021). Uncontrolled pandemic scenario demands coherent drug discovery efforts and approaches, so the regulatory bodies like US-FDA reassess the therapeutic benefit of existing drugs, including Remdesivir, a broad-spectrum antiviral drug acting on RNA-dependent RNA polymerase. Remdesivir was used against the animal and human coronaviruses. It demonstrated potent anti-SARS-CoV-2 activity in patients with mild to moderate COVID-19 symptoms (Mei and Tan 2021). Approved viral protease inhibitors, including Lopinavir and Ritonavir, were found to improve the clinical symptoms of COVID-19-infected patients but showed no benefit in hospitalized adult patients. Favipiravir inhibits viral replication by controlling RNA polymerase and has shown antiviral activity against a spectrum of RNA viruses like Ebola and influenza H1N1 (Machhi et al. 2021). Chloroquine, a broad-spectrum antiviral drug, was found to inhibit the spread of SARS-CoV-2 in vitro by blocking cell fusion, but it did not inhibit SARS-CoV-2 infection in the lungs (Purohit et al. 2020). A list of antiviral drugs, their target and mechanism of action is summarized in Table 1.

Corticosteroids

Corticosteroids are involved in various physiological processes, including inflammatory regulation, immunological response, stress, carbohydrate, and protein metabolism. Thus, corticosteroids are important in managing autoimmune, inflammatory disorders, and allergies (Annane 2021). In SARS-CoV-2 infection, the viral escape of cellular immune response and cytokine storm is an important pathophysiology. The invasion of inflammatory cells and dysregulation of cytokine usually results in lung inflammation, respiratory failure, multi-organ failure, and ultimately death. Corticosteroids have been shown to exhibit anti-fibrotic and anti-inflammatory effects. It also helps in reducing pulmonary inflammation in severe cases (Lin et al. 2021). By targeting host immune response and inflammatory cascade, corticosteroids can benefit patients with COVID-19 (Lin et al. 2021).

The guidelines recommend steroids in severe infection cases and on mechanical ventilation (2020). The principal corticosteroids used in most trials are dexamethasone and methylprednisolone because of their high lung bioavailability. Dexamethasone is a synthetic glucocorticoid previously used to treat allergic reactions, asthma, and other autoimmune disorders. It crosses the host cell membrane and then binds to the glucocorticoid receptor, initiating a series of immune cell responses, which suppresses proinflammatory cytokines, including IL-1, IL-2, IL-6, IL-8, and TNF. Compared to dexamethasone,

Table 1 List of antiviral drugs in treating various viral infections

Drugs	Target	Mechanism	Applications	Ref
Remdesivir	Viral proteases	Interference with RNA polymerase reduces synthesis of viral RNA	Ebola virus disease	Beigel et al. (2020)
Favipiravir	RNA-dependent RNA polymerase	Inhibition of RNA polymerase and replicase	Viral infections	Ghasemnejad-Berenji and Pashapour (2021)
Lopinavir, Ritonavir	Viral protease	Inhibition of viral protease	HIV infection	Verdugo-Paiva et al. (2020)
Chloroquine	ACE-2	ACE-2 glycosylation is affected	Malaria	Tong et al. (2020)
Umifenovir	S-spike glycoprotein	Inhibition of trimerization of the SARS-CoV-2 S protein	Influenza	Vankadari (2020); Kumar et al. (2021)

ACE-2 angiotensin-converting enzyme

methylprednisolone shows a quick onset of action after parenteral administration and lesser risk of long-term side effects like hypokalemia, fluid retention, dysglycemia, and hypercortisolism (Noreen et al. 2021). Side effects produced by dexamethasone include fluid retention, hormonal imbalance, and disturbed sleep pattern, while blurred vision and hemorrhage are also reported but rarely (Noreen et al. 2021).

The risks associated with using corticosteroids in COVID-infected patients include long-term complications, higher risk of secondary infections. Whereas, the excessive levels of corticosteroids cause metabolic imbalance and fluid retention leading to heart failure (Raju et al. 2021). Another big issue related to corticosteroids is the prolongation of viral excretion from the body. Thus, use of corticosteroids in SARS-CoV-2 infection has been restricted (Umakanthan et al. 2021).

Convalescent plasma therapy

Convalescent plasma therapy is an efficient passive immunization technique to boost the patient's immune system. It relies on a high titer of neutralizing antibodies present in the plasma of recovered patients. In previous studies based on MERS and SARS, it has been found that the neutralizing antibody binds to the spike proteins, which could limit the viral entry (Dhawan et al. 2022). At the early pandemic stage, convalescent plasma therapy is made into the headlines as a prospective treatment for hospitalized or high-risk patients. The antiviral antibodies from recovered individuals are isolated and injected into patients to immediately boost their immune system (Duan et al. 2020). According to US-FDA guidelines, people testing negative and waning clinical symptoms can donate blood after at least 28 days. Around the world, researchers were engaged in transfusing antibody-rich serum into patients struggling with severe illness (Purohit et al. 2020). The risks associated with convalescent plasma are HIV, hepatitis B and C, anaphylactic reactions, allergic reactions, and transfusion-related circulatory overload (Ferrari et al. 2021). On February 4 2021, US-FDA had revised the use of convalescent plasma. They limited the authorization to the high-titer convalescent plasma for hospitalized COVID-19 patients in the early disease course and to those patients who cannot produce adequate antibody response (FDA 2021).

Immunotherapy

Since no specific treatment has been approved for the SARS-CoV-2 infection, the first-line cure is a supportive treatment. This includes antibiotics for secondary bacterial infections, oxygen therapies, and mechanical ventilation for patients with respiratory failure, whereby immunotherapy modulates a patient's immune system to fight against the illness (Esmaeilzadeh and Elahi 2021). Immunotherapy includes the use of monoclonal antibodies and antibody-cocktails. In some patients, disease progression is associated with cytokine secretion (Magro 2020), causing lung damage, inflammation, and other acute respiratory distress syndrome (ARDS). Studies have shown the use of tocilizumab (humanized recombinant antibody for IL-6) in arthritis and cytokine storms, thereby reducing mortality rates. Baricitinib, a JAK1/2-selective kinase inhibitor, is used in rheumatoid arthritis treatment and severe cases of COVID-19, preventing progression to ARDS (Ai et al. 2022). Four anti-SARS-CoV-2 monoclonal antibody products have received EUA from US-FDA for non-hospitalized patients, including sotrovimab, bamlanivimab, etesevimab, and "imdevimab and casirivimab" (REGEN-COV) (https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/; Monzavi et al. 2021). Thus, developing such novel immunotherapies can target viral infection and improve the clinical outcomes.

Monoclonal antibodies

Monoclonal antibodies are proteins mimicking the ability of an immune system to fight harmful viruses. The monoclonal antibodies bind to spike protein receptor-binding domain (RBD) to neutralize the virus (ACTIV-3/TICO LY-CoV555 Study Group et al. 2021). The individuals recovered from COVID-19 infection produce antibodies against SARS-CoV-2, which persists for 5–7 months post-infection (Dan et al. 2021). Monoclonal antibodies are identical copies of an antibody that targets a specific antigen. So far, only seven antibodies have been approved for EUAs, including bamlanivimab, casirivimab, etesevimab, imdevimab, tixagevimab, sotrovimab, and cilgavimab (Hwang et al. 2022).

Sotrovimab is a derivative of S309 monoclonal antibody. It was found to cross neutralize SARS-CoV-2 by inducing S-trimer cross-linking aggregation of virions or steric hindrance. Also, S309 showed antibody-dependent cell cytotoxicity and cellular phagocytosis effector function contributing to virus neutralization in mouse models (Hwang et al. 2022). Tocilizumab is both a membrane-bound and soluble IL-6 receptor inhibitor. Administration of tocilizumab in the early stage of SARS-CoV-2 infection was found to correlate with the lower mortality rates among critically ill patients (Wei et al. 2021). Itolizumab, anti-CD-6 monoclonal antibodies, prevents cytokines storm by targeting CD antigens (Saavedra et al. 2020). Bamlanivimab and etesevimab are neutralizing monoclonal antibodies that target RBD of S-protein. In contrast, imdevimab and casirivimab are recombinant monoclonal antibodies that binds to the non-overlapping epitope of RBD of S protein (Taylor et al. 2021).

Infliximab or adalimumab, anti-TNF antibodies, may reduce mortality rates in affected patients. There are four clinical trials on infliximab (NCT04425538, NCT04344249, NCT04734678, NCT04593940) and one on adalimumab (NCT04705844) seeking evaluation for their therapeutic potential in COVID-19. The EUAs by US-FDA does not authorize monoclonal antibody for critically ill COVID-19 patients needing oxygen support or patients with co-morbidity. Table S1 includes a list of monoclonal antibodies in the pipeline against COVID-19 infection.

Recent studies discuss the sensitivity of the approved monoclonal antibodies against recently identified omicron variant (Takashita et al. 2022). It has been identified that 6 out of 9 tested monoclonal antibodies, including casirivimab, tixagevimab, bamlanivimab, etesevimab, regdanvimab, and imdevimab, were found to be inactive against the omicron. Omicron was fully resistant to etesevimab, bamlanivimab, and imdevimab. Cocktail of bamlanivimab and etesevimab failed to inhibit entry mediated by omicron, but sotrovimab was active against omicron (Hoffmann et al. 2022).

Antibody cocktails

Antibody cocktails are an effective approach for the prevention and treatment of the COVID-19 infection. The antibody cocktail is a blend of monoclonal antibodies targeting the spike protein of SARS-CoV-2 that could reduce the viral load, preventing the progression of the disease and accelerate the recovery of patients. This therapy is most suited in case of high risk patients and patients with comorbid conditions.

Sue et al. describe the generation of monoclonal antibodies using hybridoma screening (Su et al. 2021). It neutralized SARS-CoV-2 by targeting the RBD. The cryo-electron microscopy revealed the atomic details of the structural epitopes of the chimeric antibody used as cocktail therapy. A cocktail of chimeric antibodies may increase the therapeutic efficacy and decrease the potential of virus escape mutants, which could be an additional benefit in the case of emerging variants.

REGN-COV2 is a novel cocktail of human Abs Casirivimab (REGN10933) and Imdevimab (REGN10987) targeting S-protein. REGN-CoV2 was found to reduce the virus load in upper and lower airways when administered prophylactically (Tuccori et al. 2020). Ongoing trials for REGN-COV2 (NCT04425629) randomized, phase I–III adaptive, double-blind, placebo-controlled conducted on non-hospitalized patients with COVID-19 infection showed a reduced risk of hospitalization and death by 70% (Hwang et al. 2022).

Combination of tixagevimab and cilgavimab, which are recombinant human anti-SARS-CoV-2 monoclonal antibodies, binds to the non-overlapping epitopes of spike protein. Another combination, bamlanivimab and etesevimab, has also been approved by US-FDA for its emergency use on February 9 2021 (US FDA 2021). The research are evolving with emerging variants, due to mutations in the spike proteins, the prime targets for the antibody cocktail. Antibody cocktails can be used in mild to moderate cases of the COVID-19 infection; however, it showed reduced efficacy against the omicron variant as compared to the delta variant (Yu et al. 2022).

COVID-19 vaccines

Vaccines are biological preparations comprising an entire organism, nucleic acid, proteins, peptides, or sub-units that stimulates antibody production upon administration and triggers immunity against the pathogens. The already available antibodies as a cause of vaccination, attacks the organism at a much faster rate in case of reinfection with the same disease. In addition, vaccines works through "memory" created in memory cells. The major concerns with the use of vaccines include the limited efficacy, individual variation in immune response, operational, religious, social, and ethical beliefs (Giubilini et al. 2021).

Various types of vaccines were developed, including the whole virus vaccine (live attenuated or inactivated vaccine), recombinant protein vaccine (VLP or protein subunit), nucleic acid vaccines, and viral vector vaccines as shown in Fig. 1. As people worldwide receive the COVID-19 vaccines, the reports of risk of temporary side effects, including fever, headache, and pain at the injection site, kicked in. However, the risk of severe side effects outweighs the protection offered against the deadly SARS-CoV-2. Table 2 includes vaccines authorized by the WHO for their emergency use, and Table 3 includes a list of vaccines under review by the WHO.

Whole virus vaccines

The whole virus vaccine includes attenuated or inactivated form that can still grow and replicate in body to trigger immunity, but unable to cause illness. The conventional whole virus vaccines (Table S2, Table S6) include live attenuated, inactivated vaccines that elicit immune responses by targeting many viral proteins. The inactivated vaccines contain a virus, of which the genetic material is destroyed by the application of chemicals, heat, or radiation (Angeli et al. 2021).

