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SPECIAL ISSUE: REVIEW

The Post-COVID Era - Advances and Challenges in Pharmacology

Recent review of COVID-19 management: diagnosis, treatment and vaccination

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Abstract

The idiopathic Coronavirus disease 2019 (COVID-19) pandemic outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reached global proportions; the World Health Organization (WHO) declared it as a public health emergency during the month of January 30, 2020. The major causes of the rise of new variants of SARS-CoV-2 are genetic mutations and recombination. Some of the variants with high infection and transmission rates are termed as variants of concern (VOCs) like currently Omicron variants. Pregnant women, aged people, and immunosuppressed and compromised patients constitute the most susceptible human population to the SARS-CoV-2 infection, especially to the new evolving VOCs. To effectively manage the pathological condition of infection, the focus should be directed towards prevention and prophylactic approach. In this narrative review, we aimed to analyze the current scenario of COVID-19 management and discuss the treatment and prevention strategies. We also focused on the complications prevalent during the COVID-19 and post-COVID period and to discuss the novel approaches developed for mitigation of the global pandemic. We have also emphasized on the COVID-19 management approaches for the special population including children, pregnant women, aged groups, and immunocompromised patients. We conclude that the advancements in therapeutic and pharmacological domains have provided opportunities to develop and design novel diagnosis, treatment, and prevention strategies. New advanced techniques such as RT-LAMP, RT-qPCR, High-Resolution Computed Tomography, etc., efficiently diagnose patients with SARS-CoV-2 infection. In the case of treatment options, new drugs like paxlovid, combinations of β-lactum drugs and molnupiravir are found to be effective against even the new emerging variants. In addition, vaccination is an essential approach to prevent the infection or to reduce its severity. Vaccines for against COVID-19 from Comirnaty by Pfizer-BioNTech, SpikeVax by Moderna, and Vaxzevria by Oxford-AstraZeneca are approved and used widely. Similarly, numerous vaccines have been developed with different percentages of effectiveness against VOCs. New developments like nanotechnology and AI can be beneficial in providing an efficient and reliable solution for the suppression of SARS-CoV-2. Public health concerns can be efficiently treated by a unified scientific approach, public engagement, and better diagnosis.

Keywords SARS-CoV-2 · COVID-19 · Pharmacology · Complications · Vaccines · Repurpose drugs · Novel · Diagnosis and treatment

Abbreviations

ACE 2	Angiotensin-converting enzyme 2
AI	Artificial intelligence
AIGS	Automatic integrated gene detection system
CDC	Centers for Disease Control and Prevention
cDNA	Complementary dioxyribo nucleic acid
COVID-19	Coronavirus disease 2019

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CRISPR–Cas12	Clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 12
FDA	Food and Drug Administration
ICU	Intensive care unit
IT	Information technology
MERS-CoV	Middle East respiratory syndrome coronavirus
NAAT	Nucleic acid amplification tests
qRT-PCR	Quantitative reverse transcription-polymerase chain reaction
RBD	Receptor-binding domain
RT-LAMP	Reverse transcription loop-mediated isothermal amplification
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS	Transmembrane protease, serine 2
USFDA	United States Food and Drug Administration
VOI	Variants of interest
VOC	Variants of concern
VOHC	Variants of high consequence
VbM	Variant being monitored
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
WHO	World Health Organization

Introduction

The viruses are intracellular parasites that always emerge suddenly and infect numerous people within a short interval of time. The initial severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic occurred in 2002, followed by the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012, and SARS-CoV-2-triggered coronavirus disease 2019 (COVID-19) during the month of December 2019 [1, 2]. According to the World Health Organization's (WHO) updates on COVID-19 cases, there have been over 601 million identified as positive COVID-19 cases and 6.4 million deaths as of 2nd September 2022, with the numbers continuing to rise [3].

Several factors lead to complications in COVID-19 management. These include social factors (like vaccine hesitancy [4], effect of social inequities on healthcare [5], lack of social protection [6], etc.), economic factors (economic inequalities) [5], an outbreak of other infectious diseases (like monkeypox, severe acute hepatitis, multi-organ failure, black fungus eye infection, etc.). The monkeypox outbreak is currently complicating the COVID-19 management scenario [7, 8]. In a similar context, another outbreak of severe acute hepatitis of unknown etiology in children is reported in United Kingdom, regions of America, Western Pacific, South East Asia, and Eastern Mediterranean [9]. Additionally, environmental factors are also found to be associated with complications in COVID-19 management like pollution, chemical exposures, climate, and built environment [10].

The US government has constituted the SARS-CoV-2 Interagency Group (SIG), which categorizes the variants of the virus into three distinct categories—(1) Variant being Monitored (VbM), (2)Variant of Interest (VOI), and (3)Variant of Concern (VOC). There is also a fourth category in this classification, (4) Variant of High Consequence (VOHC). However, no VOHC has been identified in the US, till date [11]. Presently, the prominent VOCs are the different lineages of the Omicron variant [12–14]. The WHO has also classified the SARS-CoV-2 variants under same categories like VOI, VOC, and VOHC.

The SARS-CoV-2 virus has five different structural proteins. The spike (S) glycoprotein that makes up the virus's envelope surface is the main structural protein involved in interaction with the host cells' angiotensin-converting enzyme 2 (ACE2) receptors to enable the entrance of infectious virus particles [2]. The reports in this context reveals that the most successful medications are those that target the interaction of S glycoprotein with the ACE2 receptor [15]. However, the Omicron variant of this virus not only exhibits stronger binding with the ACE2 receptor unlike the other variants but also shows an evolved mode of invasion into the host cell in the Transmembrane protease, serine 2 (TMPRSS2) independent approach, through the endosomal route [16]. Furthermore, the BA.1 and BA.2 variants of Omicron favor the TMPRSS2-independent endosomal entry route. This corresponds to specific regions on the spike protein leading to the alteration in antigenicity and could be an important factor in rapid transmission and changes in pathogenicity of the Omicron variants [17]. The altered entry route of Omicron variants facilitate infection into several different animal species such as horseshoe bat, mice, domesticated avian species, etc., increasing the susceptibility to reverse zoonosis [16]. In the latest report of WHO, it was found that the Omicron variant constituted the 99.6% sequences reported for the period of 29th July 2022–29th August 2022 [18].

A recent study reported that the replication complex of this virus is the fastest RNA-dependent RNA polymerases among all classes of coronavirus [19]. Because of the fast elongation mechanism, it is liable to include mismatch mutations easily producing high variability in genomic sequences giving rise to numerous strains with different features. This further increases the difficulty of designing an efficient drug to target the virus [20]. Although the virus has faster transmission rates, the mutation rates are relatively lower at

1×10^{-6} per cycle than influenza viruses which have a mutation rate of 3×10^{-5}. It is due to the linear genome (instead of segmented) and the presence of proofreading (nsp14) that are absent in influenza viruses. The lower mutation rate of SARS-CoV-2 facilitates the development of vaccines with a longer duration of protection than influenza viruses [21, 22].

The generation of new variants of a virus follow two basic mechanisms—random point mutations (Alpha, Beta, Gamma, Mu, Delta, and Omicron have evolved by this approach) and recombination (coronaviruses, influenza virus, HIV, etc.) [14, 23, 24]. The factors responsible for genetic diversity, in the case of coronaviruses, are mutations coupled with recombination, horizontal gene transfer, or gene duplication. Homologous recombination and gene transfer contribute to the larger genome by increasing plasticity for the gain and modification of genes [25]. This results in coronaviruses gaining the ability to explore new hosts via the interaction between their spike protein and various cellular receptors of the host. This attributes to natural selection and the evolution of viruses [26]. The B.1.1.7, B.1.351, P.1, and B.1.1.529 lineages corresponding to alpha, beta, gamma, and omicron variants that are found to have high transmission rates [27]. The B.1.617.2 variant, also known as the Delta variant is a highly infectious variant responsible for the second wave of COVID-19 in India [28, 29] and had become the dominant variant globally in 2021 [30]. The different strains of the virus show different patterns of disease prognosis [31].

It has now become crucial to study the development of novel hybrid strains of the virus that can potentially magnify the situation of a pandemic by rapidly increasing the number of clinical cases positive. Three recombinant strains of omicron variants have been identified to date, namely, XD, XE, and XF. The recombination between delta and BA.1 lineage of omicron had led to the development of XD, whereas XF is formed by the recombination between BA.1 and UK delta variants [23]. The BA.4 and BA.5 variants of Omicron are important in its evolutionary trajectory. Though these variants possess similarities with BA.2, they contain unique mutations like L452R and F486V in the spike proteins. These variants can infect people who are immune to other variants of the virus, including Omicron, and increase hospitalization [32]. The monthly report of WHO for the month of August 2022 also stated that currently, the BA.5 lineage of Omicron is found to be dominant globally, with an increase in incidence to 78.2% per week [18].

The emergence of new variants of concern resulting from mutations in the viral genome has become a great problem in the treatment of infection and prevention by vaccination. This is because many of the widely used repurpose drugs and some vaccines are rendered ineffective when used against the new variants. There is a list of monoclonal antibodies (anti-RBD monoclonal antibodies) that are clinically used against various variants of Omicron. For example, VIR-7831 (sotrovimab), COV2-2196 and COV2-2130 (AstraZeneca), etc. However, their efficacy is greatly reduced due to the high mutation rate of S protein of the new variants of the virus in addition to the fact that monoclonal antibodies are specifically designed to target S protein [13].

To effectively manage the transmission of the SARS-CoV-2 virus in the population it is important to educate and encourage people to adhere to the emerging norms and rules pertain to prevent the infection [33]. Additionally, the public governments need to send clear updates on COVID-19 without any confusion. [34]. The major goal to mitigate and manage COVID-19 is by effective prophylactic measures and prevention, and initiation of recording patients' immune responses from time to time with the help of healthcare personnel [35]. It also involves the introduction of innovative approaches by creating safe healthcare environment for the healthcare workers who are at risk.

