Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Role of genomics in combating COVID-19 pandemic

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ABSTRACT

The coronavirus disease 2019 (COVID-19) quickly swept over the world, becoming one of the most devastating outbreaks in human history. Being the first pandemic in the post-genomic era, advancements in genomics contributed significantly to scientific understanding and public health response to COVID-19. Genomic technologies have been employed by researchers all over the world to better understand the biology of SARS-CoV-2 and its origin, genomic diversity, and evolution. Worldwide genomic resources have greatly aided in the investigation of the COVID-19 pandemic. The pandemic has ushered in a new era of genomic surveillance, wherein scientists are tracking the changes of the SARS-CoV-2 genome in real-time at the international and national levels. Availability of genomic and proteomic information enables the rapid development of molecular diagnostics and therapeutics. The advent of high-throughput sequencing and genome editing technologies led to the development of modern vaccines. We briefly discuss the impact of genomics in the ongoing COVID-19 pandemic in this review.

1. Introduction

Coronavirus disease 2019 (COVID-19) has wreaked havoc on the world, costing millions of lives, severely affecting public health systems, and inflicting social and economic crises. It has rapidly spread globally, becoming one of the most devastating outbreaks in the history of mankind. As of December 3, 2021, there have been more than 263 million confirmed cases of COVID-19 and over 5.2 million deaths worldwide (https://covid19.who.int/). Continuous attempts are being made to effectively tackle this deadly disease. Being the first pandemic in the post-genomic era, advancements in genomics contributed a lot to scientific understanding and the public health response to the COVID-19, to a greater degree which was not feasible during the past outbreaks like 2002–2003 severe acute respiratory syndrome (SARS) epidemic. Genomic technologies have been employed by researchers all over the world to better understand the viral origin, outbreak dynamics, transmission, and evolution. Integration of genomics and other omics technologies played a crucial role in the development of new diagnostics, therapeutics, and vaccines.

Genomics is a branch of biology that focuses on the study of structure, function, mapping, and editing of the entire genome of an organism (McKusick and Ruddle, 1987). Genomics has many sub-disciplines such as structural genomics, functional genomics, comparative genomics, epigenomics, metagenomics, pharmacogenomics, and others, which use bioinformatics and computational tools to explore the characteristics of genomes. The advent of next-generation sequencing platforms has transformed genomics from a discipline into a technology that is commonly used in labs around the world to solve scientific problems. Genomics is now widely employed in medicine, research, biotechnology, and agriculture.

Abbreviations: ACE2, Angiotensin-Converting Enzyme – 2; COVID-19, Coronavirus Disease; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CSIR, Council Of Scientific And Industrial Research; GISAID, Global Initiative on Sharing All Influenza Data; ICMR, Indian Council of Medical Research; ICTV, International Committee on Taxonomy of Viruses; MERS-CoV, Middle East respiratory syndrome coronavirus; NGS, Next-Generation Sequencing; NSP, Non-Structural Protein; ORF, Open Reading Frame; PANGOLIN, Phylogenetic Assignment of Named Global Outbreak Lineages; PRF, Programmed -1 Ribosomal Frameshifting; RBD, Receptor-binding domain; RdRp, RNA-dependent RNA polymerase; RTC, Replication-Transcription Complex; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TMEM106B, Transmembrane protein 106B; TMPRSS2, Transmembrane Protease Serine 2; UTR, Untranslated region; VOC, Variants of Concern; VOI, Variants of Interest; WHO, World Health Organization.

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In this review, we provide a brief history of the identification of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and its origin, outlining how genomics helps in understanding the biology of SARS-CoV-2, and discuss the importance of genomic surveillance in tracking SARS-CoV-2 variants and their spread. Finally, we highlight how genomic data is exploited in the development of molecular diagnostics, therapeutics, and vaccines to combat COVID-19 (Fig. 1).

2. Identification of causative agent and its origin

In December 2019, a cluster of cases with atypical pneumonia of unknown etiology was reported in some of the local hospitals in Wuhan city of China (Wu et al., 2020). Initial investigations identified that the pathogen was a novel coronavirus (CoV) and named 2019-nCoV by the World Health Organization (WHO). The disease has spread around the world in a very short period and crossed one hundred thousand COVID-19 cases worldwide within two months. Then, COVID-19 was declared a pandemic by WHO on March 11, 2020 (as shown in Fig. 2). During the initial stages of the outbreak, sequencing of samples from patients led to the identification of the causative organism (Wu et al., 2020; Lu et al., 2020).