Live-attenuated vaccines Codagenix is a live-attenuated viral vaccine administered intra-nasally. It is used as a

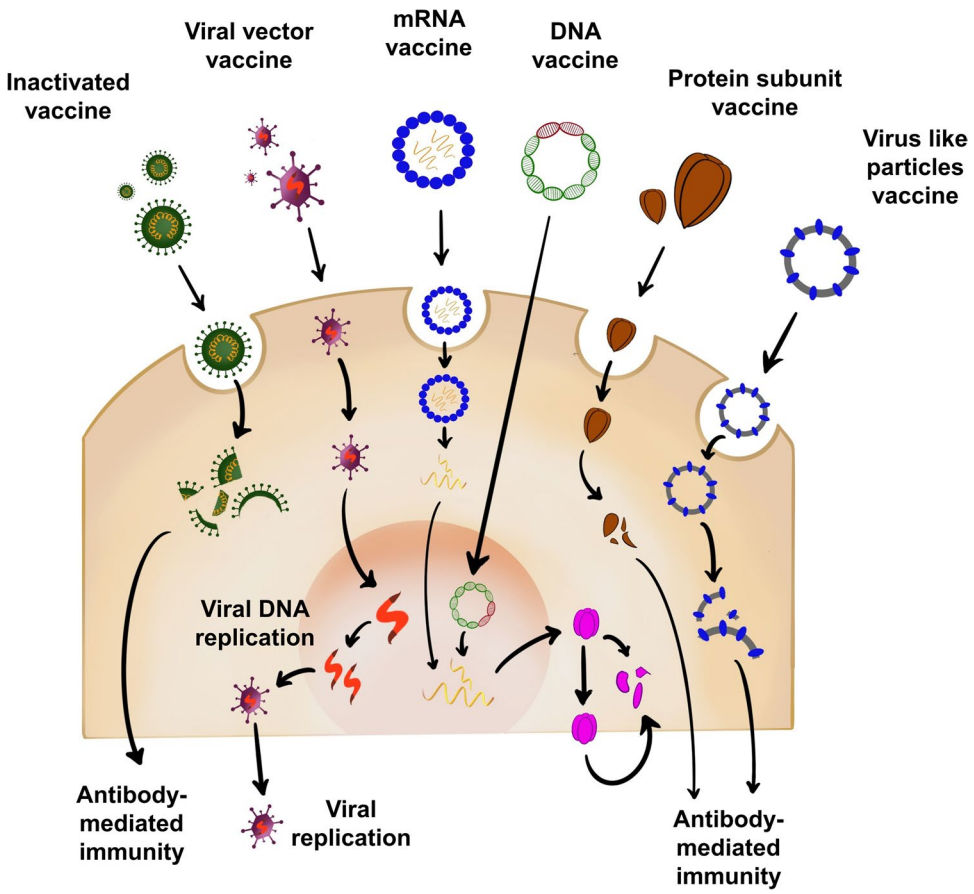

Fig. 1 Different approaches are used by vaccines against SARS-CoV-2

single or multi-dose regimen given 21 days apart, generating both cell-mediated and humoral responses (Shen et al. 2020; Chavda et al. 2021). The-live attenuated vaccines use a weak virus that does not cause infection but can still grow and replicate. The live-attenuated vaccines are produced by the passage of disease-causing viruses produced in the cultured cells, weakened and reduced virulence. Such vaccines produce humoral and cell-mediated immune responses which mimic the natural infection. These vaccines are rarely used for immunocompromised patients because of the potential to cause infection. This limitation of virulence reversal can be overcome by altering the viral genome and selecting the non-pathogenic strains incapable of causing the disease (Machhi et al. 2021).

Inactivated vaccines The inactivated vaccines use a non-live pathogen, ensuring better safety than live vaccines. The inactivated vaccines cannot induce the cellular responses and thus require additional adjuvants to stimulate the immune responses (Kyriakidis et al. 2021). Developing such vaccines requires the inactivation of the virus by chemical or radiation. This leads to the destruction of the virus's genetic material while keeping the antigenicity. In general, all inactivated vaccines possess a higher safety profile than live vaccines and are considered less reactogenic (Sanders et al. 2015; Iversen and Bavari 2021).

A phase 3 clinical trial, double-blind, placebo-controlled vaccine is used in two doses, 14 days apart. Currently, around 10 candidates are being tested in clinical trials, including CoronaVac, developed by Sinovac and Covilo/BBIBP-CorV/Sinopharm, which are approved for conditional marketing (Al Khames Aga et al. 2021) (He et al. 2021). The WHO approved emergency use, suggesting that 51% CoronaVac and 79% Covilo/BBIBP-CorV/Sinopharm were found to be effective (Mallapaty 2021). Another vaccine candidate developed by Bharat biotech BBV152/covaxin has been authorized for emergency use for people 18 years or older with 78% efficacy (WHO 2021a). As of June 24, 2022, Valneva (VLA2001) becomes the first vaccine against COVID-19 disease to receive a standard marketing authorization in Europe. It is an inactivated whole virus vaccine used in people aged 18 to 50 years (No Author 2022b).

Nucleic acid vaccines

The nucleic acid-based vaccines carry a nucleotide sequence as DNA or RNA encoding protein of interest. The RNA or

Table 2 Vaccines authorized for emergency use according to type, age group, conditions, and possible adverse effects

Vaccine type	Vaccine name	Dosage and dose frequency	Storage	Manufacturer	Route	Probable side effects	References
n-VVr	Ad5-nCoV/Convidecia	Dose-1: 0.5 ml	2–8 °C	CanSinoBio	IM	Fatigue, fever, headache	Jin et al. (2022)
n-VVr	ChAdOx1-S / Covishield	Dose-1: 0.5 ml Dose-2: 0.5 ml	2 to 8 °C	Serum institute of India	IM	Swelling, bursting, pain at the site of injection, rash	Hung and Poland (2021)
n-VVr	Ad26.COV.S / Jannssen/Jcovden	Dose-1: 0.5 ml	2–8 °C	Johnson & Johnson	IM	Fatigue, fever, headache, myalgia, pain the site of injection	McGinley (n.d)
n-VVr	ChAdOx1-S / AZ vaccine/ Vaxzevria	Dose-1: 0.5 ml Dose-2: 0.5 ml	2–8 °C	AstraZeneca	IM	Tenderness, pain, itching and swelling at the site of injection, Influenza like symptoms, rarely blood clots reported	Kiem et al. (2021)
IV	BBV152/Covaxin	Dose-1: 0.5 ml Dose-2: 0.5 ml	2 to 8 °C	Bharat Biotech	IM	Pain at the site of injection	Parida et al. (2022)
IV	Covilo/BBIBP-CorV/Sinopharm	Dose-1: 0.5 ml Dose-2: 0.5 ml	− 70 to − 20 °C	Sinopharm/Beijing Institute of Biological Products	IM	Fever, chills, fatigue, acute encephalomyelitis	WHO (2021b)
IV	Coronavac	Dose-1: 0.5 ml Dose-2: 0.5 ml	2–8 °C	Sinovac	IM	Fatigue, nausea, dizziness, pain at the site of injection	Li et al. (2022a)
m-RNA	Elasomeran,m-RNA 1273/ Spikevax	Dose-1: 0.5 ml Dose-2: 0.5 ml	− 20 °C	Moderna	IM	Chills, headache, swelling, redness	Baden et al. (2021)
m-RNA	Tozinameran / BNTI62b2/Pfizer vaccine/COMIRNATY	Dose-1: 0.3 ml Dose-2: 0.3 ml	− 80 to − 60 °C	Pfizer BioNTech	IM	Chills, headache, swelling	Britton et al. 2021)
PS	NVX-CoV2373/ Nuvaxovid	Dose-1: 0.5 ml Dose-2: 0.5 ml	2–8 °C	Novavax	IM	Tenderness, headache, pain at the site of injection	Daniela and Ngel (2021)
PS	NVX-CoV2373/ Covovax	Dose-1: 0.5 ml Dose-2: 0.5 ml	2–8 °C	Serum Institute of India	IM	Tenderness, fatigue, fever, headache, chills	Fenton and Lamb (2021)
DNA	ZyCoV-D	Dose-1: 0.5 ml Dose-2: 0.5 ml Dose-3: 0.5 ml	2–8 °C	Zydus Cadila, India	ID	Pain at the site of injection, headache, chills	Khobragade et al. (2022)

n-VVr non-replicating viral vector, *IV* inactivated, *IM* intramuscular, *ID* intradermal

DNA produce proteins in the host cells, which later acts as antigens and triggers the immune response. This approach employs a host cellular machinery to generate the foreign antigens presented to MHC class I and II molecules of antigen-presenting cell (APC), eliciting both cellular and humoral responses (Ye et al. 2020). In DNA vaccines, a piece of DNA encoding antigen is inserted into a plasmid that replicates and transfers the genes between the cells. The main challenge is crossing the membrane, which can be solved using electroporation, gene gun and encapsulating into nanoparticles for better delivery (Kowalzik et al. 2021).

DNA-based vaccines are considered stable and safer than conventional vaccines because the vectors used are non-replicating and express the gene of interest (Machhi et al. 2021). ZyCoV-D developed by Zydus Cadila uses a DNA-based technology. It is a needless vaccine requiring three doses (Dey et al. 2021). Besides ZyCOV-D, another vaccine, INO-4800, developed by Inovio Pharmaceuticals, has been developed that

Table 3 Status of COVID-19 vaccines under review for emergency use authorization by the WHO

S. no	Type of vaccine	Vaccine name	Manufacturer	Status
1	PS	CoV2 preS dTM-AS03	Sanofi	Ongoing assessment
2	PS	SCB-2012	Clover Biopharmaceuticals	Ongoing assessment
3	PS	Recombinant Novel Coronavirus (CHO)	Zhifei Longcom, China	Ongoing assessment
4	PS	Abdala	CIGB	EOI accepted and rolling data started
5	PS-NP	Nuvaxovid	SK Bioscience	EOI accepted and rolling data started
6	PS	Corbevax	Biological E	EOI under review
7	PS	GBP510	SK Bioscience	EOI under review
8	PS	Recombinant COVID-19 vaccine	Westvac Biopharmaceuticals	EOI under review
9	PS	Nanocovax	Nanogen	EOI under review
10	PS	Spikogen	Cinnagen	EOI under review
11	PS	UB-612	Vaxxinity	EOI under review
12	PS	EpiVacCorona	Vector State Research Centre of virology and Biotechnology	Pending decision
13	PS	Soverana 01 Soverana 02 Soverana Plus	BioCubaFarma	Awaiting decision
14	VVr	Sputnik-V	Russian Direct Investment Fund	Awaiting decision
15	VVr	Vaccine R-COVI	R-PHARM	EOI under review
16	VVr	AZD1222	Bio-Manguinhos/Fiocruz	EOI under review
17	IV	Verocell, Inactivated	Sinopharm	Ongoing assessment
18	IV	Verocell	IMBCAMS	Under initial development stage
19	IV	Coviran	Shifet Pharmed. Barkat	EOI accepted and rolling data started
20	RNA	ARCT-154	Arcturus Therapeutics	EOI under review
21	RNA-NP	Zorecimeran (INN) concentrate and solvent for dispersion for injection; Company code: CVnCoV/CV07050101	CureVac	Withdrawn
22	VLP	COVIFENZ	Medicago	Withdrawn

EUA emergency use authorization, *EOI* expression of interest, *VVr* viral vector vaccine, *IV* inactivated vaccine, *PS* protein subunit, *VLP* virus like particle, *NP* nanoparticle

generates both cell-mediated and humoral responses. Also, INO-4800 utilizes mammalian expression plasmids that encode S-protein expressed in humans and animals (Tebas et al. 2021).

In the case of m-RNA-based vaccines, RNA must be transported into the human cell. The lipid nanoparticle is used for its delivery, which of RNA to produce antigen protein (Forni et al. 2021). Limitations of such vaccines include stability of m-RNA at storage condition and thereby need of cold chain (de Queiroz et al. 2020). Despite the extensive use of LNPs for delivering m-RNA, it remains unclear how many m-RNA strands can be encapsulated per nanoparticle. Two m-RNA vaccine candidates, m-RNA-1273 from Elasomeran/Spikevax/Moderna and BNT162b2 from Pfizer/BioNTech, showing 94% efficacy, have been authorized for emergency use. The phase 3 study comprised 43,548 participants with 8 cases of COVID-19 among 17,411 participants in the vaccine arm and 162 cases among 17,511 participants in control arm, resulting in 95% efficacy. Mild to the moderate local reaction was reported, which resolved within 1–2 days (Kwok 2021). The meta-analysis published by Zeng et al. (2022) evaluates the efficacy of vaccines against COVID-19 variants (Alpha, Beta, Gamma, Delta, Omicron) estimating that full vaccination is highly effective against the alpha variant, moderately effective against the Beta, Gamma, and Delta variants (95% confidence interval), while the booster vaccination is more effective in delta and omicron. Also, the m-RNA vaccines showed higher efficacy against the above mentioned variants (Islam et al. 2022). Based on the data, BNT162b2 became the first vaccine against SARS-CoV-2 authorized for emergency use by US-FDA (Kwok 2021). Co-administration of multiple m-RNA types could be used as multi-target vaccination strategies, expression of protein cocktails for regeneration purposes (Zhang et al. 2021). m-RNA cocktails could also emerge as a new emerging COVID-19 treatment to produce stronger and wider immune response. There is no certain limit to the number of RNAs that can be combined and can target more than one pathogen or more than variant in the case of SARS-CoV-2 (DeFrancesco 2021). As of 17 June 2022, FDA has authorized emergency use of Pfizer-BioNTech and Moderna for

use in children of 6 months of age (FDA—Food and Drug Administration 2021).