The objective of this narrative study is to comprehensively understand the pharmacological and therapeutic domains of COVID-19 management. We aim to analyze COVID-19 management, pharmacological and therapeutical advancements as well as to provide a holistic picture of vaccination. We also discuss the major complications observed during COVID-19 and in the long COVID scenario as well as containment of the pandemic. Additionally, we have emphasized on the COVID-19 management approaches for the special populations like children, pregnant women, aged groups, and immunocompromised patients.

Current scenario: transition in COVID-19 management

The transition phase of COVID-19 is associated with many changes, it enhances the use of hand sanitizers, aerosols, surface sterilizing agents, cleaning solutions, PPE kits, face masks, and gloves [4]. It sparks the condition of health, age, including acceleration in innovation, collaboration, discovery, catalyzing future health and medicine, thereby reimaging health and medicine. It has opened a broad area of research in the field of medical technology including computational biology, gene sequencing, design, and delivery of antibodies and drugs [14, 36].

Diagnosis

The upsurge and spread of SARS-CoV-2 have given rise to severe threat to global public health. Reliable and rapid tests are needed to affirm infections. Currently, diagnostic approaches include clinical chest CT scanning including chest X-rays and laboratory diagnoses (Nucleic acid RT-PCR, RT-LAMP, qRT-PCR), protein testing, point of care

testing, and fluorescence-based biosensors tests are used to confirm COVID-19 [36, 37]. X-rays are one of the common techniques for imaging cardiothoracic and pulmonary disorders [38]. It played an important role in diagnosing pneumonia and assessing its severity. It has been discovered that CT scans of COVID-19 patients exhibit peculiar imaging with multilobar and aberrant peripheral distribution [39–41]. Nucleic acid testing involves reverse transcriptase-polymerase chain reaction (RT-PCR), which involves the generation of single-strand cDNA from RNA through retroviral DNA polymerase, accompany by PCR amplification of the target cDNA regions [42]. RT-qPCR is a highly specific, rapid, and molecular-based assay to detect infection [43]. It can also detect and measure negligible amount of antibodies from various samples [44]. Moreover, the WHO has approved some of the testing samples for laboratory purposes. In another technique, fluorescence-based biosensors are used for cheap and quick detection of antibodies in the serum [45].

The efficiency of these techniques can be improved by designing the combination of two or more methodologies. For instance, the integrated RT-LAMP and CRISPR-Cas12 method can prove to be an efficient, simple, and rapid test when designed in the form of a kit that could be used anywhere [46]. The advancement in technologies has resulted in up-gradation and improvement in the currently followed techniques making them more reliable, accurate, easy to perform, and cost-effective (Table 1). This is intending to provide benefits to a large number of people globally, irrespective of their economic status.

During the initial phases of the COVID-19 pandemic, a notable number of diagnostic companies were proactively involved in the design, development, validation, verification, and distribution of diagnostic tests. Hundreds of molecular tests and immunoassays were created quickly, albeit many are still awaiting clinical validation and approval by regulatory authorities. However, greater test refinements, substantial molecular epidemiological confirmation and official FDA certification, are still required. Furthermore, the data on biobanks and the follow-up of actual patients are insufficient. Therefore, AI and machine learning techniques for data interpretation must be created and used. To battle present and future pandemics, there must be a worldwide unity in terms of test availability, control of infectious diseases and diagnostic strategies. The person diagnosing should inform about the therapy selection and follow-up on its success. It is important to highlight that deep learning algorithms combined with imaging modalities provide only limited information regarding sick individuals. The global research scenario supports the fact that deep learning approaches cannot replace the function of physicians or clinicians in clinical diagnosis. Deep learning specialists hoped to collaborate proactively with radiologists and medical professionals in the near future to give adequate support systems for diagnosing COVID-19, particularly in the early stages of the disease, or evaluating the level of severity of the SARS-CoV-2 infection. Recently, it was found that the PCR assay, specifically the AIGS (Automatic Integrated Gene Detection System) RNA detection kit, can be used to test respiratory tract samples from COVID-19 patients for the presence of the Omicron variant. With the aid of this kit, it has been anticipated that 95.1% of all Omicron variant (BA.1 through BA.5) sublineages are prevalent [47]. This diagnosis is beneficial in identifying the individuals infected and history of infection. The specific antibodies against the SARS-CoV-2 nucleocapsid protein can be considered as a relatively early diagnostic biomarker. To quantify the specific SARS-CoV-2 immunoglobulins in SARS-CoV-2 positive and non-infected individuals, powerful, flexible, and sensitive biotools have been developed recently. These tools are based on the surface of magnetic microbeads functionalized with nucleocapsid (N) and internally expressed recombinant spike (S) proteins[48].

Prophylactic measures

Currently, there are few standard drugs available in the market that are recently approved by FDA in the USA; however, repurposing drugs is a beneficial solution, that provides a better, immediate strategy to tackle the disease. Presently available treatments include drugs of small size molecules that prevent the entry of the virus into host cells or prevent the assembly and block replication of viruses [13, 49–53]. The literature showed that remdesivir reduces the recovery time of hospitalized patients, thus reducing mortality [54]. Beigel et al. in their final report for the treatment of COVID-19 presented data on 1062 patients, where 541 patients were assigned with remdesivir and 521 on placebos. According to existing evidence, patients on treatment have an average hospitalization time of 15 days, whereas patients on remdesivir have an average hospitalization time of 11 days[55]. Chu et al. demonstrated the role of Lopinavir/ Ritonavir in the treatment of COVID-19 in 41 patients for 3 weeks. Clinical data suggested lower adverse effects in the treatment group than in the control. It has been seen that there is a reduction in infection rate and steroid usage where the patients were treated with Lopinavir/ Ritonavir combination. Thus, patients treated with these drugs show a decrease in viral load and a rise in blood cell count, thereby ensuring a positive outcome and better recovery [56]. Arbidol was found to be a more effective drug as compared to lopinavir, meta-analysis studies reveal a conversion rate of SARS-CoV-2 nucleic acid on day 7 ($p=0.03$) and day 14 ($p=0.006$). Further, it showed a higher improvement rate on day14 ($p=0.02$) and a lower rate of mortality ($p=0.007$)[57]. Mehra et al.analyzed chloroquine with and without macrolide for treatment,

Table 1 The diagnostic tests for the detection of SARS-CoV-2 including their advantages and disadvantages

Diagnostic test	Principal of detection	Advantages	Disadvantages	Remarks	References
Rapid diagnostic tests	It is a type of serological testing that detects antibodies produced on exposure to the virus. Contrary to this, it could also base on the detection of antigenic viral proteins in patients' samples	•Relatively inexpensive •Provides immediate results	•May provide false-negative results	Less sensitive than nucleic acid-based tests	[171]
RT-PCR	It depends on the enzyme Reverse transcriptase that amplifies the fragment of interest specifically. When testing for the SARS-CoV-2 virus, the first complementary DNA (cDNA) is synthesized using Reverse transcriptase followed by PCR reaction	•Rapid detection	•Can produce false-positive and false-negative results •High-purity sample •Expensive laboratory equipment •Trained specialists •Long reaction time	RT-PCR offers the highest sensitivity and specificity than the nucleic acid tests	[172, 173]
RT-LAMP (Reverse transcription Loop-mediated isothermal amplification)	4 or 6 primers bind specifically to 6 regions on the DNA of interest. When accompanied by one-step reverse transcription, considerably reduces the time of viral detection	•Does not require specialized types of equipment •Faster (result in 30 min) •One-step RNA amplification	•Under development process •Can result in false positive by generating carry-over contamination	It has high specificity and sensitivity comparable with PCR	[46, 173, 174]
RT-qPCR	SARS-CoV-2 specific primers and probes are selected. The probes anneal between both sets of the primer. The Taq polymerase degrades the probe, releasing dye that emits fluorescent signals	•Specific •Detect even a single fragment	•Reliability of result depends on standardization of measurements •Expensive	Using the SARS-COV-2 R-GENE Kit and primers for RNA-dependent RNA polymerase, it has a maximum sensitivity of about 97.9% and a minimum sensitivity of about 60.2%. (RdRp)	[175–177]
CRISPR-Cas12 based assay	The CRISPR-Cas12 system detects the E and N gene sequences on the amplified viral DNA and cuts-off other sequences	•Easy to read the colorimetric result	•Few standardized assays are available	It is quick, easy, sensitive, and specific when compared to conventional molecular diagnostics (MDx), such as PCR	[46, 178]
High-Resolution Computed Tomography	It is a non-invasive detection technique that generates cross-sectional images by using several X-ray detections on the patient's chest from various angles	More efficient and reliable	•Expensive equipment •Requires professional help or doctors for the evaluation •Does not independently diagnose COVID, but is used for screening •Exposure to X-rays can be harmful	The sensitivity and specificity of CT were 68% and 57%, respectively, compared to other PCR and diagnostic kits	[173, 179]

total of 96,032 patients with COVID-19 were hospitalized, 14,888 patients were selected, among them 81,144 people were there in the control group and 1868 and 3016 received chloroquine and hydroxychloroquine alone, whereas 3,782 and 6,221 patients received both drugs in combination with a macrolide. Unfortunately, the observed outcome showed a negative result as treatment with these drugs decreases survival and increases the frequency of arrhythmias.

Cathrine et al. in their randomized trials on chloroquine and hydroxychloroquine has found that hydroxychloroquine increases the mortality risk in COVID-19 patients; moreover, there is no benefit of chloroquine in the treatment [58].

Recent research indicates that favipiravir can reduce inflammatory mediators but not respiratory status fully. SARS-CoV-2 respiratory distress is hypothesized to be caused by both direct viral activity and chemical mediators generated by SARS-CoV-2. In some patients, inflammation and cytokine storms persisted following Favipiravir therapy, although they were manageable with steroids [59].