Identification of the origin and source of infection is very important to take necessary public health measures to reduce disease spread. The analysis of the viral genomic sequences, from Wuhan and surrounding areas, provided insights into the early transmission dynamics and enabled the determination of the times of origin and diversification (Li et al., 2020; Boni et al., 2020). Lu et al. (2020) reported that the sequences obtained from nine patients were highly similar, with more than 99.98% sequence identity. Analysis of sequence data revealed that the virus belongs to the genus *Betacoronavirus* and subgenus *Sarbecovirus* (Wu et al., 2020). Lu et al. (2020) showed that 2019-nCoV had a sequence identity of 79% with SARS-CoV and 50% with MERS-CoV. The virus was subsequently renamed as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) by the International Committee on Taxonomy of Viruses (ICTV) and the disease was named as COVID-19 (Coronavirus disease 2019) by WHO (Zhou et al., 2020b).

Phylogenetic analysis of genome sequences from SARS-CoV-2 and related viruses from other animals was carried out to determine the zoonotic origin of SARS-CoV-2. These investigations revealed that SARS-CoV2 was more closely related to two bat-derived coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 with more than 88% sequence identity (Lu et al., 2020). Zhou et al. (2020b) also showed that the genomic sequences were 96% identical to a coronavirus, BatCoV RaTG13 in horseshoe bat (*Rhinolophus affinis*). So far, the closest known sequence to SARS-CoV-2 was BatCoV RaTG13. Several studies identified SARS-CoV-2-related coronaviruses in Chinese pangolins (*Manis pentadactyla*) and Malayan pangolins (*Manis javanica*), but pangolin coronaviruses were less closely related to SARS-CoV-2 (with 85.5–92.4% sequence similarity) than bat coronaviruses (Lam et al., 2020; Liu et al., 2020). Most of the findings suggested that the bats could be the most probable natural reservoir for SARS-CoV-2 lineage (Andersen et al., 2020; Lu et al., 2020; Zhou et al., 2020b; Wacharapluesadee et al., 2021). Pangolins are suspected to be an intermediate host of SARS-CoV-2 due to sequence similarity between pangolin coronaviruses and SARS-CoV-2 (Lam et al., 2020; Liu et al., 2020; Xiao et al., 2020). Therefore, the comparative analysis of genomic and metagenomic data from various animal sources will be crucial in unraveling the origin and evolution of SARS-CoV-2.

3. Understanding the characteristics of SARS-CoV-2

In the early stages of the pandemic, genomic and proteomic analyses have proven helpful in understanding the mechanisms of viral entry and molecular interactions with hosts which are vital to the spread of the disease. SARS-CoV-2 is an enveloped, single-stranded, positive-sense, RNA virus with a genome size of ~29.9 kb classified under the genus *Betacoronavirus* in the family *Coronaviridae* (V'kovski et al., 2020). The genome comprises 5′ UTR, replicase (ORF1a/ORF1b), four structural genes, 3′ UTR, and a poly (A) tail (Hu et al., 2020). SARS-CoV-2 genome has 14 different open reading frames (ORF) which encode 27 proteins including 4 major structural proteins (Spike (S), Envelope (E), Membrane (M), Nucleocapsid (N) proteins) (Lokman et al., 2020). Apart from these, several ORFs encoding non-structural proteins (such as papain-