Viral vector vaccines

This type of vaccine contains a recombinant virus, attenuated to reduce the pathogenicity. The shell of this modified virus contains genetic material mimicking the course of infection (Fig. 1); thus, a strong cytotoxic and humoral response is induced (WHO 2021a). The viral vector vaccines can generate high levels of recombinant protein expression, which provides the basis for modern vaccine development (Lundstrom 2020). Viral vector vaccine technology has neither been used as a preventive vaccine nor tested for safety and efficacy in the long term. But major advantage offered by this method includes great efficiency and gene-specific delivery for initiation of healthy immune responses (Yadav et al. 2020). The recombinant adenoviruses are used as vaccine vectors as it accommodates large genetic payload, which triggers the immune system (Buchbinder et al. 2020; Jones and Roy 2021). Viral vector vaccines are categorized as replicating and non-replicating.

The replicating viral vector vaccines infect the cells producing vaccine antigen, whereas the non-replicative viral vaccines enter the cells producing vaccine antigen, but no new viral particles are formed. The major advantage of the replicating viral vector is its ability to mimic the natural infection resulting in the induction of cytokines and molecules, providing potent adjuvant effect (Rawat et al. 2021). These vaccines also provide an immune response, including innate immunity and rapid responses against the invading organism (Robert-Guroff 2007; van Riel and de Wit 2020).

The non-replicating viral vector vaccines are a novel approach in which around 12 vaccine candidates have been evaluated against COVID-19 (Table S4). Such vaccines use genetically modified adenovirus vectors that cannot replicate inside the human body. The modification is achieved by deleting a gene encoding the viral structural protein, preventing virus assembly. One such candidate is Ad5nCoV, which uses human adenovirus 5 with an overall 65.3% efficacy after 4 weeks. Another vaccine candidate, AZD1222 (ChAdOx1), is a non-replicating viral vector vaccine with 63% efficacy and Ad26.COV.S/Janssen/Jcovden is also a non-replicating viral vector vaccine with an efficacy of 85.4% (CDC 2021).

In a meta-analysis published by Korang et al. (2022) involving 71,514 participants and 3 trials estimated 95% efficacy of m-RNA vaccine (95% confidence interval); 48,029 participants and 3 trials estimated 61% efficacy of inactivated vaccines (95% confidence interval); 71,401 participants and 5 trials estimated 68% efficacy of viral vector vaccines; 17,737 participants and 2 trials estimated 77% efficacy of protein subunit vaccines. The data suggested that although m-RNA vaccines are clear winners in terms of efficacy, the viral vector vaccines were found to be most effective in reducing the mortality.

Recombinant viral protein-based vaccines

Recombinant protein vaccine uses spike protein of SARS-CoV-2 as a vaccine antigen that helps the body recognize and fight off the virus. Different genes encoding antigenic determinants that have been cloned, expressed as recombinant proteins, are established as vaccines. This is the most common platform for the production of vaccines because of the cost-effective production and safety profile, but it requires adjuvants for long-lasting immune response (Rawat et al. 2021).

Protein sub-unit vaccines

These are protein-based vaccines (Table S5) (Fig. 5) containing the viral protein as the antigen, eliciting the immune responses. Most vaccines use S-protein, containing multiple subunits, or RBD, which elicits the potent neutralizing antibody (WHO 2021a). The subunit vaccine provides immune protection by using some portion of the virus (Zhenghui and Moyle 2018) and includes a pathogen's protein components that induce immune responses. Most of these vaccines use a membrane-bound S-protein, containing multiple subunits or RBD (Chakraborty et al. 2021). The Novavax is a protein subunit vaccine that demonstrated 90.4% efficacy from its Phase 3 clinical trials in the US and was well tolerated (WHO 2021a; No Author 2021a).

Attempts are being made to design a multiepitope peptide-based vaccine using target envelope protein using the genomic and immunoinformatic approaches, which help in the rapid development of vaccine (Abhishek et al. 2020). NVX-CoV2373, a protein subunit vaccine developed by Novavax, contains matrix-M1 adjuvant demonstrating 89.3% efficacy (Hofman et al. 2021; Kwok 2021).

In December 2021, two subunit vaccines, NVX-CoV2373/Covovax and Corbevax, were approved for emergency use. The Serum Institute of India produces NVX-CoV2373/Covovax under license from Novavax, which is a subunit vaccine. The genetic sequence first introduced in baculoviruses and then made to infect the moth cells to produce proteins similar to the structure of SARS-CoV-2 spike protein. Corbevax is also a subunit vaccine that utilizes *Pichia pastoris* yeast and has been used to grow the RBD of SARS-CoV-2 (Marshall 2022).

Virus-like particle vaccines

The VLP vaccines are derived from virus-like structures made of different molecules that can self-assemble, and mimics the size and form of the virus. They are made up of assembled

viral proteins that lack viral genetic material. Therefore, VLP are non-infectious, highly immunogenic, eliciting both cell-mediated and antibody responses with its application in targeted drug delivery and gene therapy. Also, the VLP are subdivided (Table S6) into non-enveloped and enveloped subtypes (Hashemzadeh et al. 2020; Nooraei et al. 2021). These vaccines represent the evolution of protein sub-unit and comprise viral coat proteins that assemble into a capsid-like structure in the absence of a viral genome (Fig. 1). Such non-infective particles are coupled with multiple copies of antigens, and these clusters allow activation of B-cells and the antibody responses (Nooraei et al. 2021).

Earlier, plant-derived VLP vaccines have demonstrated efficacy and immunogenicity against influenza. Recently, Pillet et al. demonstrated plant-based vaccine candidates developed by Medicago, which use the expression of recombinant proteins in non-transgenic plant *Nicotiana Benthamiana* (Ward et al. 2021). The vector used in the study was *Agrobacterium tumefaciens* to move the targeted DNA constructs into the plant cell. Such plant-derived VLP synthesized a new S protein that is trimerized and assembled as VLP, resembling the native structure of SARS-CoV-2 variants. Thus, this form of S-protein is used as a vaccine antigen containing several epitopes. Further, to improve the vaccine efficacy adjuvants are used with VLP, which also helps in dose-sparing strategies to maximize vaccine doses. For example, cytidine phosphoguanosine CpG-1018 contains immunostimulatory oligodeoxynucleotide sequence 1018 and AS03: GSK-α-tocopherol containing o/w emulsion adjuvant system. These generally enhance immune responses by providing T_H 1 (T-helper type-1) responses, while AS03 initiates a transient immune response including both T-cell mediated and antibody meditated responses (Ward et al. 2021).

Recent clinical trial data of different vaccines effective against SARS-CoV-2

In May 2020, US-FDA launched operation warp speed, a plan to "accelerate the development" manufacturing and the distribution of vaccines to meet the increasing demand (Joffe et al. 2021). By September 2021, around 182 million people in the USA were fully vaccinated, and the clinical trial data of Pfizer-BioNTech, Elasomeran/m-RNA 1273/Spikevax/Moderna, and Ad26.COV.S/Janssen/Jcovden vaccine showed effective immunization (Xu et al. 2021). By October 2021, US-FDA authorized emergency use of Tozinameran/BNTI62b2/Pfizer vaccine/Comirnaty for preventing COVID-19 in children aged 5–11 years, and was 90.7% effective (FDA News Release 2021). A phase 3 randomized, placebo-controlled, observer-blind trial conducted to evaluate the efficacy, safety, immunogenicity of this vaccine has been conducted for people older than 18 years of age. The safety was evaluated involving 30,351 participants and 15,185 participants who received at least one dose of vaccine or placebo (Jackson et al. 2020). The adverse effects reported in participants included headache (64.7%), pain at the site of injection (92%), and fever (15.5%). Other adverse effects include fatigue, myalgia, chills, arthralgia, nausea, and vomiting (Callaway 2021a).

Multiple types of vaccines are being developed worldwide against COVID-19, including oral vaccines. Premas Biotech has developed one such vaccine, an Indian pharma company in collaboration with Oramed Pharmaceuticals, showed that oral vaccine (Oravax) was efficaious in single dose (No Author 2022b). Oravax promoted immune response (IgA), which protects GIT and respiratory tract infection and promotes systemic immunity due to the production of IgG neutralizing antibodies.

Inactivated virus vaccines for COVID-19 in clinical trials

The inactivated vaccines are easier to manufacture scale-up and do not require an ultracold supply chain. The inactivated vaccines pose no risk to the immunocompromised patients, unlike the live vaccines. Live vaccines may replicate uncontrollably in immunocompromised patients, leading to restrictions on their use (Iversen and Bavari 2021). The inactivated vaccines have a limitation of protection in the short term and weaker immune response (Angeli et al. 2021). A need for boosters arises to reach long-term immunity (Croda and Ranzani 2022). Table S2 includes the clinical trial data of inactivated vaccines effective against COVID-19. This represents the distribution of the vaccine based on different age groups as a child (aged birth, 17 years), adults (18–64 years), and older adults (65 years and above) and in different phases of the clinical trial starting with phase 1, phase 2, and phases 3 and 4. Figure 2 includes the summarized representation of clinical trials of inactivated vaccines in different phases, age distribution, and geographical distribution. The clinical data is extracted from the clinicaltrial.gov database, with the inactivated vaccine, safety, and efficacy as search terms. The data shows that maximum trials are in phase 3(30.76%) and phase 4 (26.15%), while the least number of trials in phase 2|3 (3.07%). Also, this includes 33.84% active trials and 36.92% recruiting (Fig. 2). The data also shows that the maximum number of trials were conducted only on the adult age group (73.44%) while the least on older adults (1.56%).

Nucleic acid vaccines for COVID-19 in clinical trial

DNA vaccines are comparatively more stable than a vaccine containing RNA (Shafaati et al. 2022), and thus possess a

good degree of manufacturability. However, unlike RNA, DNA needs to be assisted to reach the nucleus. Thereby, special adjuvants and carrier systems are required to stimulate immune response (Leitner et al. 1999). Also, using approaches like a microneedle patch delivery could improve storage stability at room temperature for 30 days. This may overcome supply chain limitations to remote areas with limited vaccine supply (Georgiadis and Georgiadis 2021). On the other hand, the m-RNA vaccines turned out to be a clear winner in efficacy, rapid production process, and the flexibility to switch between the multiple strains. Besides these advantages, the m-RNA vaccines' instability and ultracold storage requirements could be the limiting factors. This could be resolved by encapsulating the m-RNA into LNPs, which may be stored for 6 months at cool temperature, i.e., 2–8 °C without compromising immunogenicity (Park et al. 2021). Another approach being employed to improve the stability of m-RNA vaccines is freeze-drying which leaves the m-RNA stable for 10 months at 4 °C (Uddin and Roni 2021).

Table S3 shows the clinical trial data of nucleic acid-based vaccines (DNA & RNA) effective against COVID-19. It shows the distribution of nucleic acid vaccines as per the different age groups as a child (aged birth, 17 years), adults (18–64 years), and older adults (65 years and above) in different phases of the clinical trial starting from phase 0 (early phase 1), phase 2, and phases 3 and 4. Figure 3 summarized