Currently, molnupiravir is approved by U.S. Food and Drug Administration (USFDA) for the management of COVID-19 [60]. Molnupiravir is an oral bioavailable ribonucleoside analog of B-D-N4-Hydroxycytidine [61]. It acts as an antiviral agent showing a broad spectrum of activity against various RNA viruses. Molnupiravir inhibits the replication of viruses; it has been found that molnupiravir is highly effective for limiting nasopharyngeal viral load. B-D-N4-Hydroxycytidine-5-Isopropyl ester is a prodrug of molnupiravir (EIDD1931); after entering into the host cell, this active form of drug inhibits the replication of viruses by incorporating itself into the virus instead of uracil or cytosine. These base-pair changes lead to mutation, resulting in a viral replication error[50]. Research demonstrates that molnupiravir has been effective against various influenza and coronavirus variants[62]. Results from Phase I/II/III trials revealed that molnupiravir reduces the risk of death and hospitalization for mild COVID-19 patients. Studies on animals indicate that the administration of molnupiravir in humanized mouse models significantly reduces in vivo replication and symptoms of SARS-CoV-2 in patients[63]. During a pandemic wave dominated by the omicron BA.2 subvariant, the cohort study conducted by Wong et al., sought to assess the virological effects in relation to the consumption of molnupiravir or nirmatrelvir–ritonavir in hospitalized patients with mild-to-moderate COVID-19. Molnupiravir was administered to 1,856 of the 40,776 COVID-19 hospitalized patients. Molnupiravir-treated patients were shown to have a decreased risk of death from all causes. When compared to non-receptors, receiving molnupiravir or nirmatrelvir–ritonavir was linked to considerably lower odds of all-cause death and the overall disease progression outcome, as well as a decreased need for oxygen therapy [64]. The reduction in the mortality rate was greatly visible in patients with higher risk of hospitalization, such as those above 80 years in age [65]. In the same study, 890 patients were administered Paxlovid, the results indicates that this drug was also efficient in lowering the mortality rate [64]. Paxlovid is a combination of the second-generation protease inhibitor nilmatrelvir and the pharmacological enhancer ritonavir for the treatment of SARS-CoV-2 infectious. Paxlovid acts as an active protease inhibitor, exerting antiviral efficacy by inhibiting the virus replication process [66].

Biological products such as pAbs (polyclonal antibodies), mAbs (monoclonal antibodies), convalescent plasma, and hyperimmune γ-globulin are used as passive immunotherapy for the treatment of COVID-19 [67]. Repurposed mAbs are also used for the treatment, of hospitalized patients 12 years of age or older. Likewise, mAbs such as bamlanivimab–etesevimab, casirivimab–imdevimab, and sotrovimab are administered. It acts by neutralization of the viral proteome and by balancing the number of cytokines. Patients who are hospitalized are not given mAb therapy, and patients with hypoxia are excluded. The drugs utilized for the treatment of COVID-19 are summarized in Table 2. The research community is focusing on developing SARS-CoV-2 specific antivirals and mAbs; many of them are under different stages of clinical trials.

Administration of neutralizing monoclonal antibodies offers a prompt and passive immunization, that can reduce virus load and result in the rearrangement of immune-modulatory molecules. The monoclonal antibodies are capable of eliciting an immune response. Currently, clinical studies are going on ruvalizumab which is a recombinant monoclonal antibody that targets CS. It acts as an anti-inflammatory agent. Other mAbs under ongoing clinical trials include AK119, JMB2002, LY-CoVMab, ADM03820, HLX70 and DXP604. USFDA approved a few mAbs for emergency use in COVID-19 including tocilizumab (TCZ), regdanvimab (CT-P59), sotrivimab (VIR-7831), SCT-401 and levilimab. The mAbs that work against various variants (alpha, beta, gamma, delta and omicron) of coronavirus include sotrovimab, tixagevimab plus and cilgavimab, casirivimab and imdevimab [67].

Vaccination

Immunization plays an important role in preventing and limiting the spread of disease, to bring down this pandemic, a large proportion of the world needs to be vaccinated. According to recent data, 66.8% of the world population have received at least one dose of a COVID-19 vaccine and 12.15 billion doses have been administered globally [68]. Various vaccines have been discovered worldwide, including mRNA vaccines based on the introduction of mRNA sequences for disease-specific antigens, and DNA-based, attenuated, and vector-based vaccines are used, as they

Table 2 Common drugs prescribed for the treatment of COVID-19

Name of the drug	Type of drugs	Mechanism of action	Clinical trial outcomes	Remarks	References
Umifenovir	Antiviral	Inhibits viral replication	Reduce the viral load to zero during clinical trials	It has been determined that umifenovir is ineffective in some variants of SARS-CoV-2 in patients	[180, 181]
Favipiravir	Antiviral	It effectively prevents RNA-dependent RNA polymerase from becoming active	The primary outcome was the effect of favipiravir on reducing the time to viral clearance within 15 days of starting the treatment compared to the placebo group	Demonstrated effectiveness against several SARS-CoV-2 variants including delta and omicron	[182–185]
Remdesivir	Antiviral	It is a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp)	Clinical state differed statistically significantly after a 5-day regimen of remdesivir	In numerous in vitro studies, Omicron, Delta, and other new SARS-CoV-2 variants were discovered	[62, 186, 187]
Ribavirin	Antiviral	By attaching to the nucleotide-binding site of the enzyme, inhibits viral mRNA polymerase	Ribavirin was supposed to be effective in curing coronavirus illness due to its broad-spectrum suppression of RNA viruses	Variants that are both susceptible to and resistant to ribavirin have been discovered in increasing numbers	[188–190]
Ivermectin	Anti-parasitic	The intracellular key transport is the ivermectin acts by inhibiting host importin alpha/beta-1 nuclear transport proteins	Except in clinical trials, the Panel advises against using ivermectin to treat COVID-19	Regardless of the strain or variant of concern, alpha, beta, gamma, delta, or omicron, ivermectin demonstrated a rather homogenous in vitro action against SARS-CoV-2	[191]
Camostat	Serine protease inhibitor	Suppress SARS-CoV-2 invasion in lung cells by inhibiting the virus-activating host cell protease TMPRSS2	According to a pilot finding in clinical trials, camostat may also be useful in treating the most severe COVID-19 instances accompanied by organ dysfunction	It blocks several serine proteases linked to the SARS-CoV and SARS-CoV-2 viruses	[192, 193]
Nafamostat	Proteolytic inhibitor	Nafamostat inhibits MERS-CoV infection by blocking TMPRSS2 activity, which prevents membrane fusion between both the virus and human cells	The antiviral efficacy of nafamostat suggests that it has the potential to be an effective COVID-19 therapy option	This drug is effective against SARS-CoV-2 and MERS-Cov	[194]
Famotidine	Histamin blocker	Competitive histidine H-receptor antagonist	Decrease of inflammation within the body and reported earlier alleviation of symptoms	This drug is effective against SARS-CoV-2	[195]
Molnupiravir	Monoclonal antibody (mAbs)	It is a unique nucleoside analog with wide antiviral efficacy against SARS-CoV and SARS-CoV-2. Molnupiravir prevents the replication of many viruses	Based on clinical trial data, it appears that molnupiravir operates as a mutagenizing agent that induces an "error catastrophe" during viral replication	It has been demonstrated that molnupiravir works well against SARS-CoV-2 variants other than the Omicron type	[196, 197]

Table 2 (continued)

Name of the drug	Type of drugs	Mechanism of action	Clinical trial outcomes	Remarks	References
Babtelovimab	Monoclonal antibody (mAbs)	A recombinant neutralizing human IgG1 monoclonal antibody called bamlanivimab binds to the receptor-binding region of the SARS-CoV-2 spike protein and stops the spike protein from attaching to the human ACE2	In comparison to the placebo, bamlanivimab plus etesevima lowered the rate of hospitalization and deaths attributable to Covid-19 and hastened the reduction in SARS-CoV-2 viral load	All COVID-19 variations of interest, including BA.2, the strain that is currently dominant in the United States, are responsive to bebtelovimab	[198, 199]
Casirivimab	Monoclonal antibody (mAbs)	The clinical therapy of coronavirus disease is proposed to use neutralizing antibodies in COVID-19	Various variants of the SARS-CoV-2 spike protein's many epitopes are targeted by antibodies	It shows a better response against SARS-COV -2	[200–202]
Sotrovimab	Monoclonal antibody (mAbs)	This antibody binds to an epitope on the SARS-CoV-2 spike protein receptor-binding domain (RBD), where it blocks an unidentified process that happens after viral attachment but before the fusing of the viral and host cell membranes	It is still unknown how immunization affects the safety and efficacy of sotrovimab	It shows a better response against SARS-COV -2, but 20-fold less effective against omicron variant	[203–205]
Tixagevimab	Monoclonal antibody (mAbs)	It consists of a mixture of two human monoclonal antibodies, tixagevimab (AZD8895) and cilgavimab (AZD1061), both of which are directed against the surface spike protein of SARS-CoV-2	It maintained antiviral activity and reduces hospitalizations by more than 50% in non-hospitalized individuals	Without any obvious safety issues, AZD7442 was effective in preventing Covid-19 with a single dose	[192, 206, 207]
AT-527	Antiviral	It act as an Guanosine Nucleotide analog	Undergoing clinical trial for efficacy in COVID-19	It has been shown to be effective against Hepatitis C virus and can play role in SARS-CoV-2	[50]
Niclosamide	Antihelmint drug	It decreases the replication of virus by inhibiting S- phase kinase associated protein activity	Undergoing clinical trial for efficacy in COVID-19	It inhibits COVID-19 infection and decrease cytokine stroms in COVID-19 patients	[50]
Dexamethasone	Corticosteroids drug	Suppress Immune System	Found to be effective in COVID-19 patients	Improve recovery, prevent cytokine stroms in COVID-19 patients, decrease inflammmtion and fluid retention in lungs	[50]
Artesunate	Antimalarial	It decreases the replication of viruses	Found to be effective in COVID-19 patients	It's a combination of two drug such as Artesunate and pyronaridine and shows a broad spectrum of antimalarial activity	[50]

provide a promising, faster, and cheaper alternative to conventional approaches. Different types of vaccines are shown in Fig. 1. Even vaccines for veterinary usage are approved in different parts of the world to seize transmission from household pets [69].