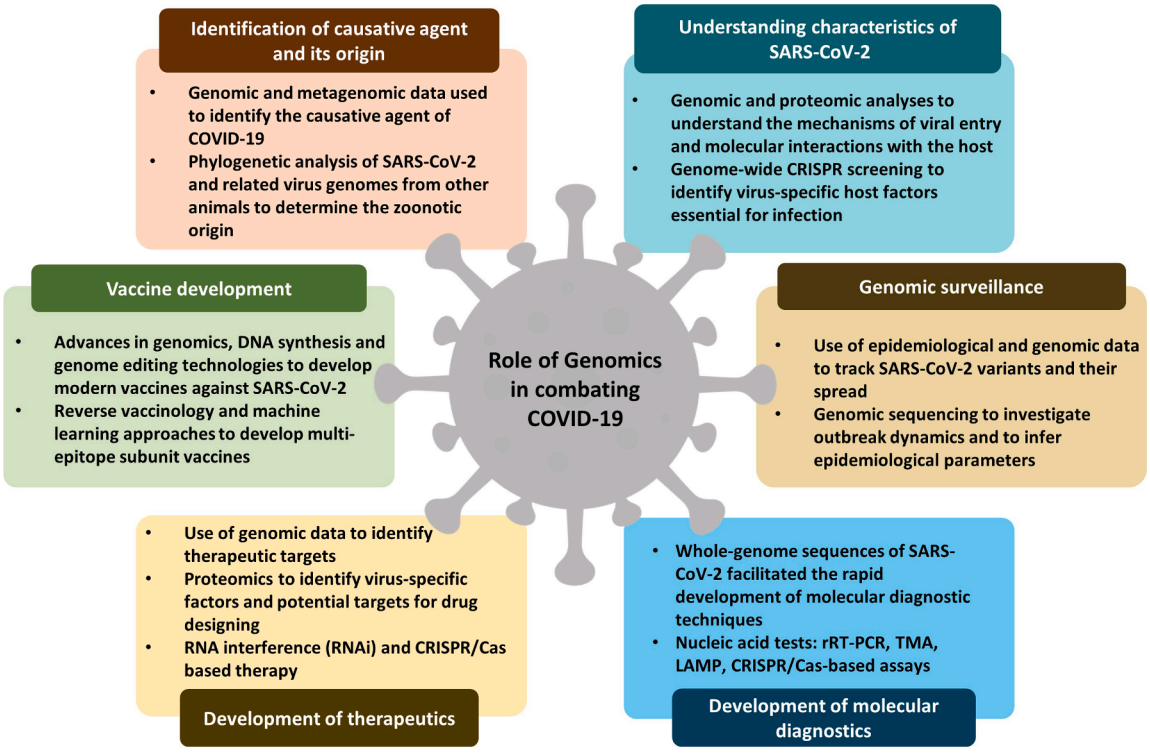

Fig. 1. A summary of various roles of genomics in the fight against COVID-19 pandemic.

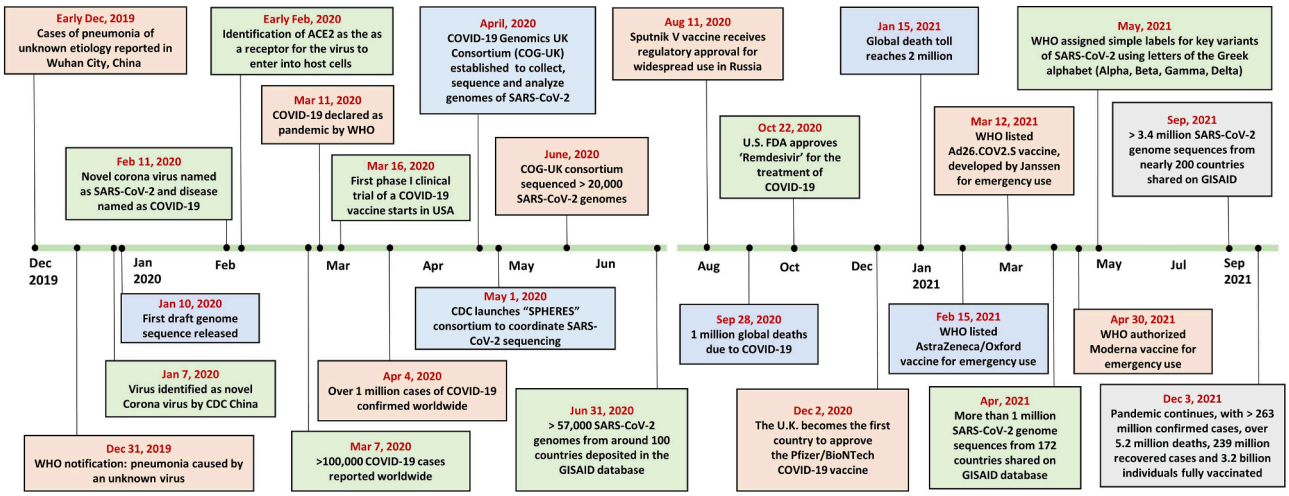

Fig. 2. Timeline of key events of COVID-19 and genomics, starting from the first report in December 2019 to the current situation as of December 2021.