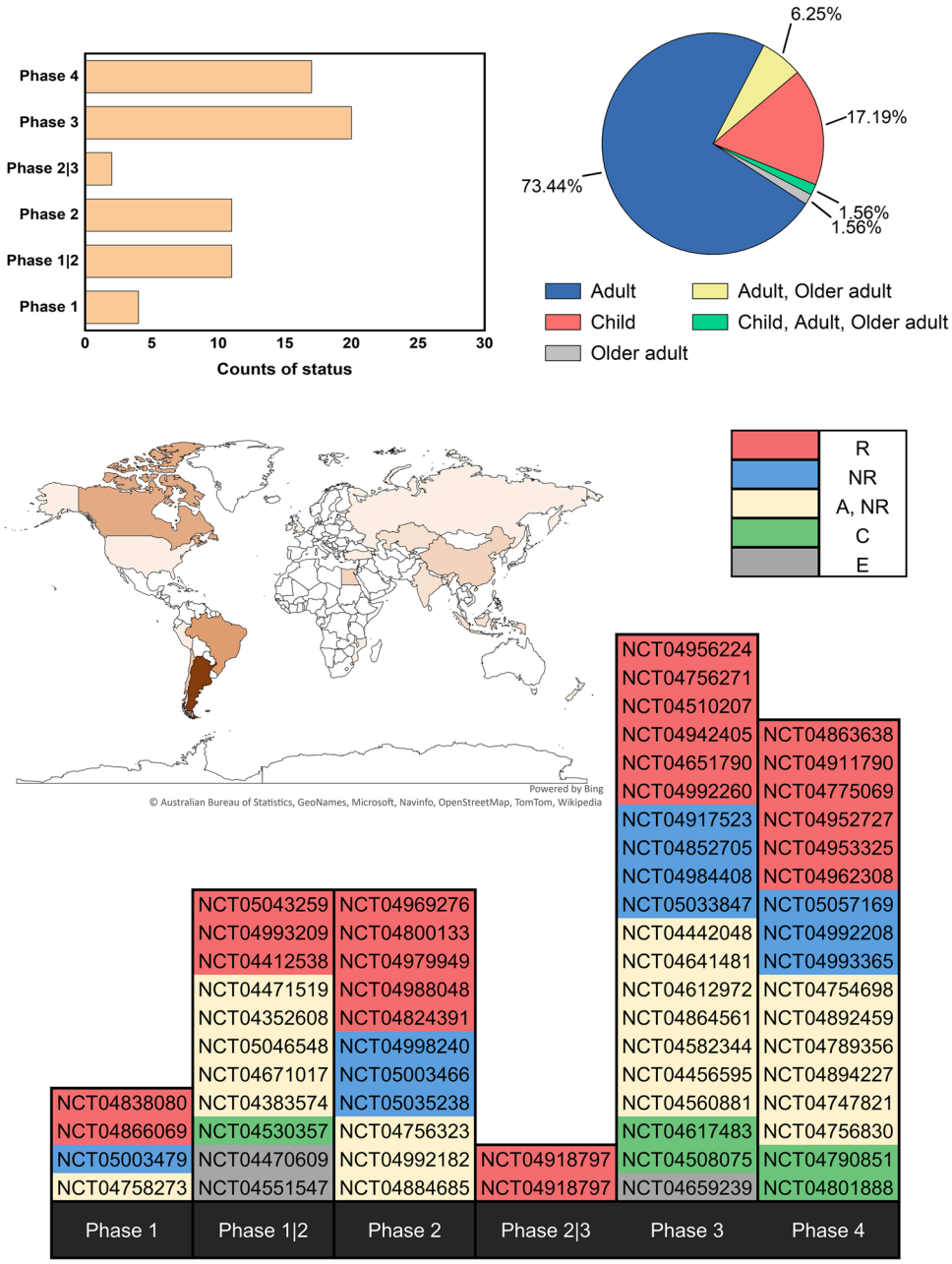

Fig. 2 Results of the clinical trial of inactivated vaccines against SARS-CoV-2 considering trials being conducted among people with different age groups, geographical diversity, and in distinct phases giving an idea that the maximum number of trials are being conducted in China and nearly 73.44% trials are being conducted among adults, i.e., 18 years and older and 1.56% on older adults and child, adult, and older adult. Also, maximum trials are in phase 3 of the clinical trial. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

the clinical trials of nucleic acid vaccines in different phases, age distribution, and geographical distribution. The clinical data is extracted from the clinicaltrial.gov database, with the DNA vaccine, m-RNA vaccine safety, and efficacy as search terms. The outcomes drawn from the studies are maximum candidates in candidates in the case of nucleic acid vaccines, including 63.88% active trials and 43.51% recruiting ones. The maximum studies, i.e., 21.29% trials alone, are in phase 2, and the least number of studies nearly 1.85% are in the early phase 1. Out of all clinical trials on the nucleic acid-based vaccines, 85.18% were based on m-RNA vaccines, and 14.81% were based on DNA vaccines. 60.19% of the trials were conducted on adults and 2.78% on older adults, while the least number of trials, 0.93% were conducted on children and adults (Fig. 3).

Viral vector vaccines for COVID-19 in clinical trials

The viral vector vaccines are a game changer in terms of storage stability. This makes it cost-effective without the need for special supply chain conditions. One popular example of this category is the vaccine candidate from Janssen. Compared with other vaccines, a single jab vaccine promotes patient compliance and reduces vaccine hesitancy. The modified genes could elicit allergic reactions, leading to rare and adverse effects (Cerda and García 2021). This problem could be solved by using non-viral vectors, which could be lipid or polymer-based. Other problems associated with the viral vector vaccines include lack of strong and long-lasting immunity after single-dose and pre-existing anti-adenovirus immunity (Velikova and Georgiev 2021). Despite such limitations, the viral vector vaccines are easy to scale up, include multiple epitopes, and are considered more immunogenic than the other vaccine types.

Table S4 includes clinical trial data of viral vector vaccine effective against COVID-19. It shows the distribution of vaccines as per the different age groups as child (aged birth, 17 years), adults (18–64 years), and older adults (65 years and above). Also, the vaccine status in distinct phases such as phase 1, phase 2, and phases 3 and 4 has been discussed. Figure 4 summarized the clinical trials of viral vector vaccines in distinct phases, age distribution, and geographical distribution. The clinical data is extracted from the clinicaltrial.gov database, with the viral vector vaccine, safety, and efficacy as search terms. The outcomes drawn from the studies are maximum in phase 1 of the clinical trial, which accounts for 24.07% trials in phase 1, subsequent 23.52% trials in phase 1|2 of the clinical trials, and round 7.4% trials in phase 4. Also, 31.37% active trials and 29.41% recruiting ones. Also, 67.71% of the trials were conducted on adults and 2.94% trials on child, while the least number of trials, 1.96%, were conducted on child, adults, and older adults.

Protein subunit vaccines for COVID-19 in clinical trials

The subunit vaccines contain protein fragments from the pathogen that can produce an effective immune response with reduce side effects. Compared to the live and inactivated vaccines, PS vaccines are considered much more efficient in inducing cell-mediated and humoral responses as the risk of handling pathogen is eliminated (Khan et al. 2021). PS vaccines are limited in efficacy, which can be improved using adjuvants (Fathizadeh et al. 2021). The third booster of these vaccines after the "priming shot" of inactivated vaccine could produce the safer and highly immunogenic response in adults (Ai et al. 2022). People receiving 2 shots of inactivated virus vaccines showed a suboptimal level of protection against omicron transmission. Even after the third dose of inactivated vaccine, neutralizing antibodies stay low. Studies show that PS vaccines elicit a response (89.3% efficacy) (Table 4), and a booster of PS after an inactivated virus vaccine produced a better humoral response. Thus, the protein subunit vaccines are a better choice.

Table S5 includes clinical trial data of protein subunit vaccines effective against COVID-19. It shows the distribution of subunit vaccines as per the different age groups as a child (aged birth, 17 years), adults (18–64 years), and older adults (65 years and above). Figure 5 summarized the clinical trials of protein subunit vaccines in distinct phases, age distribution, and geographical distribution. The clinical data is extracted from the clinicaltrial.gov database, with the protein subunit vaccine, safety, and efficacy as search terms. The outcomes drawn from the studies are maximum candidates in phase 1 of the clinical trial, accounting for 31.88% trials in phase 1, subsequent 27.72% trials in phase 1|2 of the clinical trials, and 1.44% trials in phase 4. Also, the protein subunit vaccines include 36.23% active trials and 37.68% recruiting ones, while the maximum trials were conducted on adults, older adults (nearly 65.22%), and 27.54% trials on adults 1.45% on child, adult, and older adults (Fig. 5).

Other vaccine types for COVID-19 in clinical trials

The live-attenuated vaccines use a weak form of the virus that does not cause infection. However, they may revert the pathogenicity to cause disease in the immunocompromised patients (Machhi et al. 2021). To overcome this limitation, codon deoptimization can substitute the nucleotides from the virus coding sequence. The virus-like particles vaccines bear a similar structure and antigenicity to the parent virus (Okamura and Ebina 2021). Also, the VLP vaccine can be engineered to display foreign epitopes. Compared with the other viral vector vaccines, the VLP does not infect cells for antigen expression and does not induce neutralizing antibodies against themselves, but is similar to the structure of

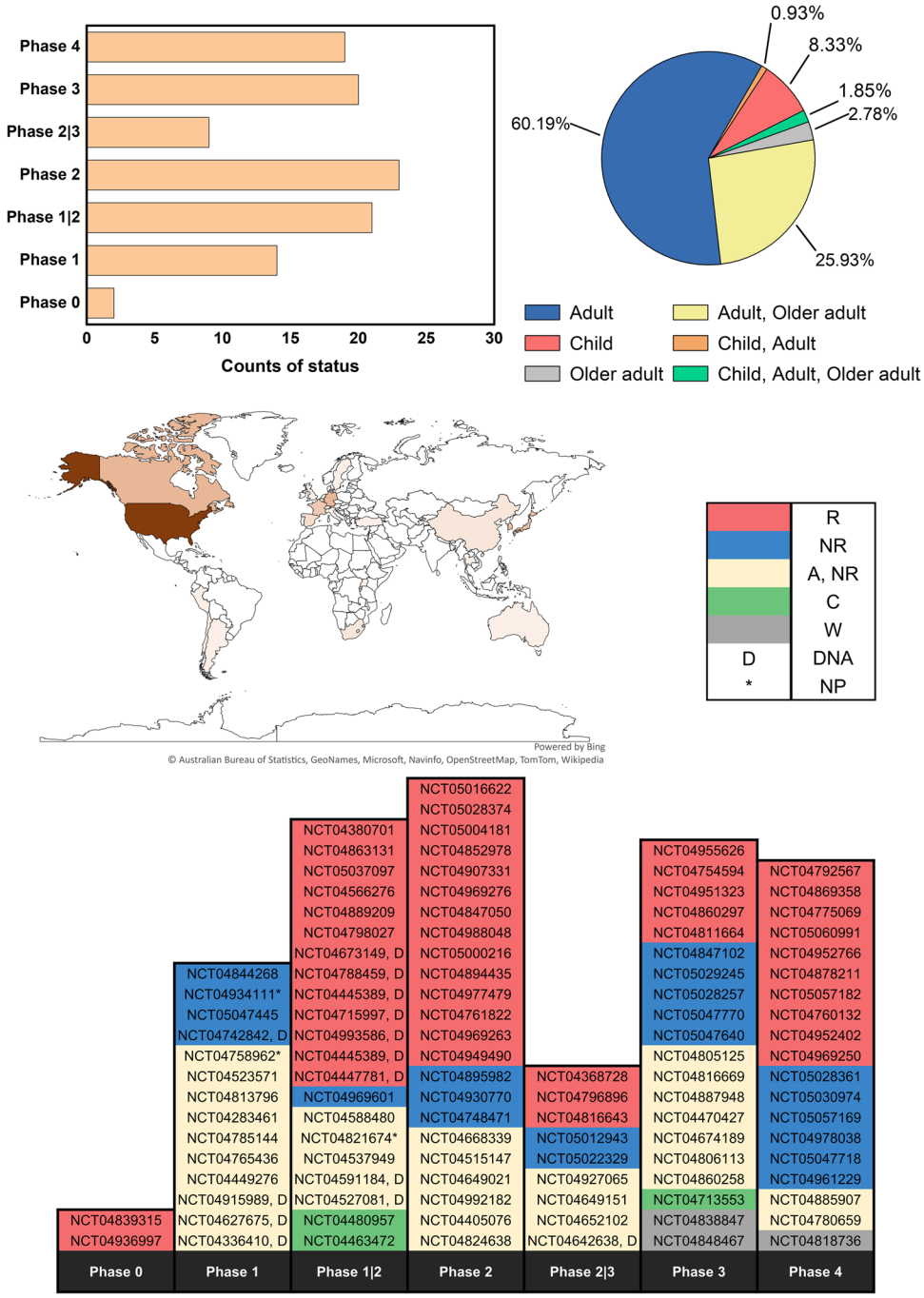

Fig. 3 Results of the clinical trial of nucleic acid-based vaccines effective against SARS-CoV-2 considering trials being conducted among people with different age groups, geographical diversity, and in distinct phases giving an idea that the maximum number of trials are being conducted in the US among adults, i.e., nearly 60.19% trials among 18 years and older and 0.93% of trials on child, adult. Also, maximum studies were found to be in phase 2 of the clinical trial, and the least number of trials were found to be in early phase 1. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

the virus. They can induce stronger immune responses and offer a strong safety profile (Zha et al. 2021). The VLP, due to its smaller size, can be taken up by APC, which presents the disease particles to the lymphocytes. Once taken up by APC, the VLP are degraded and activate T-cell response to an infection. On the other hand, nanoparticle VLP-based vaccines show high specificity, efficiency, and good pharmacokinetic characteristics, eliminate the need for injectable vaccines, and can be administered by inhalation route. Such VLP vaccines are considered safe as no viable VLP material is present, and can be self-administred (Li et al. 2022b). As the viruses mutate rapidly, it makes other available vaccines either less effective or ineffective. In contrast, the VLP-bearing surface proteins can be modified to fight against the novel version of the virus (Belete 2021).