The inactivated vaccine consists of whole virus particles that have been killed or inactivated by heat or chemicals such as formaldehyde or formalin, thus destroying the pathogen's ability to replicate, though they retain some epitopes so that the immune system can still recognize it [70]. The attenuated vaccine contains active pathogens particles that have been weakened or modified by attenuation but can replicate inside the body eliciting a long immune response. Subunit vaccines use only part of an antigen that stimulates an immune response. Another class of vaccine includes toxoid vaccines, conjugated vaccines, and Nuclei acid vaccines like RNA, and DNA vaccines which use a piece of mRNA or DNA to produce the same antigenic molecules as a disease-causing pathogen [71]. Table 3 summarizes details of approved vaccines for the prevention of COVID-19.

The US Food and Drug Administration has just fully approved the Pfizer/BioNTech vaccine for human use, while 38 vaccine candidates are undergoing emergency use licensing [72]. Almost 60% of the world population, i.e., around 12 billion vaccine doses have been injected with a single vaccine dose as of May 2022. Since SARS-CoV-2 vaccines follow quick regulatory paths, vaccinovigilance (Phase 4 of the clinical trial) and the development of a comprehensive

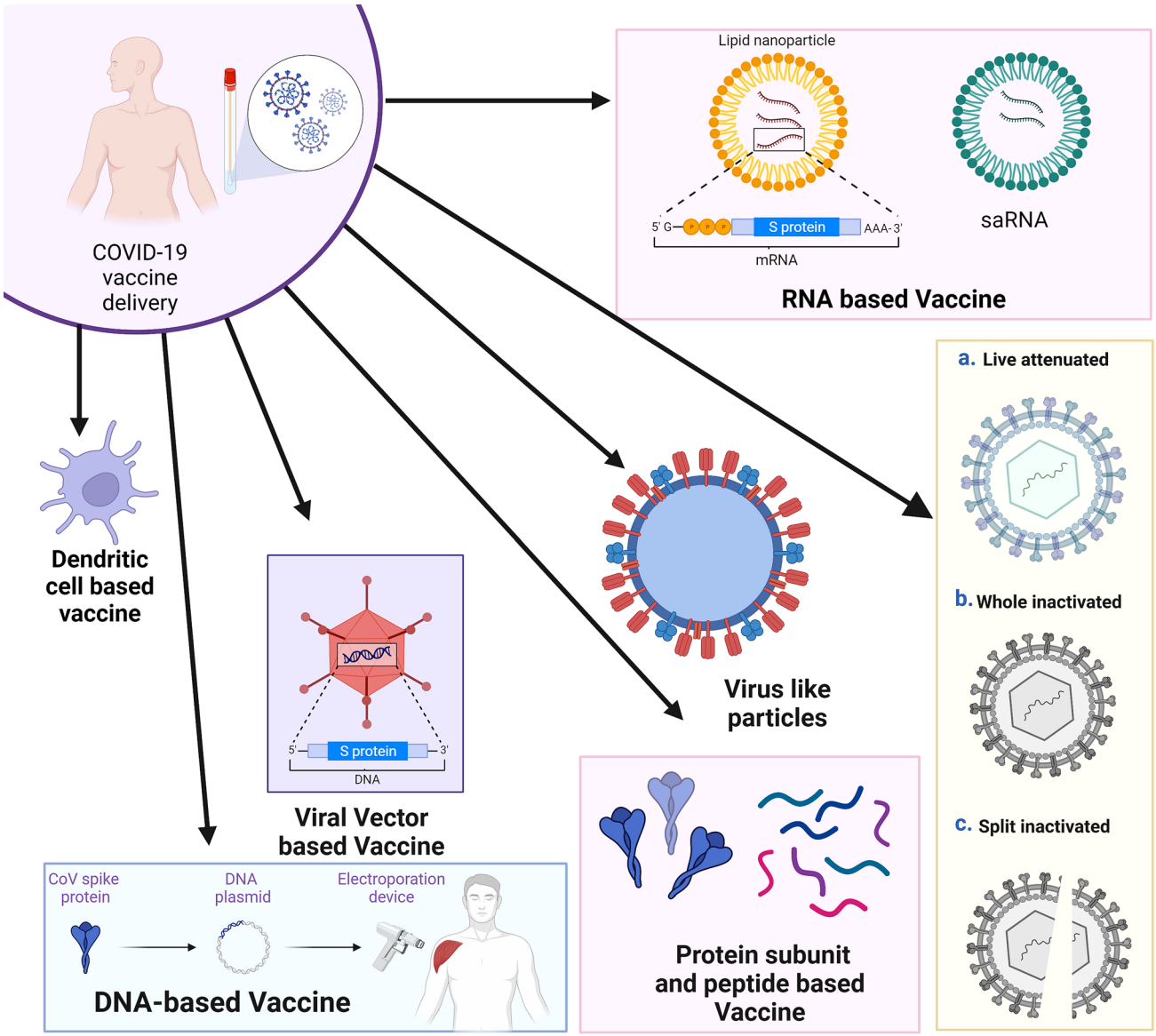

Fig. 1 Different types of vaccine platforms explored for the COVID-19. (Created with Biorender.Com)

Table 3 Details of approved vaccines for the prevention of COVID-19

Vaccines	Brand	Details	Remarks	References
RNA/DNA Vaccines	Comirnaty	Pfizer- BioNTech Developed by German company BioNTech and the American company Pfizer	•FDA Approved mRNA vaccine (August 23, 2021) •Intramuscular injection •87.9% effectiveness against symptomatic disease caused by the delta (B.1.617.2) variant •87.0–93.4% against beta variant •95.0% effectiveness against symptomatic disease caused by the alpha (B.1.1.7) variant •35% against omicron variant	[208, 209]
	Spikevax	Developed by American company Moderna, US National Institute of allergy and infectious diseases, US biomedical advanced research, development authority and coalition for epidemic preparedness innovations	•Intramuscular injection •FDA Approved mRNA vaccine (January 31, 2022) •95% efficacy in preventing COVID-19 infection	[210]
	ZyCoV-D	It is a plasmid-based vaccine, developed by the Indian pharmaceutical company Cadila healthcare, the biotechnology industry research assistance council	•Efficacy to be 67.6% against symptomatic COVID-19 •DGCI approved •DNA plasmid vector vaccine •Intradermal injection	[211]
Adenovirus vector vaccines	Covishield/ Vaxzevria	Oxford Astra Zeneca, developed by the British university of oxford, British Swedish company AstraZeneca, coalition for epidemic preparedness innovations	•Intramuscular injection •66.1–70.4% against beta variant •59.8% against the delta variant •62.1–76.0% effective against the alpha variant	[209, 210]
	Jcovden, Johnson & Johnson	It is a vector vaccine, produced by Janssen pharma, beth Israel deaconess medical center	•Viral vector vaccine •FDA Approved vaccine •66.1% effective against the alpha variant •85% efficacy in preventing severe COVID-19 •100% efficacy in preventing hospitalization or death caused by the disease	[209, 210]
	Sputnik V	It is a vector-based vaccine, produced by the Russian Gamaleya research institute of epidemiology and microbiology	•91.6% effective against the alpha variant •Combination vector vaccine •Overall efficacy of the vaccine above 97.8%	[209, 212]
	Sputnik light	It has an Ad26 vector, developed the by Russian Gamaleya research institute of epidemiology and microbiology	•A vaccine based on recombinant adenovirus type 26 (rAd26) vector •70.2% efficacy in preventing severe COVID-19	[213]
	Convidecia	Developed by the Chinese company CanSino Biologics and the Beijing Institute of Biotechnology of the academy of military medical sciences	•Phase III trials completed •Single dose viral vaccine •65.9% efficacy in preventing moderate symptoms of COVID 19	[214]

Table 3 (continued)

Vaccines	Brand	Details	Remarks	References
Inactivated virus vaccines	Covaxin	It is developed by the Indian company Bharat Biotech in collaboration with the Indian council of medical research national institute of virology	•65% effective against asymptomatic cases •8.1% effective against symptomatic disease •65.2% effective against delta variant •ICMR approved	[215]
	Sinopharm BIBP	It is produced by the China national pharmaceutical group, Beijing institute of biological products	•Phase III trials completed •78.2% effective against symptomatic cases •74.0% effective against asymptomatic cases •78.1% effective against the alpha variant	[216]
	CoronaVac	Produced by Chinese company Sinovac Biotech	•66.0% effective against symptomatic COVID-19 •89% against hospitalization •WHO approved	[217]
	VLA2001	It is an inactivated vaccine developed by French biotechnology company Valneva SE and Dynavax technologies	•Whole inactivated viral vaccine •Phase III trial completed with approx 4000 persons •EMA approved	[218]
	Sinopharm WIBP	Developed by China's national pharma group, the Wuhan Institute of biological products	•72.9% effective against symptomatic cases •Phase III trials completed	[219]
	CoviVac	Produced by the Chumakov center at the Russian Academy of Sciences	•Phase I/II trial started •Required two doses •Transported and stored at normal refrigerator temperature	[220]
	QazVac	It is also called as QazCovid-in vaccine, developed by a research institute for biological safety	•Phase III trials continue •Stored at standard refrigeration temperatures •Safe and no adverse effect	[221]
	Minhai PPV23	It is an inactivated vaccine, by Minhai biotechnology Co, Shenzhen Kangtai biological products Co. Limited China	•Injected intramuscular •Approved by national regulatory authorities •Phase III trials started	[222]
	COVIran Barekat	By Shifa Pharmed Industrial Co	•Injected intramuscular •Approved by national regulatory authorities •Phase III trials showed safe and effective results •Trials going on children	[223]
	Chinese Academy of medical sciences COVID vaccine	It is developed by the Chinese academy of medical sciences	•Injected intramuscular •Approved by China authorities	[224]
	FAKHRAVAC	It is an inactivated vaccine, developed in Iran by the defensive innovation and research organization	•Injected intramuscular •Phase III trials continue •Approved by Iran authorities	[225]
	Turkovac	Developed by the health institute of turkey, Erciyes University	•Phase III trials completed •Approved	[226]