like protease, 3-chymotrypsin-like protease, RNA-dependent RNA polymerase, helicase) and accessory proteins are distributed in the SARS-CoV-2 genome (Chan et al., 2020). These accessory proteins play a significant role in modulating host responses to infection, such as enhancing or inhibiting the production of pro-inflammatory cytokines, and are the determinants of the pathogenicity of the virus (Shang et al., 2020). The virus binds to the host cell using surface spike glycoproteins that comprise 2 functional subunits, S1 and S2. The receptor-binding domain (RBD) of the S1 subunit recognizes and attaches to the host cell receptor, while the S2 subunit is needed for fusion with the host cell membrane (Wrapp et al., 2020). Thus the Spike proteins were mostly used as therapeutic targets to prevent the entry of the virus into the host cells (Letko et al., 2020). SARS-CoV-2 and other related coronaviruses share genetic similarities in the spike protein RBD motif, which facilitated in identifying the cell entry receptor to which SARS-CoV-2 attaches, and hence the type of cells that it may infect. Experiments using reverse genetics methods have shown that the SARS-CoV-2 uses the same receptor angiotensin-converting enzyme 2 (ACE2) as SARS-CoV to enter into the human cells, but with higher affinity than the SARS-CoV virus (Letko et al., 2020). The spike protein is cleaved and activated by the host proteases mainly transmembrane protease serine 2 (TMPRSS2), cathepsin L1 (CTSL), and furin, which make necessary conformational changes for the fusion and entry of the virus into the target cell (Shang et al., 2020).

During the translation of the SARS-CoV-2 RNA genome, programmed −1 ribosomal frameshifting (PRF) is a critical step in which the translational reading frame is switched at the junction of ORF 1a and 1b (Bhatt et al., 2021). PRF is necessary for the synthesis of RNA-dependent RNA polymerase (RdRp) and downstream proteins which are crucial for virus propagation. The replication-transcription complex (RTC) and RNA-dependent RNA polymerase (RdRP) activity facilitates a more complicated replication and transcription process in coronavirus genomes than in other kinds of RNA viruses. RNA polymerase synthesizes complementary negative-strand RNAs from the positive sense template genomic RNA (gRNA). The continuous replication leads to full-length gRNAs, whereas discontinuous jumping of RdRP is called template switching which yields subgenomic RNAs (sgRNAs) with shared 5′ and 3′ ends. Next-generation sequencing (NGS) and nanopore sequencing technologies enabled the researchers to identify hundreds of template switches and to construct the subgenomic landscapes of SARS-CoV-2 (Wang et al., 2021). As a result, the molecular basis for deciphering subgenome synthesis and developing new antiviral drugs will be laid. Understanding the structural biology of the viral proteins is also very essential for improving therapeutic and preventive measures. Proteins are the prime targets in immunological interventions since they are the key factors responsible for viral pathogenicity (Naik et al., 2020). Sequence-based prediction studies generated a vast amount of data on SARS-CoV-2 proteins and their interactions with other molecules. As of December 2021, the PDB repository (https://www.rcsb.org/) contains 1640 files related to SARS-CoV-2. Genome-wide CRISPR (clustered regularly interspaced short palindromic repeats) screening has uncovered several key features of SARS-CoV-2 including the virus-specific host factors that are essential for infection (Wei et al., 2021). For example, TMEM106B is a lysosomal protein that acts as a proviral host factor for SARS-CoV-2 infection (Baggen et al., 2021). Availability of genomic and proteomic information along with the *in-vitro* and *in-vivo* studies enabled the researchers to better understand the characteristics of SARS-CoV-2.

4. Genomic surveillance

The pandemic has opened a new era of genomic surveillance, wherein scientists are monitoring changes of the viral genome in real-time to understand the evolution of SARS-CoV-2 and to predict the emergence of new variants at the global and national levels (Cyranoski, 2021; Joonlasak et al., 2021). Genomic surveillance involves the use of epidemiological, genomics, and phenomics data to monitor the emergence of new strains and to track pathogen transmission and evolution (Lo and Jamrozy, 2020). Both genomic and epidemiological information should be brought together promptly to guide public health and social measures (PHSMs), diagnosis, treatment, and vaccination. Genomic epidemiology has been widely applied in various countries to track the origin and routes of transmission of COVID-19 (Deng et al., 2020; Fauver et al., 2020; Miller et al., 2020; Rockett et al., 2020; Seemann et al., 2020).

4.1. *Sequencing initiatives across the world*

Advances in next-generation sequencing have enabled the rapid and efficient production of entire viral genomes at a low cost. Genomic sequencing plays a major role in the continuous monitoring of the evolution of SARS-CoV-2 genome. The WHO recommended the nations speed up genome sequencing and share the genomic data and findings in a coordinated way through a publicly accessible database. To coordinate sequencing operations, several initiatives and consortia have been formed in various countries (Table 1). For example, in April 2020, the COVID-19 Genomics UK Consortium (COG-UK) was formed in the United Kingdom to collect, sequence, and analyze SARS-CoV-2 genomes to understand viral transmission and evolution (https://www.cogconsortium.uk/). Other initiatives such as CDC's "SPHERES" (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and

Table 1
List of SARS-CoV-2 Genomic Consortia in various countries.