Table S6 includes clinical trial data of live-attenuated vaccines, APC, and VLP vaccines effective against COVID-19. It shows the distribution as per the different age groups as child

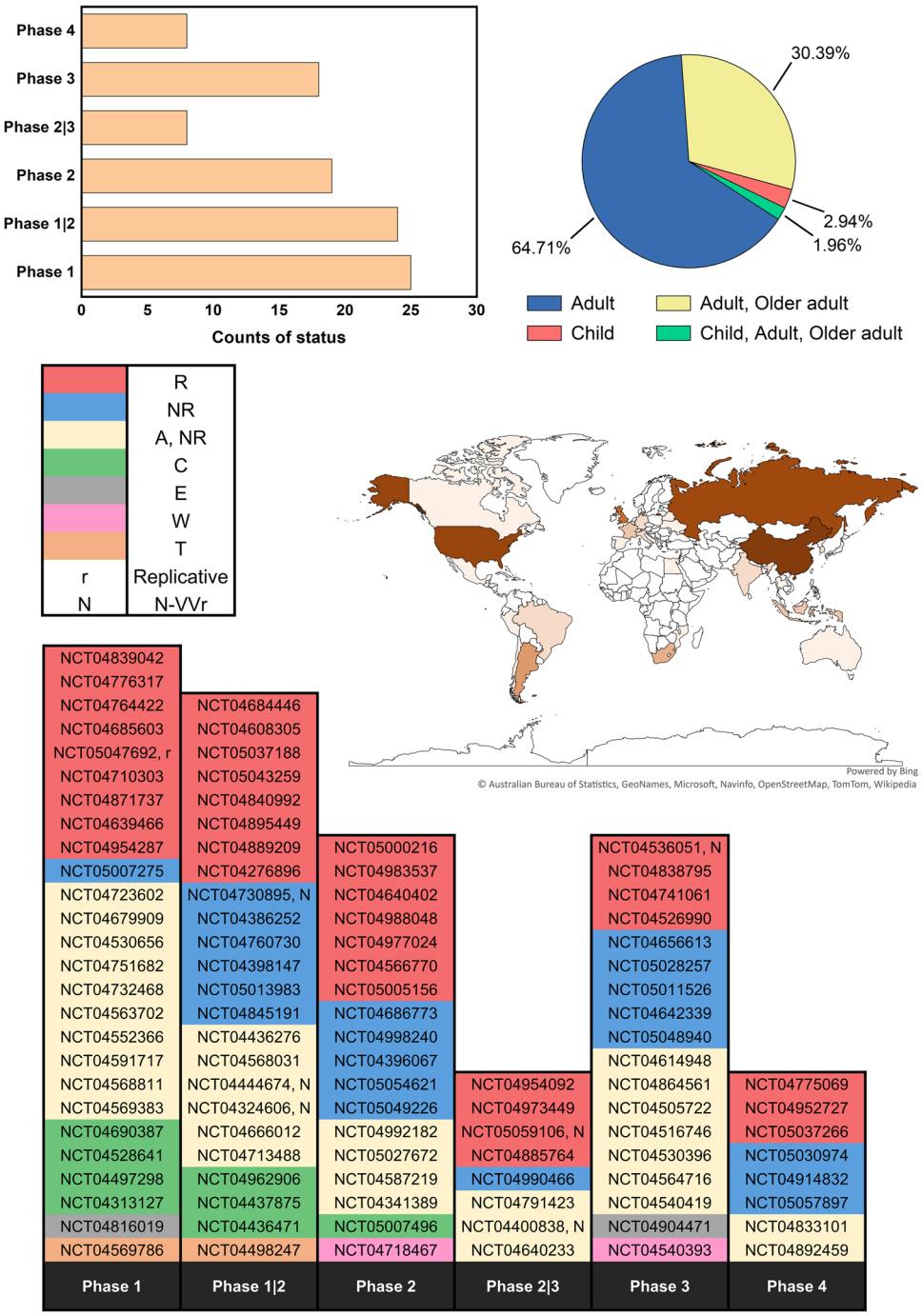

Fig. 4 Results of the clinical trial of viral vector vaccines effective against SARS-CoV-2 considering trials being conducted among people with different age groups, geographical diversity, and in distinct phases giving an idea that the maximum number of trials are being conducted in China and 64.71% on adults, i.e., 18 years and older while only 1.96% trials on child, adult, and older adult. Also, maximum studies were found in phase 1 of the clinical trial. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

(aged birth, 17 years), adults (18–64 years), and older adults (65 years and above). Also, the status of the vaccine in distinct phases such as phase 0 (early phase 1), phase 2, and phase 3 and 4 have been discussed. Fig. 6 summarized the clinical trials of live attenuated, APC, and VLP vaccines in distinct phases, age distribution, and geographical distribution. The clinical data is extracted from the clinicaltrial.gov database, with the protein subunit vaccine, safety, and efficacy as search terms. The data shows that the maximum studies are in phase 1 clinical trial. It accounts for 40% trials in phase 1, and the least number of trials (6.67%) in phase 2|3 (Fig. 6). 54.54% trials were conducted on adults, 9.09% in older adults, and 9.09% in child, adult, and older adults, including 46.66% recruiting and 20% active trials.

Nanotechnology-based COVID-19 vaccines in clinical trials

Nano drug delivery systems are being explored to deliver antiviral drugs efficiently (Szunerits et al. 2015). Nano size is comparable to the virus size that improve the treatment's

Table 4 Efficacy data of different type of vaccines effective against SARS-COV-2 infection. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

Vaccine	Type	Doses	Age group	Pregnancy and breast-feeding	Efficacy	Special warning by US-FDA	NCT number
BBV152 (Covaxin)	IV	2	18 years or older	Insufficient data to assess safety in pregnancy	78%	No such data available	NCT04641481
AZD1222 (Covishield)	N-VVr	2	18 years or older	Given only if benefit outweighs the potential risks	63.09%	No such data available	NCT04794946, NCT05059106
Ad26.COV2.S (Janssen)	N-VVr	1	18 years or older	Given only if benefit outweighs the potential risks and can be given in breastfeeding women	66%	Risk of rare but serious risk of thrombosis with thrombocytopenia Increased risk of Guillain Barre syndrome	NCT04436276, NCT04505722
BNT162b2 (Pfizer BioNTech)	m-RNA	2	12 years or older	Given only if benefit outweighs the potential risks and can be given in breastfeeding women	95%	Risk of heart inflammation (myocarditis)	NCT04848584, NCT04614948
Moderna	m-RNA	2	18 years or older	Pregnant women may choose to receive vaccine	94%	Risk of heart inflammation (myocarditis)	NCT04470427, NCT04649151, NCT04796896, NCT05074368
Novavax	PS	2	18–84 years old	No such data available	89.3%	No such data available	NCT04611802
Covilo/BBIBP-CorV/Sinopharm	IV	2	18 years or older	Insufficient data	79%	No such data available	NCT04560881, NCT04659239, NCT04852705, NCT05126550

IV inactivated, *N-VVr* non-replicating viral vector, *PS* protein subunit

efficacy in many ways. Various approaches like fabricating the polymeric nanoparticles for rapid mucus penetration or modifying the surface nanoparticles by conjugating using PEG are explored (Rashidzadeh et al. 2021). The "nano vaccines" are the new generation vaccines used to aid antigen delivery into the body. Both Elasomeran,m-RNA 1273/Spikevax/Moderna and Tozinameran/BNTI62b2/Pfizer vaccine/COMIRNATY are formulated with the lipid nanoparticle as a delivery vehicle. m-RNA when draped with positively charged lipids, forms the self-assessed lipid nanoparticles (Reichmuth et al. 2016). The LNPs also prevents the m-RNA degradation mediated by RNase, which is easily available in biofluids at site of injection (Schoenmaker et al. 2021).

Various other biocompatible lipid or inorganic nanoparticles can encapsulate the cargo vaccine for better delivery (Chung et al. 2020). Polymer-based nanoparticles encapsulated with antigen, when administered intra-nasally, triggers much stronger immune responses. In LNPs, lipid portion enhances encapsulation of m-RNA and self-assembly acts as a stabilizing agent, polyethylene glycol conjugated lipids increases the half-life and boosts circulation time. It also offer various other advantages like simple synthesis methods, serum stability, small size, and improved efficacy in nucleic acid delivery. As the nucleic acids are negatively charged, it binds with positively charged lipids in LNPs, and help in the delivery of m-RNA across the biological barriers. The LNPs have been found to show low immunogenicity and cytotoxicity compared to the liposomes (Cullis and Hope 2017). The LNPs are characterized for their particle size and distribution, zeta potential, degree of polymorphism, drug loading, release, and entrapment (Schwarz et al. 1994).

Nanomaterials are also used to diagnose and treat viral infection by conjugating with the specific viral constituents forming nano biohybrid platforms, such as colorimetric analytic devices that used silver nanoparticles to detect MERS-CoV (Bidram et al. 2021). Nanomaterials like silver colloid, diphyllin nanoparticles, and titanium dioxide are the promising drug delivery platform for effective coronavirus management (Rashidzadeh et al. 2021). Table S7 includes studies and clinical status of the vaccines based on nanotechnology used against SARS-CoV-2.

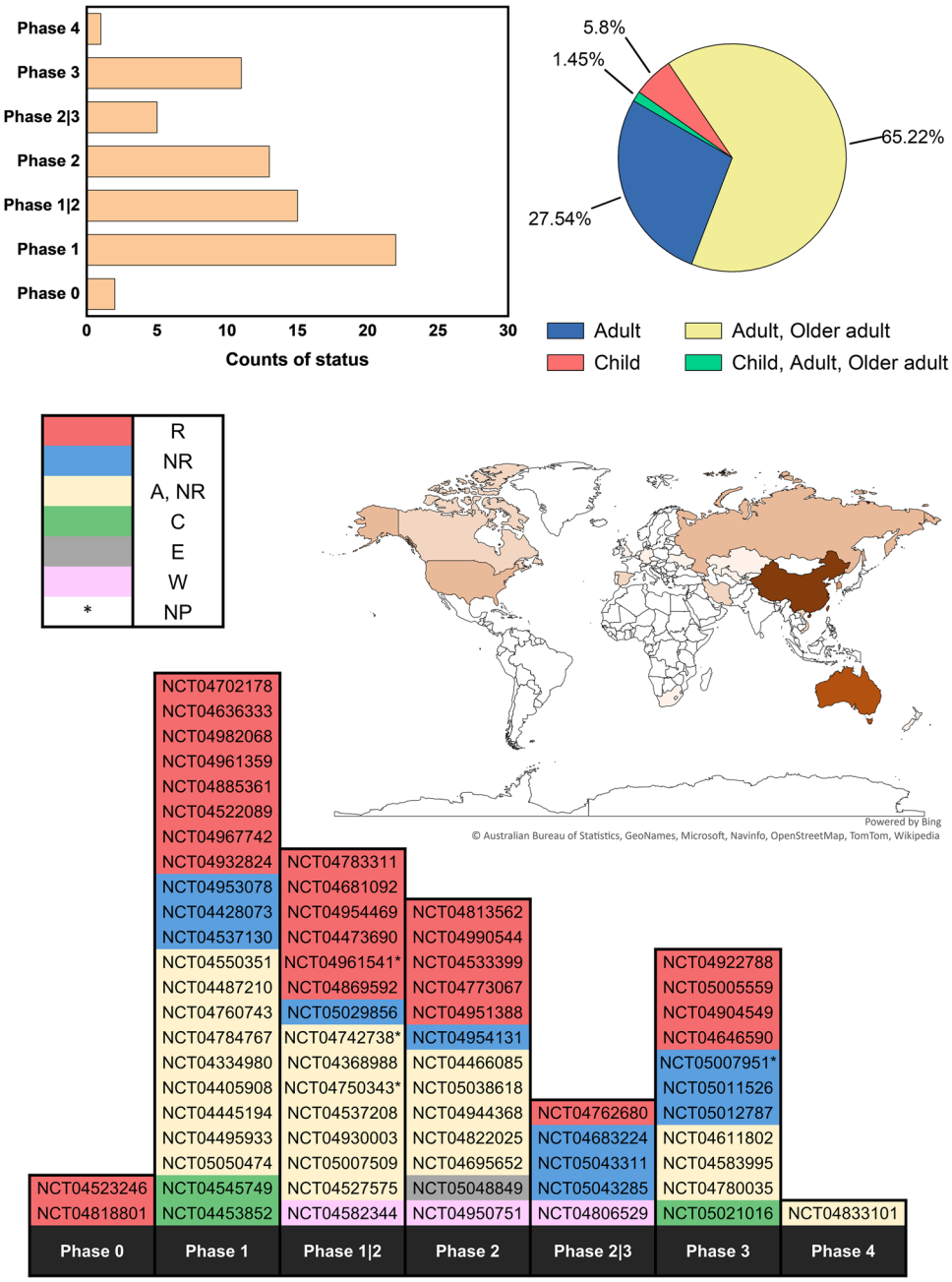

Fig. 5 Results of the clinical trial of protein subunit vaccines effective against SARS-CoV-2 considering trials being conducted among people with different age groups, geographical diversity, and in distinct phases giving an idea that the maximum number of trials are being conducted in China among adults and 65.22% trials were conducted on adults, older adults, 1.45% trials on child, adult, and older adult. Also, maximum studies were found to be in phase 1 of the clinical trial. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

Emerging strategies to combat uncertain COVID-19 disease

Despite the progress of the vaccines, there are still many obstacles that hinder efficient use of COVID-19 vaccine. This include cold chain storage requirements, higher costs, scalability concerns, efficacy issues, painful injection, multiple jabs, and occurrence of rare side effects in immunocompromised patients, which are causing vaccine hesitancy among individuals. The next generation vaccines need to overcome these major limitations. The alternative vaccine delivery systems are needed to improve the immune responses, enhance stability, and offer desirable routes of administration. Moreover, the vaccine delivery should be less invasive, reducing the need for trained medical staff and allowing self-administration (Hossain et al. 2020).