Table 3 (continued)

Vaccines	Brand	Details	Remarks	References
Subunit vaccines	Novavax, Covovax	It is a subunit vaccine, developed by Novavax and coalition for epidemic preparedness innovations, undertrials in India	•89.3% (phase III US) effective against the alpha variant •93.6% (phase III trial US/Mexico) effective against the beta variant	[227]
	Abdala	Developed by the center for genetic engineering and biotechnology in Cuba	•Phase III trials completed •Injected intramuscular •Approved •92.2% efficacy rate •Phase I/II trials for children continue	[228]
	MVC-COV1901	It is a protein vaccine that is actually made in Taiwan by Dynavax technologies and Medigen vaccine biologics	•Recombinant S-2P spike protein •Injected intramuscular •Immune-bridging trial continues	[229]
	EpiVacCorona	The Russian state research institute for virology and biotechnology, Vector, invented the peptide vaccine	•Injected intramuscular •Phase III trials completed •Ineffective against delta variant	[230]
	Zifivax	Anhui Zhifei Longcom Biopharmaceutical developed the adjuvanted protein vaccine	•Uzbekistan approved (1 March 2021) •Efficacy of 82.0% against the disease of any severity (August 2021) •93.0% against the alpha variant •78.1% against the delta variant	[231]
	Soberana	It is a conjugated protein vaccine, by Finlay Institute in Cuba	•91.2% effective after two doses •Approved for the children aged 3–18 years old	[228]
	Corbevax	Developed by Texas children's hospital in Texas	•Phase III trials completed •Approved	[232]
	COVAX-19	It is also called as SpikoGen, developed by Vaxine and CinnaGen	•Recombinant protein subunit vaccine •Approved by Iran •Clinal trials completed	[233, 234]
	Razi Cov Pars	Developed by Razi Vaccine and Serum research institute	•Recombinant protein-based vaccine •Approved •Three doses, two intramuscular and one intranasal spray	[235]
	Sinopharm CNBG COVID 19	It was actually created by the Chinese national Biotec Group	•It is a recombinant vaccine •Intramuscular injected	[236]
	Soberana plus	It is a conjugate vaccine produced by the Finlay institute	•Efficacy 91.4% against symptomatic cases	[237]
	Noora	It is a protein subunit vaccine that was developed by Baqiyatallah University of Medical Science	•Recombinant vaccine •Intramuscular injected	[238]
	SKYCovione	SK Bioscience developed the protein-based vaccine	•Recombinant vaccine •Approved	[239]

*The information provided in the table is according to the latest data and survey (September 2022)

vaccination program are essential for the protection of public health. Vaccination is the safest method for combating the COVID-19 pandemic. According to a recent press release by US FDA, they have authorized limited use of Johnson and Johnson (J&J) COVID-19 vaccine for the individuals that are 18 years or greater in age but do not have access to the approved vaccines as well as to those who opt for J&J vaccine [73]. Almost 7.7% of the US population has taken primary vaccination with the J&J vaccine. The reports define the safety concern relating to rare events of blood clots reported previously also for the adenovirus-based vaccines [74]. This reaction is triggered by antibodies to aggregates generated between adenovirus and platelet factor 4. This aggregate is bound by antibodies, resulting in platelet activation. The sequence of events leads to the life-threatening step, i.e., thrombosis with thrombocytopenia syndrome. A recent report has been made for other vaccines like AZD122, which indicates that the population vaccinated with these vaccines experience skin rashes, characteristic vesicular plaque formation, muscle weakness, pitting edema on the hands, and foot neuropathic pain [75]. FDA officials concluded the revision based on the detailed investigative reports submitted for such post-vaccination events as well as data on the safety and efficacy of the vaccine. There is currently a boom in mRNA clinical research for infectious diseases, especially as the impact of mRNA-based technologies is becoming apparent as these first-generation vaccines are deployed globally. This prompts industry researchers and experts to see increased interest in other therapeutic areas, especially mRNA platforms in oncology and rare autoimmune diseases and neurodegenerative disorders. In contrast to the initial SARS-CoV-2 virus, the Omicron (B.1.1.529) variant of concern has shown to be more contagious and infectious [76]. Ad26.COV2.S or BNT162b2 vaccine recipients exhibited long-lasting spike-specific CD8 + and CD4 + T cell responses that displayed significant cross-reactivity against both the Delta and the Omicron variants[77]. Multiple doses of vaccine has been proven to be efficient in eliciting immune response against several variants of the virus. In the same context, a booster dose is intended to restore vaccine efficacy from the immune protection point that has been determined to be insufficient. A third booster dose is also being advised currently because, in the words of Agrawal and colleagues, "Omicron symbolises a significant challenge to the existing two-dose vaccination tactic currently adopted by many countries globally (17–22-fold reduction in neutralization titers)"[78]. There are various mRNA vaccines available commercially and among them the effectiveness of the BioNTech/Pfizer BNT162b2 messenger RNA (mRNA) vaccine against the Omicron variant was examined by Muik et al. [76]. According to their findings, three doses of BNT162b2 mRNA are inevitably mandated to defend against Omicron-driven COVID-19 [76].

In December 2020, the alpha variant was confirmed as a variant of concern. It can be also written as B.1.1.7. The variant has a total of seventeen variations in its genome and was found to increase its transmissibility rate [79, 80]. Beta variant (B.1.351) was detected in South Africa (May 2020). It contains three mutations located in RBD. More recently omicron (B.1.1.529) has been detected in multiple countries (Nov 2021), it has more mutations that are located in the receptor-binding domain [81]. WHO approved various vaccines for emergency use. These vaccines can be categorized based on their manufacture and mode of action. Table 3 summarizes details of approved vaccines for the prevention of COVID-19.

Lauring et al. conducted a study to compare the effectiveness of mRNA vaccines and to characterize the clinical severity of covid19 patients with different variants of viruses. A total of 11,690 population participated and the outcome shows that the mRNA vaccine has the effectiveness of 85%, 94% and 65% for alpha, delta and omicron variants, respectively. Finally, the mRNA vaccine was effective over almost every variant of coronaviruses. Therefore, vaccinated people show lower severity against COVID-19 [82].

On January 2021, drug regulators in India granted emergency approval for the covid vaccine co-developed by AstraZeneca and the university of Oxford. Mahadevaiah et al. in their study of immunogenicity, safety, and efficacy of covishield vaccine, showed seropositivity of 69.67% which is an acceptable level of safety profile[83]. Another study on BNT162b2 mRNA vaccine phase III clinical trial consist of 43,548 individuals, among 17,411 individual 8 cases of COVID-19 positive were identified, and among 17,511 individuals 162 COVID-19-positive cases were confirmed showing 95% of vaccine efficiency [84]. BNT162b2 efficacy in volunteers aged between 16 and 55 years was 95.6% and for individuals above 55 years, above or equal to 65 or 75 years of age, efficacies were found to be 93.7%, 94.7% and 100%. Lindsey conducted a phase III trial in the United States across 99 centers for checking the efficacy and safety of mRNA vaccines. The setup consists of 30,420 individuals who were randomly administrated with vaccines or placebo in a ratio of 1:1. The mRNA vaccines showed a 94.1% efficacy rate at preventing COVID-19 infections [85].

SARS-CoV-2 impact on children, pregnant women, and aged populations

The COVID-19 caused by the SARS-CoV-2 virus infect people from all age groups; however, there are variations in severity observed. The symptoms of infection observed in children on exposure to the virus is similar to adults and sign and symptoms include fever, cough, sore throat, malaise, nasal discharge, sometimes vomiting, nausea, body pain and

diarrhea [86]. The major observation is that in the majority of cases the infected children are asymptomatic. These children are carriers for transmission to other age groups with greater susceptibility [87]. However, the severity is more in children with chronic conditions like cancer, chronic pulmonary or heart disease, neurological diseases, known immunodeficiency, or cardio-vascular diseased condition [87, 88]. The infection caused in children is mild and the severity is lower than that of adults with an exception of infants who on exposure to the virus experiences serious illness [87, 89]. The severe health implication in children during COVID-19 infection is in the form of the multisystem inflammatory disorder [88] and it is thought that as the virus is transitioning from pandemic to epidemic, a greater proportion of children will be affected by the SARS-CoV-2 infection like in the scenarios of other epidemic coronaviruses [90].

In the case of pregnant women, it was found that the symptomatic patients are more susceptible to serious disease conditions and can have adverse pregnancy with neonatal outcomes like pre-term delivery or intrapartum fetal distress [91, 92]. On the contrary, expecting mothers with asymptomatic COVID-19 infections faced complications similar to non-infected ones [92]. The novel variants with high transmission rates are a threat to the health of pregnant women and neonates. To protect them from the disease and complications, it is essential to prioritize vaccination and immunization schedule [93].

It is found that aging is accompanied by immunosenescence which is diminished activity of the immune system. On the other hand, the aged population also shows constant production of inflammatory mediators and cytokines [94]. In patients, who are 65 years and above, SARS-CoV-2 infection shows a high mortality rate in addition to more percentage of hospitalization [95, 96]. Chronic conditions like cardiovascular diseases, diabetes, obesity, etc., are the risk factors that increase the virus infection [96].