Name of the genomics consortium/sequencing initiative	Country/ region	Source link
Africa CDC Institute for Pathogen Genomics	Africa	https://africacdc.org/institutes/ipg/
Canadian COVID Genomics Network (CanCOGeN)	Canada	https://www.genomecanada.ca/en/cancogen
Coronavirus Sequencing in Quebec (CoVSeQ)	Quebec, Canada	https://covseq.ca/
COVID-19 Genomics UK Consortium (COG-UK)	United Kingdom	https://www.cogconsortium.uk/
COVID-19 Network Investigations (CONI) alliance	Thailand	https://coni.team/
Danish Covid-19 Genome Consortium (DCGC)	Denmark	https://www.covid19genomics.dk/home
Deutsche COVID-19 OMICS Initiative (DeCOI)	Germany	https://decoi.eu/
Indian SARS-CoV-2 Genomics Consortium (INSACOG)	India	https://dbtindia.gov.in/insacog
Irish Coronavirus sequencing consortium	Ireland	https://www.teagasc.ie/
Mutational Dynamics of SARS-CoV-2 in Austria	Austria	https://www.sarscov2-austria.org/cemm/
National Institute of Infectious Diseases	Japan	https://www.niid.go.jp/niid/en/
RIVM – National Institute for Public Health and the Environment	Netherlands	https://www.rivm.nl/en/coronavirus-covid-19
SeqCOVID – genomic epidemiology of SARS-CoV-2	Spain	http://seqcovid.csic.es/
SPHERES consortium (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance)	United States of America	https://www.cdc.gov/coronavirus/2019-ncov/variants/spheres.html
Switzerland's Swiss SARS-CoV-2 Sequencing Consortium (S3C)	Switzerland	https://bsse.ethz.ch/cevo/research/sars-cov-2/swiss-sars-cov-2-sequencing-consortium.html
ARTIC network's Real-Time Molecular Epidemiology For Outbreak Response	Global	https://artic.network/
COVID-19 High Performance Computing (HPC) Consortium	Global	https://covid19-hpc-consortium.org/
Public Health Alliance for Genomic Epidemiology (PHA4GE)	Global	https://pha4ge.org/
The COVID-19 host genetics initiative	Global	https://www.covid19hg.org/

Surveillance) (https://www.cdc.gov/coronavirus/2019-ncov/variants/spheres.html), Canadian COVID Genomics Network (CanCOGeN) (https://www.genomecanada.ca/en/cancogen), Germany's Deutsche COVID-19 OMICS Initiative (DeCOI) (https://decoi.eu/), Switzerland's Swiss SARS-CoV-2 Sequencing Consortium (S3C) (https://bsse.ethz.ch/cevo/research/sars-cov-2/swiss-sars-cov-2-sequencing-consortium.html), and Irish Coronavirus Sequencing Consortium (https://www.teagasc.ie/). Indian SARS-CoV-2 Genomics Consortium (INSACOG) was formed by the Department of Biotechnology, Ministry of Science & Technology, Government of India along with CSIR and ICMR, including 28 national laboratories to sequence and monitor the SARS-CoV-2 genomic variations (https://dbtindia.gov.in/insacog). Apart from the national initiatives, several global networks are also involved in SARS-CoV2 genome sequencing and surveillance (Table 1).

Sequencing data of SARS-COV-2 genomes from multiple countries across the world are now shared through open access repositories like Global Initiative on Sharing All Influenza Data (GISAID). GISAID was originally developed for rapid international exchange of all influenza viral genomes and related clinical data (Shu and McCauley, 2017), but it has now been expanded to include SARS-CoV-2 genomic data. The first SARS-CoV-2 whole-genome sequences were made publicly available on GISAID's SARS-CoV-2 database on January 10, 2020, allowing for worldwide responses to the pandemic (Lu et al., 2020). Within six months more than 57,000 SARS-CoV-2 genomes from around 100 countries were deposited. GISAID combines sequence data with epidemiological information and provides real-time genomic surveillance to monitor the emergence of SARS-CoV-2 variants in different parts of the world. GISAID is the most commonly used database for the SARS-CoV-2. As of December 2021, more than 5.7 million SARS-CoV-2 genome sequences from nearly 200 countries around the world were shared on the GISAID database (https://www.gisaid.org/). The largest proportion of sequences shared from Europe (58.2%), then North America (31.8%), Asia (5.8%), South America (1.9%), Africa (1.16%), with the fewest from Oceania (0.91%) (https://www.gisaid.org/). In addition to GISAID, other existing genomic and proteomic databases have been updated and used to provide SARS-CoV-2 resources (listed in Table 2). Some databases like China National Center for Bioinformation (CNCB) (https://ngdc.cncb.ac.cn/ncov/) combine information from five different sources – National Microbiome Data Collaborative (NMDC), China National Genebank Database (CNGdb), GISAID, Genome warehouse, and NCBI GenBank. However, accurate SARS-CoV-2 genomic surveillance has been hampered by several issues. The sequencing quality of SARS-CoV-2 genomes in public databases varies for a number of reasons like sequencing methods and laboratory-specific implementation, which can lead to significant bias while studying SARS-CoV-2 variants and evolution dynamics. Due to the lack of proper quality control for genomic data, there were many sequences that were significantly shorter or longer than the reference genome (Zelenova et al.,