The strategies are being explored to stabilize the S protein in its pre-fusion conformation and enhance its expression, which can improve the quantity and quality of vaccine-induced antibodies production in body. Whereas, for m-RNA vaccines, the m-RNA translation occurs in the cytoplasm to avoid the risk of genomic integration. Of all vaccines, industries have preferred m-RNA vaccines mainly as they offer rapid development, large-scale development, and trigger both antibody and

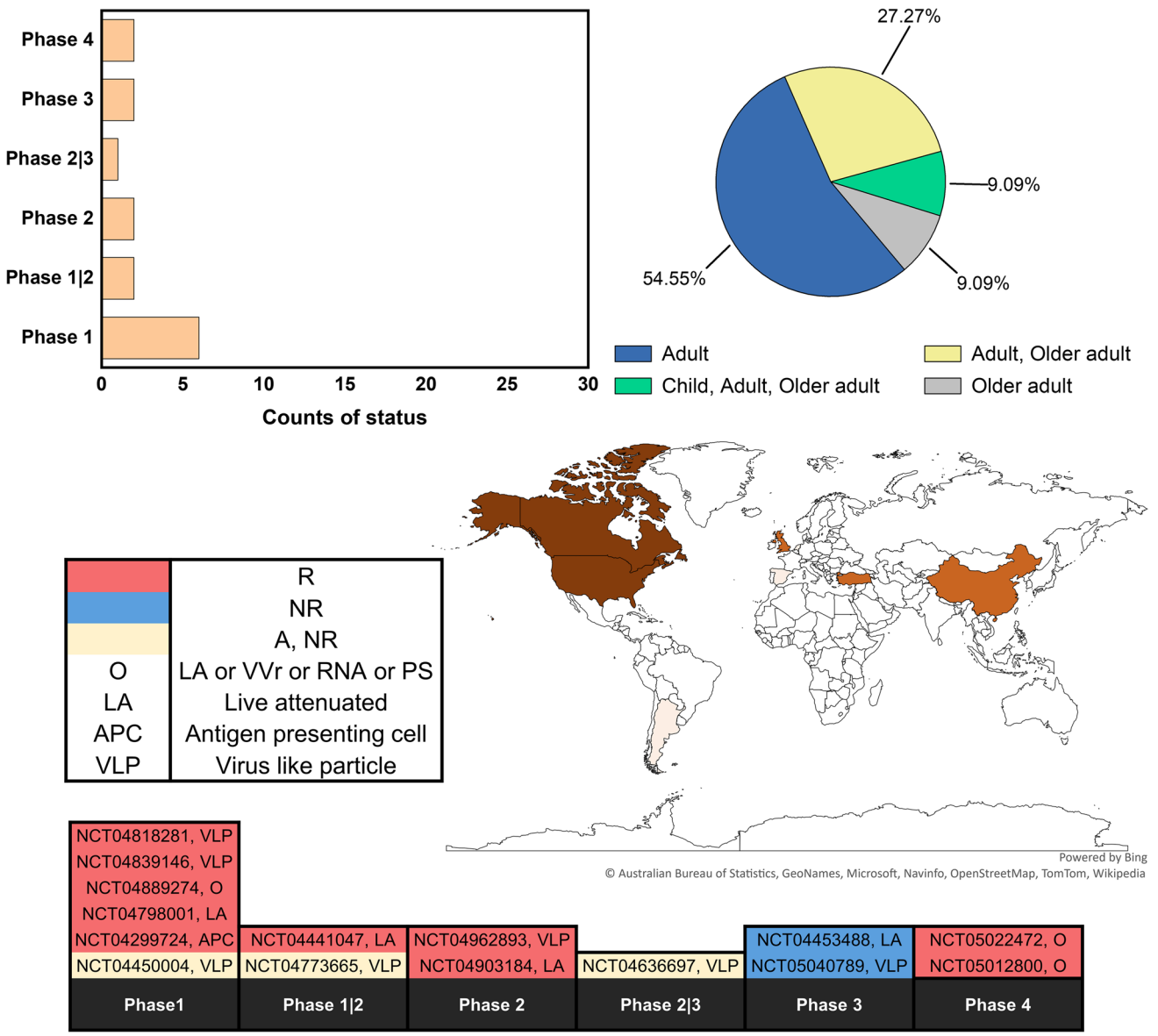

Fig. 6 Results of the clinical trial of live-attenuated, APC, and VLP vaccines effective against SARS-CoV-2 considering trials being conducted among people with different age groups, geographical diversity, and in distinct phases giving an idea that the maximum number of trials are being conducted in Canada and USA among adults, i.e., 18 years and older (54.55%), 9.09% in older adult and 9.09% in child, adult, and older adult. Also, maximum studies were found to be in phase 1 of the clinical trial and the least number of trials were found to be in phase 2|3. Data obtained from clinicaltrial.gov (accessed on October 31, 2021)

T-cell responses. However, m-RNA being unstable requires low temperature for storage and transportation. Further, the efficacy of vaccines for the elderly population has been lower as they are more susceptible to the infection (Uddin and Roni 2021).

Also, Moderna has announced its preclinical data on COVID and flu combination vaccines. Tozinameran/BNTI62b2/Pfizer vaccine/COMIRNATY has been approved for children in 12–15 years of age group, which include 2 shots, 21 days apart. A US manufacturer also released the results for the second and third staged clinical trials of Teen COVE on 3732 children. In India, BBV152/Covaxin, ChAdOx1-S/Covishield, and sputnik V are developed, but none is approved for children below 18 years. Recently, ZyCoV-D, which is the world's first DNA vaccine, got its approval for emergency use against the SARS-CoV-2 for individuals 12 years and above (Momin et al. 2021). It is a 3-shot vaccine and requires storage at 2–8 °C. It uses a portion of genetic material from the virus, which gives instructions from DNA to make specific proteins recognized by the immune system. Each vaccine has its pros and cons; however, there is a need to focus on new strategies and vaccines that could effectively treat against

COVID-19 infection, while preventing side-effects, reduce number of dose and enable self-administration.

Safety and efficacy concern of COVID-19 vaccines with emerging variants

As many of the vaccines require ultracold chain technology that is expensive to maintain, major concerns come to the insufficient data to prove for how long these vaccines will remain effective over time. With the rise of new variants of SARS-CoV-2, in November 2021, the WHO designated this B.1.1.529 strain as the variant of concern named omicron (Callaway and Ledford 2021). This variant has more than 30 mutations in the spike protein that reduced susceptibility to the available monoclonal antibodies. Earlier, the alpha variant had shown increased transmissibility and infectivity, while the beta variant was less sensitive towards the neutralization by vaccine and the infection-induced antibodies (Gupta and Topol 2021).

On the other hand, the delta variant had different mutations in the spike protein from the alpha, beta, and gamma variants. The mutation in the spike protein can affect the ability of viruses to cause infection and makes it even harder for the immune cells to attack pathogens. Preliminary studies have shown that omicron, the heavily mutated Covid strain, reduces the efficacy of the two dose vaccine. Thus, three doses are required, including two preliminary shots and a booster shot showing a significant level of protection against the omicron variant (Callaway 2021b).

Although, researchers are working at breakneck speed to gather more information about the severity. However, transmissibility of the new variant and its ability to evade the vaccine effects, and chances of causing reinfection are increasing. It is known that omicron can infect 3–6 times as many people as delta variant over the same period. Earlier studies based on spike mutation suggest that the variant blunts the potency of neutralizing antibodies. Even though omicron can dodge neutralizing, it does not mean that responses triggered by the vaccination will not offer protection against the variant. Thus, a third dose may help supercharge the neutralizing antibodies level (Callaway and Ledford 2021; Karim and Karim 2021).

Pfizer, on December 8 2021, stated that a third dose might increase the neutralizing antibodies level against omicron by 25-fold compared to the two doses. It also announced results from an initial study that serum antibody induced by Tozinameran/BNTI62b2/Pfizer vaccine/Comirnaty neutralized SARS-CoV-2 omicron variant after three doses (Pfizer 2021). As vaccine effectiveness against symptomatic omicron infection is lower than the delta variant suggesting that after 2 doses of m-RNA vaccine from Moderna or Pfizer, the efficacy against the symptomatic infection is 30% in omicron than 87% in delta (Burki 2022). A booster dose may be given at least 6 months after completing the primary vaccination series (Pfizer 2021).

As vaccines were developed quicker than usual development time, their safety and efficacy must be continuously monitored. As of August 2022, over 12 billion doses of vaccines have been given, and data show that the vaccines are safe and effective. Data shows that m-RNA vaccines are clear winners in efficacy, followed by protein subunit vaccines. The inactivated virus vaccines also one of the top vaccines in use.

The effectiveness of 2 doses of m-RNA or adenoviral vectored vaccines wanes over time, but the emerging studies show that a 3rd booster dose could restore the effectiveness $>90\%$. A study data of 6-month follow up shows 6% reduction in the vaccine efficacy every 2 months for Tozinameran/BNTI62b2/Pfizer vaccine/Comirnaty (Kertes et al. 2022). However, some studies have also confirmed the reduction in serum concentration of neutralizing antibodies 4–6 weeks after the vaccination. The responses to booster doses given after 6 months from the last dose have shown induction of considerably high amounts of neutralizing antibodies. Earlier studies in Israel showed that more than 1.1 million people aged over 60 years who have received m-RNA booster doses after 6 months after the second dose resulted in the restoration of vaccine effectiveness (Collie et al. 2022). The study published by Ssentongo et al. (2022) shows that the efficacy of vaccines against SARS-CoV-2 reduces from 83 to 22% after 5 months of completing original vaccination series. Against the symptomatic COVID-19, vaccine efficacy declines from 94% in first month to 64% by fourth month. Data clearly showed the waning of vaccine efficacy against the infection suggesting the need for booster vaccines. Table 5 includes clinical status of COVID-19 vaccines in phase IV of the clinical trial. The table also includes mix and match vaccine studies, vaccine study in specific disease condition, and booster dose study in different age groups. m-RNA cocktails could also emerge as a new emerging platform for COVID-19 treatment to produce an even stronger immune response. This could be since there is no certain limit to the number of RNAs that can be combined and can target more than one pathogen or more than variant in the case of SARS-CoV-2 (DeFrancesco 2021). Efficacy data of the different types of vaccines effective against SARS-COV-2 infection is mentioned in Table 4.

Additional dose

US-FDA and CDC recommended additional doses of vaccine to the following individuals: aged 5 years and older, are on active cancer treatment, are diagnosed with HIV and have low CD4 count, are diagnosed with any immunodeficiency disorders, received an organ transplant or on immunosuppersants, and have received a stem cell transplant

(FDA—Food and Drug Administration 2021). An additional dose is required to improve their immune response to the initial vaccine series as they are at a greater risk of serious illness. There is a difference in the additional and booster dose of vaccine. The booster dose is termed as the third dose given to people who had received Elasomeran,m-RNA 1273/Spikevax/Moderna or Pfizer-BioNTech vaccine at least 6 months after compeletion of vaccine series, while for Ad26.COV.S/Jannssen/Jcovden at least 2 months after completion of their vaccine series. Booster is also given if the protection against the virus over time has decreased, which can be measured using antibody titers in blood (Dunkle et al. 2022).

Mix and match vaccines

For the first time, researchers have shown that the "mix and match" vaccine combination as a new emerging strategy for better preotection against SARS-CoV-2. Vaccines that are already in used have shown some rare adverse effects leading to the discontinuation of specific vaccines in some countries. Other struggles include its supply and availability issues, and emergence of new variants, which has necessitated the use of heterologous vaccination approach known as mixing vaccines (Rashedi et al. 2022). Studies by Richardson (2022) shown protection against COVID-19 by mixing m-RNA, spike adjuvant, and adenoviral vaccines for protection against SARS-CoV-2.

These vaccines have turned out to be highly effective, safe, producing stronger immune responses, and exceeding the performance of m-RNA vaccines (Callaway 2021a). Mix and match vaccines produce stronger immune responses and are used in immunocompromised patients. Also, there is a possibility that mixing the vaccines could protect the organ-transplant recipients. Studies have claimed that having an m-RNA vaccine dose after the Oxford-AstraZeneca dose imparts better protection against the SARS-CoV-2 than giving two doses of Oxford-AstraZeneca (Lewis 2021b).

In April 2021, a Spanish Combivac trial enrolled 663 people who had received the first dose of Oxford-AstraZeneca vaccine and 232 who had received a booster. Two-thirds of the participants were picked randomly to receive the m-RNA vaccine (Pfizer) at least 8 weeks after their first dose. After the second dose, the participants began to show higher levels of antibodies, and these antibodies recognized SARS-CoV-2 (Callaway 2021c).