Immunocompromised patients and patients with comorbidities are found to be at greater risk of mortality and complications during hospitalization than the normal population [97, 98]. The infection can alter their primary disease condition which worsens their situation [97]. Such people are more likely to be admitted to intensive care units (ICUs) and have an increased risk of mortality. This category includes people with conditions like cancer, hematopoietic cell transplant, solid organ transplant, diabetes mellitus, hypertension, etc.[97, 99]. The disease pathogenesis in such patients is very rapid and serious, irrespective of the age group of patients (Fig. 2) [99]. Thus, it is a major cause of concern today to save the lives of immunocompromised patients and patients with comorbidities.

Some monoclonal antibody treatment regimes (like bamlanivimab–etesevimab, casirivimab–imdevimab and sotrovimab) have been authorized for emergency use for patients with 2 more risk factors. These factors include age above 65 years, pregnancy, immunocompromised patients, patients with comorbidities or chronic conditions like hypertension, diabetes, obesity, etc. Therefore, monoclonal antibody based treatment is appropriate for the above mentioned special groups in the population [67]. Molnupiravir-based treatment is also applicable for the patients with high risk of hospitalization, older age groups and patients with chronic health conditions. However, it is not recommended for pregnant and breast-feeding women and children [100]. According to the USFDA, The Moderna COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine may be used for COVID-19 prevention in children as young as 6 months old under emergency circumstances [101].

COVID-19 and associated complications

The SARS-CoV-2 virus affects the lower respiratory tract. The pathological symptoms range from asymptomatic (mild infection) to severe complications, which could eventually become life-threatening. Mild symptoms are cured in about a week [102]. Patients from the older age group, having chronic health conditions or compromised immune system are more prone to severe infection which could also lead to death [102, 103]. However, even the younger population without any pre-existing health condition has been found to develop severe infections. The major causes of mortality due to this infection include hypoxemia and cardiovascular complications which could lead to anomalous blood clotting. Cases with strokes, kidney injury, cardiac injury, and ecchymosis are attributed to disseminated intravascular coagulopathy[102].

The COVID-19 is also linked with the initiation of autoimmune responses. Development of autoimmune thyroid diseases, Guillain–Barre syndrome, autoimmune hemolytic anemia, Kawasaki disease, immune thrombocytopenic purpura, and identification of autoantibodies indicates that SARS-CoV-2 virus is capable of generating autoimmune responses. However, more research is required in this domain for a complete understanding of the potential impacts of this virus on the host body [104].

SARS-CoV-2 pathogenesis comprises multiple factors that result in severe damage, first in the lungs and then with systemic dissemination. Acute lung failure, acute liver failure, acute kidney damage, and cardiovascular illness, in addition to a wide spectrum of hematological abnormalities and neurological problems are characteristics of multi-organ dysfunction (Table 4) [105]. The most important pathways are linked to SARS-CoV-2 and indirect pathogenic properties. Even though the presence of ACE2, a SARS-CoV-2 receptor, has been confirmed in the lung, heart, kidney, liver, and nervous system, there are some worries about

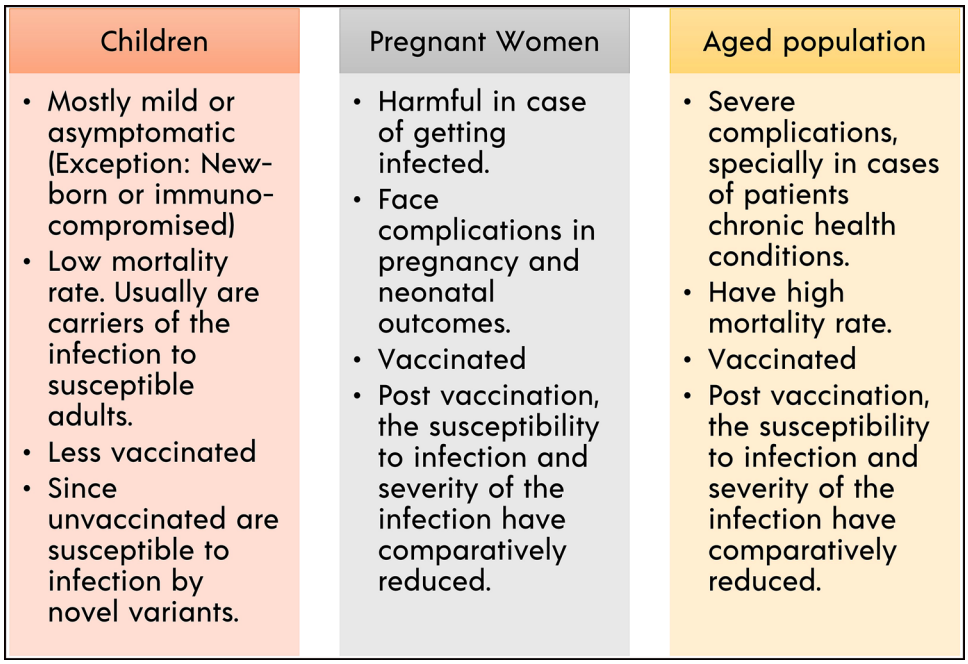

Fig. 2 Basic differences explaining the variations in the impact of infections in the 3 categories of population

the presence of SARS-CoV-2 RNA in these organs [106]. COVID-19 has the greatest impact on the lungs, heart, brain, kidney, liver, and gastrointestinal tract. As a result, measures should be taken, and patients should be consulted before they are discharged from the hospital to understand other possible anomalies that may emerge during the post-COVID healing phase [107]. One of the numerous variables is an increase in the rates of blood clots reported in COVID-19 patients, which will cause a slew of downstream difficulties. Another major explanation for the rapid development of mucormycosis is the use of steroids as a treatment for seriously and critically sick covid patients [107, 108]. Many COVID-19 patients who have recovered reveal hypercoagulation diseases ranging from disseminated intravascular coagulation to venous thromboembolism, all of which can contribute to cerebrovascular illness. Signs and symptoms of the antiphospholipid syndrome include antiphospholipid antibodies and the lupus anticoagulant, as well as venous and arterial thrombosis [109]. Cardiovascular problems can arise during the post-COVID recovery period, resulting in cardiac arrest and, in extreme circumstances, a heart attack. COVID-19 is an inflammatory illness that also causes blood vessel inflammation. An increase in blood thickness occurs, which leads to clot formation in the lungs and heart arteries, producing symptoms such as shortness of breath, very rapid or slow heart rate, dizziness, and unconsciousness in those recovering from COVID-19 [110, 111]. After recovering from COVID-19, patients with moderate to severe symptoms from SARS-CoV-2 infection have various organ damage and additional consequences. Patients with a history of various health issues or illnesses are more likely to have serious consequences. Mental health issues have emerged as a result of the extended epidemic, which is caused by multiple lockdowns and stay-at-home situations [14].

Limitations of COVID-19 management

The SAR-CoV-2 virus-caused pandemic has a significant impact on every aspect of life around the world, including society, politics, the economy, health, and professional fields.. This results in numerous challenges in these domains. The major challenge to controlling the pandemic is the mass vaccination of people. Despite the fact that 66.8% of the world's population has received at least one dose of vaccine, the entire course of vaccination is necessary to control the global epidemic.This requires increasing the production of vaccines which can be done by constructing more manufacturing units and obtaining suitable quantities of the required raw materials. The aim should be to provide vaccines to all especially in low-income countries, which are unable to afford them. In addition to infrastructural challenges in the production of vaccines, there are also certain limitations associated with its efficacy against all variants of the virus. To ensure the development, approval, dissemination, administration, and monitoring of efficient vaccines, there are also strict policy matters and challenges that have to be looked upon [112]. The health care centers, procuring necessary oxygen cylinders and quarantine facilities should be well equipped in advance, with all these requirements and necessities to prevent the rise in mortality, specially in cases where

mutations in the virus leads to development of variants of concern which could have catastrophic effect on the population. For instance, the situation of delta variant which claimed numerous lives resulted in second or third wave of infection in many countries.The facilities should be designed and constructed focusing on effective operation during the situation of emergency. Some of the important factors for operational design are healthcare networks, patient safety, indoor air quality, etc. The designed facilities should have the capacity and necessities for critical care for terminally ill patients [113]. It is also discovered that front-line employees and healthcare professionals face a variety of difficulties throughout their careers, including increased workload, psychological stress, a lack of high-quality personal protective equipment (PPE), social exclusion and stigmatization, an absence of incentives, a lack of coordination, and improper management. [114]. The improper disposal of contaminated wastes like PPE kits, gloves, etc., also poses an important challenge as these become a cause of environmental pollution and a source for transmission of infection [115, 116]. Thus, it results in a new environmental crisis. This can only be controlled by promoting sustainable plastic waste management and implementing policies to ensure the safe disposal of harmful wastes [113]. Many new challenges arise as a result of the emergence of omicron virus subvariants. Although BA.4/5 is significantly (4.2-fold) more resistant, it is also more likely to cause infections that result in the development of vaccine-resistant strains. The SARS-CoV-2 Omicron lineage is still evolving, producing subvariants that are not only more contagious but also quite resistant to antibodies[117]. There has been a geographical divide observed in the prevalence of different variants of Omicron, dominant over different regions of the world. The high percentage of positive cases in Europe and other continents can be attributed to this high transmissibility rate, for example, the BA.2 variant of Omicron. According to preliminary findings from Denmark's Statens Serum Institut (SSI), BA.2 is 1.5 times more highly infectious than BA.1. The high transmissibility of BA.2 was demonstrated in Denmark, where the number of positive cases doubled in less than a week. [118]. In Gauteng, the omicron variant prevailed over the B.1.617.2 (delta) variant and accounted for 98.4% of all new cases sequenced in South Africa in December 2021[119]. Following the initial Omicron (BA.1) peak in January 2022, the almost total replacement of Omicron BA.1 by BA.2 resulted in a second peak in SARS-CoV-2 infections and previously unheard-of levels of infection in England in March 2022[120]. In lower-income nations, there are still nearly one billion unvaccinated individuals as of May 22, 2022. 70% of the population has been vaccinated in only 57 nations, almost all of which are high-income nations[121].