Table 2
List of commonly used SARS-CoV-2 genomic/proteomic databases.

Database	Data type (No. of entries)[1]	References	Source link
GISAID SARS-CoV-2 database	SARS-CoV-2 genome sequences (3,445,483)	Khare et al., 2021	https://www.gisaid.org/
DNA Databank of Japan (DDBJ)	Sequence data of SARS-CoV-2 (47 entries)	Okido et al., 2021	https://www.ddbj.nig.ac.jp/
EMBL-EBI COVID-19 Data Portal (CDP)	Sequences (485,396), Raw reads (167,051), Sequenced samples (376,298), Studies (392), Genes (22), Browser (1), Variants (12,691)	De Silva et al., 2021; Harrison et al., 2021	https://www.ebi.ac.uk/ena/pathogens/covid-19 https://www.covid19dataportal.org/
NCBI SARS-CoV-2 Resources	SRA runs (1,107,163), Nucleotide records (1,368,700), Clinical studies related to COVID-19 (6,533), PubMed (175,769), PMC (202,051)	Sayers et al., 2022	https://www.ncbi.nlm.nih.gov/sars-cov-2/
NGDC-CNCB's Resource for Coronavirus 2019 (RCoV19)	Coronavirus Sequence (7,801,242), New Coronavirus Strain (3,597,465), Novel Coronavirus Sequence (3,617,804).	Gong et al., 2020; Song et al., 2020; Zhao et al., 2020	https://ngdc.cncb.ac.cn/ncov/
PDBe-KB (Protein Data Bank in Europe) – COVID-19 Data Portal	Entries (1849), Macromolecules (867), ompounds (725), Protein families (171)	Varadi et al., 2022	https://www.ebi.ac.uk/pdbe/covid-19
CoV3D	SARS-CoV-2 protein structures: spike (467), protease (374), NSP (458)	Gowthaman et al., 2021	https://cov3d.ibbr.umd.edu/
RCSB-PDB (Protein Data Bank)	PDB Structures (1449 files)	Burley et al., 2021	https://rcsb.org/covid19

[1] As of 03.12.2021.

2021). A database update can be highly recommended in order to increase the quality of the genomic data. So many user-friendly web-based tools were created to overcome the problem of data processing and interpretation, for example, Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) (https://pangolin.cog-uk.io/) for lineage assignment, Nextstrain (https://nextstrain.org/), CoVizu (http://filogeneti.ca/covizu/), and Microreact (https://microreact.org/) for data visualization. All these databases aided the scientists in deciphering SARS-CoV-2 mutations, developing appropriate diagnostic kits, and tracking the outbreaks all around the planet.

4.2. Tracking SARS-CoV-2 variants and their spread

SARS-CoV-2, like other viruses, changes over time to adapt to changing environments. The majority of mutations are neutral that have little effect on the functional properties of the virus. There are certain mutations that may be significant, for example, when they encode essential components like the SARS-CoV-2 spike glycoprotein, which serves as a key for the virus to enter host cells and initiate infection (Zhang et al., 2020a). Genomic analyses indicate that some changes may confer a selective advantage to the virus and lead to increased fitness such as antiviral drug resistance and immune escape (Harvey et al., 2021). Even a single amino acid change may alter the severity of illness it causes, infectivity, transmissibility, host immunity responses, the effectiveness of vaccines, therapeutics, and other public health measures (Van Dorp et al., 2020). Since the beginning of the SARS-CoV-2 pandemic, the World Health Organization (WHO) and its international networks have been tracking the evolution of the SARS-CoV-2 genome and updating the variants of interest (VOI) and variants of concern (VOC) (Konings et al., 2021). As of December 2021, there are five variants of concern (VOC) designated by WHO such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Alpha (B.1.1.7) variant, the first VOC exhibiting greater transmissibility, was emerged in the United Kingdom (UK) in September 2020 (Davies et al., 2021). The Delta (B.1.617.2) variant, first identified in December 2020 in India, is now replacing the pre-existing lineages such as Kappa (B.1.617.1) and Alpha (B.1.1.7) and causing re-emergence even in countries with high vaccination coverage (Kannan et al., 2021). Genomic sequencing plays a major role in identifying the viral variants and hotspots of transmission. Korber et al. (2020) designed a bioinformatics pipeline to monitor SARS-CoV-2 variants using the data from the GISAID SARS-CoV-2 sequence database. The pipeline tracks the changes in spike glycoprotein overtime to find the variants that are increasing in different geographic regions at the same time. Their findings showed that during a month, a SARS-CoV-2 variant bearing a specific spike mutation (D614G) became globally dominant.