Nasal vaccine

Vaccines are administered through invasive routes producing circulating immunoglobulin G antibodies that fights off the pathogens. It has been found that nasal epithelium has the highest concentration of angiotensin converting enzyme-2 receptors, and it plays a significant role in entry of SARS-CoV-2 into cells. Thus, it is expected that replication of virions takes place mostly in the nasal mucosa. The intranasal vaccine produces IgA, which evokes stronger immune responses at the site of virus entry, and it is more efficacious in destroying the viruses at an early stage than IgG, which avoids further damage to the lungs (Lund and Randall 2021). Also, this route offers the advantage of inducing both strong local and systemic immune responses. Furthermore, the nasal administration of vaccines does not require specialized medical staff, which improves patient compliance, and it is cost-effectiveness and efficient route of delivery (Tiboni et al. 2021).

A study (Reichmuth et al. 2016) showed intranasal delivery exploring the feasibility of Venezuelan equine encephalitis virus replicon that encodes both light and heavy chains for antibody expression in lungs preventing SARS-CoV-2 infection. This approach suggests the expression of neutralizing antibodies in lungs using m-RNA could be a potential approach for prophylaxis of SARS-CoV-2 infection. Besides codagenix, another adenoviral-vectored vaccine is under development. It is a simple and painless way of administering the vaccine by using nasal drops. This vaccine was found to be well tolerated. Also, BB154, a live attenuated vaccine is being developed by Bharat Biotech International Limited, is currently under animal trials (Hassan et al. 2020).

Strategies to overcome COVID-19 vaccine administration and stability

Antiviral pill

The pharmaceutical firm Merck has recently announced the development of an antiviral pill Molnupiravir which could force the virus to mutate itself to death. Thus, it cut hospitalizations and deaths by 50% in mild to moderate COVID-19 cases (Cascella et al. 2020). The drug is under review by US-FDA, and if approved, it would turn out to be the first oral antiviral treatment for COVID-19 infection (Willyard 2021). Molnupiravir targets RNA-dependent RNA polymerase, introducing errors in the viral genome, hampering its replication (Gordon et al. 2021).

Another antiviral pill PAXLOVID was launched by Pfizer in November 2021. It is a combination of ritonavir and nirmatrelvir that inhibits SARS-CoV-2 replication. A phase 2|3 clinical on protease inhibitor antiviral therapy showed that PAXLOVID could significantly reduce hospitalizations and deaths by 89%, making it more efficacious than molnupiravir (Robinson 2021). Pfizer is seeking emergency use authorization of PAXLOVID designed to combat the SARS-CoV-2 infection and is not recommended in patients with kidney or liver impairment. At the same time, molnupiravir may affect

Table 5 Clinical status of COVID-19 vaccines in phase IV. Data obtained from clinicaltrial.gov (accessed on July 6, 2022)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
m-RNA	Humoral response in immunocompromised adults	C	18 years and older	196, 200	Centre Hospitalier RÃ©gional d'OrlÃ©ans	NCT04952766, NCT05047718
m-RNA	Immune response in patients with cancer undergoing vaccination	R	18 years and older	525	Jules Bordet Institute; Roche Pharma AG	NCT05075538
m-RNA	Vaccination of immunodeficient persons	A, NR	18 years and older	540	Karolinska University Hospital; Karolinska Institutet	NCT04780659
m-RNA	Reactogenicity and immunogenicity	R	5 years to 11 years	150	KK Women's and Children's Hospital; Duke-NUS Graduate Medical School	NCT05329064
m-RNA	Vaccine and tozinameran study in patients with Dermatologic diseases	NR	18 years and older	160	Mahidol University	NCT05406908
m-RNA	Detection of neutralizing antibodies	NR	65 years and older	414	Mark Loeb; McMaster University	NCT04978038
m-RNA	COVID-19 vaccine for indirect protection	W	Child, adult, older adult	0	McMaster University; University of Alberta; University of SaskatchewanlUniversity of Manitoba	NCT04818736
m-RNA	Immune responses after vaccination	A, NR	18 years and older	700	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04952402
m-RNA	Mix and match vaccine	A, NR	20 years to 69 years	220	National Taiwan University Hospital	NCT05079633
m-RNA	Efficiency of vaccine in multiple sclerosis and drug interaction studies	A, NR; R	18 years to 100 years	41, 40, 66	Novartis Pharmaceuticals; Novartis	NCT04792567, NCT04869358, NCT04878211
m-RNA	Effectiveness and safety of vaccines	R	18 years and older	10,000	Jens D Lundgren, MD; Ministry of the Interior and Health, Denmark; Rigshospitalet, Denmark	NCT04760132
m-RNA	Safety, efficacy and immunogenicity of fourth BNT162b2 vaccine dose	A, NR	18 years and older	1000	Sheba Medical Center	NCT05231005
m-RNA	Booster vaccine study	A, NR	30 years and older	300	The University of Hong Kong	NCT05057182
m-RNA	Third dose of Moderna COVID-19 vaccine in transplant recipients adverse events	A, NR	18 years and older	120	University Health Network, Toronto	NCT04885907

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
m-RNA	Immunosuppression adjustment on COVID-19 vaccination response in kidney transplant recipients	R	18 years and older	50	University of California, Davis; CareDx	NCT05060991
m-RNA	Allergic reaction adverse events realted to dose	R	18 years and older	200	University of Michigan; The Wallace Foundation	NCT05212610
m-RNA	Mix and match vaccine	A, NR	18 years and older	640	International Network for Strategic Initiatives in Global HIV Trials (INSIGHT); University of Minnesota; National Institute of Allergy and Infectious Diseases (NIAID); University of Copenhagen; Kirby Institute; Washington D.C. Veterans Affairs Medical Center; AIDS Clinical Trials Group; National Heart, Lung, and Blood Institute (NHLBI); US Department of Veterans Affairs; Prevention and Early Treatment of Acute Lung Injury (PETAL); Cardiothoracic Surgical Trials Network (CTSN); Medical Research Council	NCT04969250
IV	Safety and efficacy of vaccine	A, NR	18 years and older	27,711	Butantan Institute	NCT04747821
IV	Mix and match vaccine	R; C	18 years and older	3000	Centers for Disease Control and Prevention, China	NCT05298800
IV	Immunogenicity and safety of an vaccine in people with a disease conditions	R; NR	18 years and older; 60 years and older	400, 400, 400, 400, 400, 400, 4400, 1440	China National Biotec Group Company Limited|Hubei Provincial Center for Disease Control and Prevention|Wuhan Institute of Biological Products Co., Ltd	NCT05075044, NCT05075057, NCT05075070, NCT05075083, NCT05105295, NCT05104216, NCT04863638, NCT05104437
IV	Safety and Immunogenicity of vaccine	A, NR	18 years and older	1200	D'Or Institute for Research and Education; Butantan Institute	NCT04756830

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
IV	Vaccine study in pulmonary tuberculosis patients	R	18 years to 75 years	240	Jiangsu Province Centers for Disease Control and Prevention	NCT05148949
IV	Effectiveness of the vaccine	A, NR	18 years to 49 years	6233	FundaÃ§Ã£o de Medicina Tropical Dr. Heitor Vieira Dourado; Butantan Institute	NCT04789356
IV	Safety and immunogenicity of vaccine	A, NR	18 years and older	400	Huashan Hospital	NCT05095298
IV	Immunogenicity with autoimmune rheumatic diseases and HIV/AIDS	A, NR	18 years and older	2067	University of Sao Paulo General Hospital	NCT04754698
IV	Safety and immunogenicity of vaccine and the adverse events of special concern	R; NR; A, NR; C	3 years to 17 years; 18 years and older	121,000, 33,000, 1320, 480, 340, 400, 180, 270, 2520, 1080, 1400, 480	Sinovac Research and Development Co., Ltd.; Sinovac Biotech Co., Ltd	NCT05107557, NCT05079217, NCT05398926, NCT04911790, NCT04992208, NCT04993365, NCT05165732, NCT05165966, NCT05198336, NCT05329038, NCT04953325, NCT05112913, NCT04894227, NCT04962308, NCT04801888
n-VVr	Safety and immunogenicity in immunocompromised patients	A, NR	18 years to 130 years	360	AstraZeneca	NCT05057897
n-VVr	Immunogenicity and safety	R	18 years to 80 years	200	Zhejiang Provincial Center for Disease Control and Prevention	NCT05373030
n-VVr	Immunogenicity and the safety of the vaccine in different age groups	R	18 years and older	120	Centre Hospitalier Universitaire de Saint Etienne	NCT05037266
VVr	Safety and effectiveness of vaccine	C	18 years and older	1050	Jiangsu Province Centers for Disease Control and Prevention	NCT05313646
n-VVr	Vaccine effectiveness	NR	18 years and older	600	Shabir Madhi|AstraZeneca; University of Witwatersrand, South Africa	NCT04914832

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
PS	Immunogenicity and safety of vaccine	R	20 years to 64 years	200	Taoyuan General Hospital; Medigen Vaccine Biologics Corp	NCT05097053,
PS	Antibody response, safety and immunogenicity of a third dose of vaccine	R; A, NR	18 years and older	662, 1264	The Immunobiological Technology Institute (Bio-Manguinhos) / Oswaldo Cruz Foundation (Fiocruz)	NCT05142488, NCT05157178
IV|n-VVR|RNA	Mix and match vaccine	NR	18 years to 60 years	2880	Albert B. Sabin Vaccine Institute; Aga Khan University; Oswaldo Cruz Foundation; Stanford University	NCT05343871
m-RNA|IIV4	Mix and match vaccine	S	12 years and older	450	Duke University; Centers for Disease Control and Prevention; Johns Hopkins University; Children's Hospital Medical Center, Cincinnati	NCT05028361
m-RNA|IV|n-VVr	Mix and match vaccine	R	18 years and older	900	Humanity & Health Medical Group Limited	NCT04775069
m-RNA|VVr	Mix and match vaccine	C	18 years and older	336	University Medical Center Groningen; Radboud University Medical Center; Erasmus Medical Center; Academisch Medisch Centrum—Universiteit van Amsterdam (AMC-UvA); ZonMw: The Netherlands Organisation for Health Research and Development	NCT05030974
VVr|PS	Mix and match vaccine	C	18 years and older	120	Jiangsu Province Centers for Disease Control and Prevention	NCT04833101
LA or VVr or PS or RNA	Efficiency, safety, immunogenicity of vaccine in comorbid conditions	R	18 years to 60 years	200, 300	Beijing 302 Hospital	NCT05085145, NCT05012800

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
LA or VVr or PS or RNA	Mix and match vaccine and safety, efficacy in co-morbid conditions	C; A, NR; NR	18 years and older; 60 years and older	1133, 1404, 1440, 1440, 1440	China National Biotec Group Company Limited; Chengdu Institute of Biological Products Co., Ltd.; Changchun Institute of Biological Products Co., Ltd.; Beijing Institute of Biological Products Co Ltd.; Sichuan Center for Disease Control and Prevention; Shanghai Municipal Center for Disease Control and Prevention; Shanxi Center for Disease Control and Prevention	NCT04790851, NCT05079152, NCT05104333, NCT05065892, NCT05065879
LA or VVr or PS or RNA	Vaccine response in rheumatology patients	NR	18 years to 85 years	1000	Jeffrey Curtis; University of Alabama at Birmingham; University of Nebraska; University of Pennsylvania; AbbVie; Bristol-Myers Squibb; Novartis; Eli Lilly and Company; Pfizer; Foundation for Advancing Science Technology Education and Research	NCT05080218
Behavioral: COVID-19 Individual Awareness and Education.|Behavioral: COVID-19 Community Outreach & Health Promotion.|Behavioral: COVID-19 Individual Health Education & Linkages to Medical and Supportive Services.|Pop-up community vaccination sites	Change in COVID-19 Vaccine acceptance|Change in Vaccine Hesitancy|Change in Health literacy|Change in COVID-19 risk perception (probability and severity)|Change in Preparedness and Perceived self-efficacy|Change in Prevention (own behaviors)|Testing and tracing|Access to health care and utilization|Health History	R	18 years to 99 years	1000	Argentina Servin, MD, MPH; San Ysidro Health Center; National Institute on Minority Health and Health Disparities (NIMHD);University of California, San Diego	NCT05022472

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
BCG	BCG to reduce absenteeism	A, NR	18 years and older	668	University of Southern Denmark; Institute of Hygiene and Tropical Medicine, NOVA University, Lisbon, Portugal; University of Cape Verde, Praia, Cape Verde; National Institute of Public Health of Cape Verde, Praia, Cape Verde; Centro de Investigacao em Saude de Manhica; European and Developing Countries Clinical Trials Partnership (EDCTP); Bandim Health Project, Bissau, Guinea-Bissau	NCT04641858
BCG	Clinical evolution of COVID-19|SARS-CoV-2 elimination|Seroconversion rate and titration|Local and systemic adverse events to BCG vaccination	A, NR	18 years and older	400	University of Campinas, Brazil; Conselho Nacional de Desenvolvimento CientÃfico e TecnolÃ³gico; PontifÃcia Universidade CatÃ³lica de Campinas, PUC-Campinas; State Hospital Dr. Leandro Franceschini, SumarÃ©, Unicamp; PaulÃnia Municipal Hospital	NCT04369794
BCG	Prevention of respiratory tract infection and Covid-19 through BCG vaccination	R	60 years and older	5200	UMC Utrecht	NCT04537663
BCG	Disease severity study	A, NR	18 years to 75 years	1800	Texas A&M University; Baylor College of Medicine; M.D. Anderson Cancer Center; Cedars-Sinai Medical Center; Harvard University	NCT04348370