Innovative and novel approaches for COVID-19 management

The discovery of new drugs, vaccines, repurposing of drugs, in vitro drug screening, in silico screening platforms, development of new technologies, and novel diagnostic techniques have added new directions to the field of science. Artificial intelligence (AI) is one of the most emerging areas of research, which provides a new direction to research and development leading to the identification and development of new drugs [122, 123]. It involves early detection and diagnosis of the infection via CT scanning, X-ray, lab testing, and genome sequencing. It shows a tremendous capability for contributing toward novel drug discovery and repurposing of available drugs that could be used for treating COVID-19 [124, 125]. It utilizes several datasets to identify potential inhibitory human coronavirus activities [126]. Recently, it has been noticed that due to side effects and reduced efficiency of many drugs there is a decline in the number of new FDA-approved drugs. Earlier the process of drug discovery was very costly and sophisticated, however, it has been seen that AI can accelerate various scenarios including repurposing and drug discovery. AI helps us to determine the protein structure of the virus and, thus, plays an important role to determine its function inside the cell for the development of drugs and vaccines to combat COVID-19 [127]. AI is being used successfully for the identification, diagnosis, and treatment of disease. Further, it helps in contact tracing, finding the risk of mortality, and discovering new drugs and vaccines, moreover reducing the burden on healthcare workers [128]. The list of companies using AI for the development of treatment against COVID-19 by repurposing drugs includes Innoplexus, gero, healx, and deargen. Exscientia lktos and SRI International are some of the companies that developed new drugs by applying AI for the treatment of COVID-19 [125].

Drug repurposing is also known as repositioning of the drug [129]. It is a procedure that seeks to identify new application and utilities of existing drugs and is considered a cost-effective approach [130]. The outbreak of COVID-19 has challenged health workers, scientists, and pharmacists to select an appropriate drug for treatment; however, discovery of new vaccines and drugs was costly and time-consuming with a success rate of only 2.01% [129], hence considering the cost and time lag, the repurposing of drugs for the treatment of COVID-19 came into existence. The systematic approach to drug repurposing can be classified into computational and experimental approaches [131]. Several drugs used for the treatment of different stages of COVID-19 include lopinavir, hydroxychloroquine, atazanavir, nintedanib, tocilizumab, and remdesivir [132, 133].

Table 4 Complications identified with COVID and Long COVID effects in humans

Complication	COVID associated or post-COVID	Reasons	Management	Remarks	References
Happy Hypoxemia	COVID associated	It is caused due to abnormal blood clotting. The micro-thrombosis of pulmonary vasculature occurs on activation of pulmonary endothelium which leads to the development of hypoxemia	•Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a therapy that can replace cardiopulmonary function temporarily and improve the hypoxemia condition	This condition wherein the arterial blood has abnormally low oxygen is an indicator of the COVID infection	[102, 240]
Acute respiratory distress	COVID associated	It is caused by damage to the alveoli. The fluid from blood vessels enters the alveoli through the damaged walls which consequently leads to inflammation inhibiting the normal gaseous exchange in the lungs	•Oxygen therapy •Breathing support like ventilators, and non-invasive ventilation •Drugs like acid-reducing medicines, antibiotics, blood thinners, muscle relaxants, and sedatives	The most prominent complication on the occurrence of the infection	[102, 241]
Cardiovascular complications	COVID associated	It is caused by the binding of the spike protein of the virus with the ACE 2 receptor on the endothelial cells, cardiomyocytes, and pericytes in the heart leading to direct infection by the virus The cytokine storm or enhanced immune response also is an important factor in the development of cardiovascular complications	•It focuses on supportive care and infection control •An early diagnosis is an important approach •Antiviral therapy •AVOId non-steroidal antiviral drugs	Increases mortality and causes cardiovascular injuries, including myocarditis, cardiac rhythm abnormalities, endothelial cell injury, thrombotic events, and myocardial interstitial fibrosis in COVID-19 patients	[102, 107]
Cytokine storm and inflammatory response	COVID associated	It is triggered by the entry of the virus into the host cell which consequently leads to acute respiratory distress and finally death	•Immunosuppression by immune-modulatory drugs like hydroxychloroquine additionally inhibits the replication of the virus	The hyperinflammatory responses in the infected host result in myocardial injury and increased death rates	[107, 242]
Multi-organ complications	COVID associated	It is mainly attributed to the fact that multiple organs (like kidney, heart, and liver in addition to the heart) in the body contain the ACE 2 receptor which binds to the Spike protein of the virus. These organs during the progression of infection fail and consequently lead to the death of the patients	•Effective anti-viral therapy •Supportive interventions •Hospitalization of symptomatic patients with pneumonia-like symptoms •Oxygen/ breathing support •Pharmacotherapy	Multi-organ complications precede multi-organ failure which ultimately causes death	[243]

Table 4 (continued)

Complication	COVID associated or post-COVID	Reasons	Management	Remarks	References
Autoimmune responses	COVID associated and post-COVID	The virus triggers autoimmunity by cross-reaction with the host cells and disturbs the self-tolerance of host cells	•Initiation of early treatment on early diagnosis •Immuno-modulatory drugs	The COVID-19 infection is similar to autoimmune disorders in terms of pathogenesis, immune response, and mechanisms The COVID-positive patients showed the presence of autoantibodies which are prevalent in autoimmune disorders	[244]
Long-term psychiatric sequelae	Post-COVID	Develops during hospitalization or quarantine period as it affects the psychology of patients	•Regular follow-up check-ups for 30 or 60 days •Diagnosis in 14–90 days posts infection	Patients may develop post-traumatic stress disorder (PTSD), insomnia, anxiety, and depression post-infection	[105]
Neurological complications	Post-COVID	Direct infection of the virus, systemic inflammation, cerebrovascular changes, or a combination of these factors	•Neuropsychological testing of patients to identify symptoms	It is accompanied by a loss of smell and taste. The findings suggest that systemic inflammation plays a crucial role in neurological complications	[105]
Dermatological complications	Post-COVID	Viral infections can cause dermatological complications that could last for 6 months	•The hair loss can be reversed by using medications like minoxidil, finasteride, and topical corticosteroids	Reports on the development of rashes and hair loss in patients months after the infection. The commonly prevalent complication is cutaneous manifestation	[105]
Renal Complications	Post-COVID	Direct damage by a virus, systemic hypoxia, effects of inflammatory cytokines, and abnormal coagulation are the factors that could lead to complications	•Regular follow-ups with a nephrologist	It leads to new-onset renal dysfunction and certain cases could require renal replacement therapy	[105]
Gastrointestinal complications	COVID associated and post-COVID	SARS-CoV-2 is found to have prolonged fecal shedding and these complications imply replication of the virus in the gastrointestinal tract	•In the cases of survivors of the infection, the liver condition may take from weeks to months to normalize. A proper diet should be followed	Diarrhea, nausea, vomiting, abdominal pain, and loss of appetite are some long-term symptoms	[105]
Musculoskeletal complications	COVID associated and post-COVID	It is caused by direct infection by the virus as the skeletal muscle and synovial tissue also contain the ACE2 receptor for adherence to the virus	•Understanding the need for effective rehabilitation is critical in helping patients return to pre-infection mobility and function	The SARS-CoV-2 virus leads to the development of myalgias and arthralgias, unlike inflammatory arthritis. Severe COVID-19 infection causes catabolic muscle wasting because of systemic inflammation, prolonged bed rest, and malnutrition	[105]

Remdesivir was the first drug to be approved for the treatment of coronavirus disease. It acts as an analog of nucleoside mainly ATP that inhibits RNA polymerase [134]. It is an antiviral drug that inhibits the replication of the virus [135] and exhibits a wide antiviral spectrum among RNA viruses including ebolavirus, MERS-CoV, and SARS-CoV-2 [136]. Recently available evidence about the antiviral effects of remdesivir against viruses is majorly based on in vitro and in vivo studies [137]. Moreover, effective and positive studies against coronavirus led to the emergence use of the drugs during COVID-19 [138]. Lopinavir/ ritonavir is another class of drug which has been repurposed for the treatment of COVID-19, It acts as protease inhibitor used for treating HIV infection [139]. Currently, studies indicate that both these drugs can be useful in inhibiting SARS-CoV 3C-like protease enzyme [140].

Recent clinical trials on COVID-19 patients showed that nintedanib leads to a decrease in the expression of IL-1 and IL-6, which play a major role in the COVID-19 cytokine storm leading to fibrogenesis in the lungs [141]. It is given to COVID-19 patients who have Idiopathic Pulmonary Fibrosis, as it may provide a novel approach for managing COVID-19 [142]. Ivermectin is an FDA-approved anti-parasitic drug that is devised as an 80:20 mixture of the equipotent homologous 22,23-dihydro ivermectin, which has shown to inhibit SARS-CoV-2 in vitro with an undisclosed mechanism of action [143]. An extensive computational analysis was done to distinguish the best docking of ivermectins to viral proteins and, later, to analyze potential structural alterations with molecular dynamics. Ivermectins can bind to the protease 3CL-superficial and internal pockets, as well as the HR2-domain, causing unfolding/folding and altering the native conformation of these proteins [144]. Chloroquine (CQ), an aminoquinoline, for many years malaria was traditionally treated with chloroquine phosphate. It is a quinolone with anti-inflammatory properties as well as some amoebic properties. Chloroquine's anti-viral and anti-inflammatory activities may be responsible for CQ's efficacy in treating COVID-19 patients [145].