4.3. Inferring epidemiological parameters and transmission dynamics

Various studies used whole-genome sequences (WGS) as a surveillance tool to investigate outbreak dynamics (Bandoy and Weimer, 2021; Oude Munnink et al., 2020; Bukin et al., 2021) and to infer epidemiological parameters like reproductive number (Geidelberg et al., 2021). For instance, Banu et al. (2020) analyzed the phylogenetic clusters of SARS-CoV-2 genomes to rule out the emergence of COVID-19 in India and suggested that the common ancestor might have emerged at the end of January 2020 and resulted in an outbreak followed by the nationwide spread. Bousali et al. (2021) performed phylogenetic and phylodynamics analysis using SARS-CoV-2 genome sequences derived from ten European regions to investigate the Molecular Transmission Clusters (MTCs). Pan et al. (2021) conducted a phylogenetic analysis using a large number of SARS-CoV-2 genomic sequences from GenBank and GISAID databases to identify the epidemiological traits of COVID-19 and observed the diverse sources of transmission and transmission routes of SARS-CoV-2 in different countries. Geidelberg et al. (2021) estimated the growth rate and reproduction number of SARS-CoV-2 by phylogenetic analysis of genetic sequences obtained from confirmed COVID-19 cases in China. Similarly, Romero et al. (2021) estimated effective reproductive number (Rt) using genomic data of SARS-CoV-2 in Peru. Based on these studies, researchers were able to combine genomic data with epidemiological data to understand the transmission dynamics of SARS-CoV-2 and to take timely public health measures, including regional lockdowns and travel restriction.

5. Role of genomics in diagnosis and therapy of COVID-19

Genomic medicine is an advanced discipline that focuses on how genomic information is used in clinical diagnosis, therapy, and predicting outcomes (Oishi et al., 2015).

5.1. Development of molecular diagnostics

Management of COVID-19 requires prompt diagnosis, effective therapy, and future prevention. The availability of the first whole-genome sequences of SARS-CoV-2 facilitated the rapid development of molecular diagnostic techniques, particularly nucleic acid-based diagnostic assays such as real-time reverse transcription-polymerase chain reaction (rRT-PCR), Transcription-Mediated Amplification (TMA), loop-mediated isothermal amplification (LAMP), and CRISPR/Cas-based assays (Broughton et al., 2020; Carter et al., 2020; Caruana et al., 2020; Corman et al., 2020; Shen et al., 2020; Wang et al., 2020). These approaches were further improved and refined to make them more specific to the viral variants in different geographical regions. Because of its sensitivity and specificity, RT-PCR is considered the 'gold standard' among nucleic acid tests for detection and screening of COVID-19 (Corman et al., 2020). Viral genomic sequences are needed for designing the primers and probes that would efficiently bind to SARS-CoV-2 nucleic acid. Several SARS-CoV-2 genomic areas, including the RdRP gene in the ORF1ab sequence, the S gene, N gene, and E gene, are used in RT-PCR assays to diagnose COVID-19 (Wang et al., 2020). Mutations in the primer and probe-target areas of the SARS-CoV-2 genome can lead to false-negative results (Khan and Cheung, 2020). Therefore to improve the accuracy of detection and to reduce the risk of false negatives, the virus is detected with several targets, such as multiplex real-time RT-PCR methods targeting two or more sections of the viral genome (Ishige et al., 2020; Tahamtan and Ardebili, 2020). The risk of diminished diagnostic efficiency is also avoided by developing diagnostics based on relatively stable conserved regions of the genome (Ascoli, 2021). As the virus continues to evolve, genome sequencing is necessary for monitoring the mutations that would hinder the ability of diagnostic assays to detect SARS-CoV-2 (Jain et al., 2021). Advancements in genomics and proteomics enabled the cloning and expression of SARS-CoV-2 viral proteins, which aided the development of inexpensive rapid diagnostic tests for detection of SARS-CoV-2 at the point of care such as antigen and serological tests (Toptan et al., 2021; Mercer and Salit, 2021).