Table 5 (continued)

Interventions	Objectives	Status	Age	Enrollment	Sponsor/collaborators	NCT number
BCG	SARS-CoV-2 related hospital admission|the duration of hospital admission due to documented COVID-19|the cumulative incidence of documented SARS-CoV-2 infection|the cumulative incidence of self-reported acute respiratory symptoms or fever|the cumulative incidence of death due to documented SARS-CoV-2 infection|the cumulative incidence of hospital admission for any reason|the cumulative incidence of intensive care admission due to documented SARS-CoV-2 infection	Unknown status	60 years and older	2014	Radboud University Medical Center	NCT04417335
BCG	Vaccine immunity in children for allergy and infection reduction	A, NR	5 years to 11 years	51	Murdoch Childrens Research Institute	NCT05168709
BCG	BCG vaccine in COVID-19	C	50 years and older	301	Hellenic Institute for the Study of Sepsis	NCT04414267
OPV	OPV as potential protection against COVID-19	A, NR	50 years and older	3400	Bandim Health Project	NCT04445428
Ultrix Quadri	Influenza vaccination During coronavirus disease	R	65 years and older	200	Samara Regional Cardiology Dispensary	NCT05232292
Drug: theraputic heparin|Drug: prophylactic heparin|Drug: P2Y12|Drug: Crizanlizumab Injection|Drug: SGLT2 inhibitor	Prevention of adverse outcomes in COVID-19 patients	R	18 years and older	3000	Matthew Neal MD; National Heart, Lung, and Blood Institute (NHLBI); University of Pittsburgh	NCT04505774
IPV	Prevention of coronavirus disease	A, NR	18 years to 80 years	300	E-MO Biology Inc	NCT04639375

R recruiting; *A,NR* active, non-recruiting; *NR* non-recruiting; *C* completed; *W* withdrawn; *PS* protein subunit; *IV* inactivated; *n-VVr* non-replicating viral vector; *LA* live attenuated

bone and cartilage growth in patients younger than 18 years of age. It may cause fetal abnormalities in the case of pregnant individuals (Pfizer Inc 2021). Thus, these pills offer a great advantage over currently available vaccines in terms of self-administration avoiding the need of a skilled person to inject the vaccine, associated pain and fear of injection. Using oral pills enhances patient compliance and eliminates cold chain storage requirements.

Microneedle patch delivery system

Another novel approach is a microneedle patch to deliver a DNA vaccine against SARS-CoV-2 infection (Fig. 7). It can be stored at room temperature for 30 days or longer (Konrath et al. 2022). Earlier the vaccines required controlled cold storage that restricted its distribution due to limited resources. A microneedle patch could efficiently deliver the vaccine under the skin without the need of cold chain or painful injections. Recently, DNA vaccine was used, which was comparatively easier to make than the RNA or proteins. DNA being more stable added a great advantage. However, unlike the RNA, the DNA must find its way inside the nucleus, so nanoparticles were used along with an adjuvant to stimulate the immune responses. Further coating the microneedle patch with the vaccine nanoparticles could painlessly deliver the vaccine into the skin (Yin et al. 2021).

Preparedness to next pandemic

Infectious diseases are inevitable but their effects can be mitigated by investing in the prevention and preparedness methods for such pandemics. Combating the COVID-19 pandemic has been an enlightening for humanity. It has been tackled well with the joint efforts of NGO's, government, healthcare workers, two years of breakneck research and a collection of therapies to treat COVID-19 infected patients. Although vaccinations has led to decline in certain diseases but hesitance to enroll in the clinical trials has been raising (Sidik 2022). The pandemics management include containment strategies, lockdowns, accurate tracing of infection source and infected individual, isolation of infected individual and proper treatment of patients. Other mitigation strategies include social distancing, use of facemasks, which helps in decreasing the spread of infection (Coccia 2021b).

As the world roll out of vaccines against the COVID-19, the global inequalities of vaccine distribution and race against vaccine development for the COVID-19 variants might favor wealthy nations by stocking vaccine doses. COVAX is an alliance led by coalition for epidemic preparedness innovations that together GAVI and WHO ensured global vaccine equity. Another major aim is to accelerate development and manufacturing of COVID-19 vaccines, including for new infectious varriants. The massive global effort are needed to fast-track development of vaccines against COVID-19 and its distribution in both low- and middle-income countries. Herd immunity can only be achieved through mass vaccinations. Even after more than a year of vaccine distribution, the vaccine waste is found to be as high as 30%. So the effective supply chain management in low income countries should be improved. It may overcome the practice of supplying "about to expire" vaccines doses to low income countries, which exacerbates wastage of vaccines (Lazarus et al. 2022a).

Other non-pharmaceutical interventions (NPIs) include actions apart from vaccinations and use of medicines, that are implemented to slow down the spread of infections. During the start of pandemic, NPIs were the only solution to decrease the transmission for both governmental (top down) and self-initiated (bottom up) measures (Perra 2021). NPIs are considered most accessible keeping in mind the time taken by the pharmaceutical companies to develop specific vaccines (Coccia 2020). Such strategies play a key role in reducing the transmission and reduce overall impact of pandemic (WHO 2019).

However, the impact of pandemic and measures to control has raised questions about the preparedness to next pandemic. The new technology and preventive measures could control the emergence of such pandemics. In local epidemic outbreak, contact tracing within the epicenter could limit the human-to-human transmission. In COVID-19 pandemic crisis, major pharmaceutical measures included vaccinations to support disease prevention and aid faster recovery (Coccia 2022a). Currently, 48 COVID-19 vaccine candidates are undergoing the clinical evaluation. Real world data is suggestive of an edge to m-RNA vaccines in terms of efficacy, market penetration, and scalability (MacIntyre et al. 2022).

Vaccinations have been essential to prevent healthcare systems from collapsing and also helps in achieving the herd immunity in faster and safer way. Women with low income and lower level of education were found to be reluctant in receiving the vaccines. Vaccine hesitancy is basically the reluctance of people to receive safe and available vaccines. A 5C model of drivers of vaccine hesitancy include confidence, convenience, complacency, risk calculation and collectively (Machingaidze and Wiysonge 2021). As per reports the major variables associated with decision making processes regarding the vaccination (Cerda and García 2021). The study included an online survey of 370 respondents in Chile, and the results showed 49% were willing to take the vaccine while 28% undecided or 77% individuals potentially willing to be inoculated. Other factors associated with vaccine hesitancy include depression, fear of COVID-19 and generalized anxiety because of re-infection even after multiple doses of vaccines (Sekizawa et al. 2022). The public trust

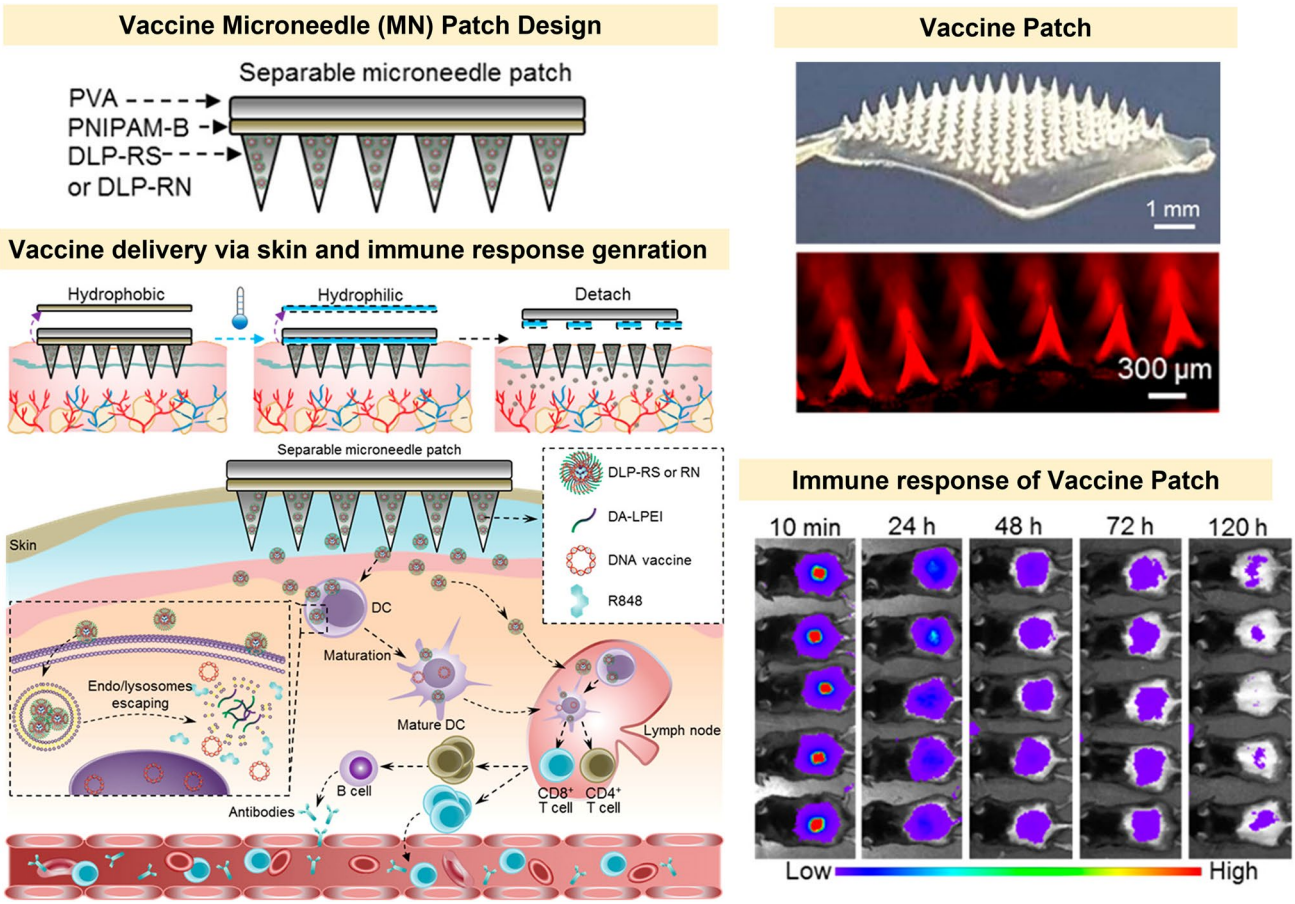

Fig. 7 Schematic (left) showing the microneedle (MN) patch design for vaccine delivery via skin and generating an immune response. MN patch loaded with the vaccine in tips (right) and delivered to mice via skin and transfection of DNA vaccine over 120 h, showing good reproducibility. Copyright (2021) American Chemical Society

in vaccines plays a major role and it is influenced by spread of misinformation through advertisements and social media. As the doses are trickling in, resistance to get vaccinated is also emerging as a issue. Also, vaccine safety concern are also there as the vaccines have been developed at a very fast speed and their recommendations have been changing quite often (Mallapaty 2022) (Coccia 2022b). A behavioral study in the Phase IV clinical trial is studying the association of social, individual and contextual factor with vaccine hesitancy and vaccine acceptance (NCT05022472). The outcome of this study may help government bodies in proper planning and minimize vaccine wastage.

Conclusion

The COVID-19 vaccine has been in the market worldwide and is already used in billions of people. Until the world's population get completely vaccinated, COVID-19 will continue as a global public health with emergence of resistant variants. Patients with comorbid conditions like diabetes, obesity, cardiovascular disease, and chronic kidney disease are at greater risk of developing such infections. The management and prevention of such highly transmissible viral illness requires holistic and professional approaches including specialties, physicians, pharmacists, nurses and government authorities. COVID vaccines are effectively safe, but the emergence of new variants has led to a decrease in their efficacy. WHO, GAVI and Covax are making significant efforts to carry out mass immunization to control and end the pandemic. Despite advances in the production of vaccines, there are several obstacles to improve the vaccine's effectiveness, which include safety, efficacy for different variants, and sustained antiviral immune responses. Approval of Covid vaccines and vaccine acceptance among people are the major steps in combating SARS-CoV-2. With the rise in new variants, strategies have been developed to fight against the upcoming variants, including approval of antiviral pills and microneedle delivery systems; however, not yet clinically approved. Both come with a major advantage

of non-invasive methods of drug administration and reducing vaccine hesitancy. Also, the newly approved mix and match vaccines have become highly effective and have made global implications. It also showed stronger immune response in immunosuppressed individuals. Most vaccines appear to be safe and effective, but a double doses or higher are recommended. More research is needed to investigate the long-term safety and efficacy of the vaccines. Of all vaccines, m-RNA vaccines have been mostly used, but its limitation of being unstable and maintaining ultracold chain storage has led to limited access to remote areas. In contrast, VLP vaccines could be the next-generation vaccines; however, maximum studies are still in Phase I. As the viruses are known to mutate rapidly, making other vaccines ineffective, the VLP bearing surface proteins can be modified to fight against the emerging variant virus. Further, their stability can be enhanced by formulating into nanoparticle VLP, and they do not require cold chain storage.

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Code availability Not applicable.

Declarations

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