In an expanding pharmaceutical market collaboration between medicines, and regulators are essential. The regulatory agency needs to ensure the safety, efficacy, quality, and performance of medical products. National regulatory agencies are responsible for ensuring pharmaceuticals and biological products meet standards of quality and safety. A global training network on vaccine quality is also available to identify gaps and support plans. Other agencies like EMA, CHMP, COVID-ETF, SAWP, FDA, MAHs, and ICMR have been working in collaboration with each other to fight COVID-19 worldwide.

Nanotechnology is one of the emerging areas in the era of COVID-19. The study in this direction helps us to manipulate, organize and assay molecule and atomic level in nanometres. It converges various fields like biotechnology, computational biology, biological sciences, diagnosing and treating COVID-19. It is used for drug discovery and brings out new opportunities for inexpensive detection methods and vaccines against COVID-19. Several nanomaterials can be used for the prevention of COVID-19, such as the integration of nanomaterials into personal protective equipment kits that can protect health workers. Cellular binding of the viral particles can be prevented by targeting nanoparticles against ACE receptors, moreover, nanoparticle-based vaccines, and drug delivery systems can be used to prevent SARS-CoV-2 [146]. Nanosensors and nano-filter face masks can be used to prevent infectious diseases [147]. Recently field effect transistor-based biosensing has been developed to detect infection, Some nanomaterials like carbon black, graphene, gold, and silver particles are used in biosensors for detecting SARS-CoV-2 infectious [148]. However more research is needed to be done to find the application of nanotechnology in the era of this pandemic, safety measures must be encouraged as well as the use of nanoparticles for covid management must be accelerated. Moreover, expansion in the field of nanotechnology can help us to control and eliminate the spread and reoccurrence of COVID-19 [149].

Viruses invade humans via the nasal portal during inhalation, therefore researchers around the world are focusing on the vaccines that can prevent the aerosols which invade the nose. The intranasal vaccine can intercept the virus and triggers the immunity to combat the viruses at the site of viral entry, thus preventing the multiplication of viruses[150]. Nasal vaccines are easy to administer and produce secretory IgA, which can elicit an immune response at the site of virus entry[151, 152]. A recent study from India, which tested nasal vaccine, comparing it with mRNA and traditional vaccines, found that nasal vaccine can reduce replicating lower the viral load considerably, prevent inflammation and pneumonia more efficiently than other vaccines and can show higher neutralization capacities [153]. Nasal vaccines are sprayed into the nostrils, therefore can also be a solution for people who are reluctant to get vaccinated as it involves syringes. Another study from Hong Kong found that a single dose of nasal vaccine resulted in eliciting immune response in both the upper and lower respiratory tracts of hamsters, thereby preventing viral spreading [154]. Several other studies indicated that nasal vaccines can enhance systemic immunity. Fabispray recently received regulatory approval as part of the accelerated approval process. It is found that this spray can be effective in killing about 94% of viral load in the upper respiratory tract within 24 h of administration and within 48 h it can reduce viral load up to > 98%. According to a study conducted at the Utah state university USA, the nasal spray was found to kill 99.9% of the SARS-CoV-2 virus including all the variants of the coronavirus [155].

Recent clinical trial data show that a nasal vaccine consisting of nitride oxide is safe and effective to inhibit SARS-CoV-2 infection. King et al. in their studies on mice found that a single dose of intranasal vaccine administration can elicit both mucosal and systemic immune responses [156].

Frank et al. in their research study found that nasal spray with povidone-iodine exhibits anti-virucidal properties. A nasal spray containing povidone-iodine (1.25%) completely inactivates SARS-CoV-2 within 15 s of contact and this spray also provides a protection layer for up to 4 h, thus reducing viral loads and transmission of disease [157]. Some of the examples of nasal vaccines are ChAdOx1 nCoV-19, Ad5-nCoV vaccine, NasoVAX, DelNS1-nCoV-RBD LAIV, and Mv-014–212, these are currently in phase I and Phase II trials [150].

The scientific study reveals that a unified, scientific approach, public engagement, and better prophylactic measures are the three key steps to combat against such public health emergencies in the long run. This outbreak has led China and other nations to learn the importance of enhancing readiness to quickly detect and control the dissemination of evolving infectious disease. Ultimately, the biggest lesson learned from COVID-19, in our opinion, is that global pandemic regulation depends on the sustained pandemic response at local, international, and regional levels that is quick, efficient, synchronized, and efficient [158]. The current global pandemic has highlighted the importance of rapid reaction strategies at both the regional and international levels to prevent possible future outbreaks [159].

SARS-CoV-2 binds to its host receptor, angiotensin-converting enzyme-2, by the receptor-binding domain (RBD) of the spike protein. The RBD glycoprotein is a key target for the development of neutralizing antibodies and vaccines against SARS-CoV-2 [160]. Nanobodies are small size effective molecules which can be produced easily. Several recent studies showed that these nanobodies can bind to RBD thereby inhibiting and neutralizing the viruses [161]. Tingting Li et al. in their study demonstrated the protecting ability of nanobodies in mice from SARS-CoV-2. They constructed a potent antagonistic mechanism to block the RBD-ACE2 interaction. Using crystallography, they have tested the efficacy and analyzed the binding mechanism; furthermore, they developed an effective platform to produce neutralizing sybodies, with a higher neutralizing ability and stability making it suitable for the treatment of COVID-19 [162]. Other studies reported that sybody 23 shows high neutralization activity when binded to the recombinant RBD. An X-ray scattering model and cryo-EM structure of Sb23 indicate that it effectively blocks ACE2 binding [160].

Notable outbreaks include those caused by SARS-CoV-1, MERS-CoV, Ebola, and H1N1, and also the lessons learned from each: the value of good personal hygienic practices, testing when feasible, isolating those who are exposed to the virus, personal protective materials for healthcare professionals and many others related to the care of the infected persons and the exhaustive search for therapies and immunizations [163]. The COVID-19 pandemic has led the researchers, scientists, and medical practitioners to explore more areas in the field of animal and environmental research on the virus origin, epidemiological studies, clinical characterization and management, research in therapeutics and advancement, development of vaccine research and ethical considerations for the research [164]. The current global pandemic has highlighted the importance of rapid reaction strategies at both the regional and international levels to prevent possible future outbreaks [159].

Conclusion and future prospects

COVID-19 has posed a great challenge to the healthcare system, but it has also created an opportunity for the creation of new and innovative roles that could have far-reaching implications for the healthcare system. The COVID-19 outbreak has emphasized the significance of public healthcare as well as the need for novel strategies to mitigate global pandemics. The COVID-19 pandemic has emphasized on the significance of quick diagnosis [165]. Diagnostic approaches like Nucleic Acid Amplification Tests (NAAT) like RT-PCR are the most widely used approaches for the detection of SARS-CoV-2 infection, followed by Rapid Antigen Tests. However, they tend to provide false-positive and false-negative result, respectively [166]. Thus, the design and development of more reliable tools for efficient diagnosis of the infection is important. In the case of treatment options, newly developed drug, Molnupiravir is found to be efficient in treating Omicron variants. Some of the currently used drugs are found to be facing a reduction in their efficacies against the emerging novel variants and subvariants of the virus. In a similar context, many of the vaccines are also reducing their effectiveness. However, with the advancement in technology and a wide range of ongoing research in the domain of pharmacology and therapeutics, novel and reliable treatment and vaccination approaches are being developed. For enhanced mitigation and containment of the infection, a new strategy of Genomic surveillance is being applied. It involves sequencing (using next-gen sequencing tools) and phylogenetic analysis of the viral genome to study the evolutionary pattern of the variants and anticipate new variants. Consecutively, we can initiate containment approaches on time, in case of an outbreak of new variants [167]. This approach also helps to identify patients infected with multiple variants and understand the rearrangement of the viral genome to generate a hybrid. For instance, in the case of Deltacron infected patients, this hybrid was produced

in host patient's cells which were simultaneously infected with Delta and Omicron variants.

For efficient containment and management of the infection, it is necessary to conduct a mass vaccination drive on a global scale. With improvement in scientific understanding and research methodologies, novel personalized vaccines could be developed, considering the environment and susceptibility of an individual towards different variants of the virus.

The large-scale global research aims to develop different aspects associated with COVID-19 including diagnostic methods, treatment (development of specific large and small molecules) and vaccines are being considered by the support of different government agencies. Currently, according to the Clinical trial reports by the US government, there are about 4,653 ongoing trials [168].

It is crucial to raise the level of awareness and readiness among the persons of the targeted society, particularly the less skilled ones, as the COVID-19 vulnerability on a worldwide scale continues to emerge [169].

Due to the emergence of COVID-19, many digital sensing technologies were designed and developed. This led to the rapid development of new technologies and research concepts during COVID-19. High-performance infrared thermal cameras and smartphone software were developed by many countries and designed due to COVID-19 and it aids in the detection of fever [170]. Also, many IT and AI-based industries have made it easier to monitor people and stop the transmission of infection, which has aided in COVID-19 preparation [170]. AI might speed up the judicial process by analyzing health records, treatments, and lab results, which would enhance the monitoring of patients [34].

Consequently, AI might be developed to recognize lesions that resemble coronavirus infection, assess the thickness, volume, and structure morphology, and evaluate different lung lesions from the picture. Furthermore, the current growth trajectory of telemedicine is expected to continue in the post-pandemic era, since face-to-face physician appointments are not always possible in the atmosphere of the COVID-19 pandemic, patients have typically been contented with remote medical care service providers. During the pandemic, telemedicine facilities emerged as an effective healthcare delivery approach, and this trend is expected to continue in the future. As a result, telemedicine services can be easily adopted in the post-COVID-19 era. Until we discover efficient and medically verified therapeutics further than vaccines, the world battle against COVID-19 may last a long time [165]. Whenever it is feasible, smart working and remote work should indeed be followed. If this is not feasible, social segregation and safety precautions including protective gear, hygiene practices, and antimicrobials must be made available everywhere. To survive this challenging moment, innovations and development of feasible technologies for safeguarding the human population is necessary to combat emerging idiopathic infections [34].

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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