5.2. Development of therapeutics

Having access to the genome of the SARS-CoV-2 virus allows researchers to identify therapeutic targets and to build models of epitopes and immune responses, allowing the development of new therapeutics and vaccines (Chellapandi and Saranya, 2020; Li et al., 2020; Zhou et al., 2020a; Peng et al., 2021). Both genomics and proteomics enabled the rapid understanding of viral protein function and pathogenesis, as well as the identification of virus-specific factors and potential targets for drug design. COVID-19 might be treated using drugs that target any of the key proteins involved in viral replication (Table 3). For example, the drug Remdesivir inhibits RdRp (RNA-dependent RNA polymerase) and has been approved for the treatment of COVID-19 in various countries after showing improvement in clinical studies (Beigel et al., 2020;

Table 3
List of potential antiviral drugs for SARS-CoV-2 infection.

Drug	Mechanism	References
Favipiravir	RdRp (RNA-dependent RNA polymerase) inhibitor	Driouich et al., 2021
Lopinavir and Ritonavir	Mpro (main protease) inhibitors	Rut et al., 2020
Mizoribine	IMPDH (Inosine-5′-monophosphate dehydrogenase) inhibitor	Borbone et al., 2021
Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir	RdRp inhibitor	Beigel et al., 2020; Buckland et al., 2020; Elfiky, 2020
Tocilizumab	IL-6 receptor inhibitor	Gupta and Leaf, 2021; Salama et al., 2021

Buckland et al., 2020; Riva et al., 2020; Rubin et al., 2020). Apart from these antiviral drugs, several other potential therapeutic approaches have been developed by various researchers to combat COVID-19 such as RNA interference (RNAi) and CRISPR/Cas based therapy that target viral RNAs to functionally disrupt the virus (Berber et al., 2020). Chen et al. (2020) developed an RNAi-based approach using small interfering RNA (siRNA) molecules that inhibit gene expression and block SARS-CoV-2 replication. Genomic knowledge serves as the basis for theoretical predictions of the potential siRNA targets in the SARS-CoV-2 genome. On the other hand, the CRISPR/Cas technique employs guide RNAs (gRNAs) that simultaneously target and degrade different regions of the virus-like replicase-transcriptase (ORF1ab) and spike (S) genes (Nguyen et al., 2020). RdRp gene of the SARS-CoV-2 can also be targeted by the CRISPR-Cas system due to its highly conserved amino acid sequence and chemical structure (Kumar et al., 2020). Abbott et al. (2020) suggested a CRISPR-Cas13-based COVID-19 treatment called Prophylactic Antiviral CRISPR in huMAN cells (PAC-MAN) to suppress SARS-CoV-2. The CRISPR-Cas13 system allows for the rapid development of guide RNAs that specifically target highly conserved regions of the viral genome, allowing it to combat rapidly mutating SARS-CoV-2 strains (Kumar et al., 2020). Apart from the viral targeting agents, the host factors that are necessary for viral replication and transcription could be used as therapeutic targets (Li and De Clercq, 2020). For example, soluble ACE2, TMPRSS2, and CTSL inhibitors have been demonstrated to have significant antiviral activity and might be used to treat COVID-19 (Ghanbari et al., 2020; Gordon et al., 2020; Hoffmann et al., 2020). Therefore, understanding the genomics of both virus and host is critical for developing and delivering therapeutics for COVID-19.

6. Modern vaccine technologies

In order to combat the ongoing COVID-19 pandemic, an effective and safe vaccine is very important. The availability of genomic information together with advances in DNA synthesis and genome editing technologies enabled the researchers to develop modern vaccines such as RNA-based, DNA-based, protein subunit, and recombinant viral vector vaccines. According to the recent report by WHO, around 135 vaccine candidates were undergoing clinical trials, with 194 in preclinical development, as of December 3, 2021 (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). Of the 135 candidates, 39 are undergoing phase 3 or phase 4 clinical trials (Table 4). At present, eight vaccines including three viral vector-based, two RNA-based, and three inactivated virus vaccines are approved for emergency use by WHO (Table 4). Supplementary Fig. S1 and Table S1 depict the relative progress of vaccine candidates in various phases of clinical development. The majority of the SARS-CoV-2 vaccine candidates (>70%) were developed through genomic methodologies.

Advances in bioinformatics, immunogenetics, and molecular simulations led to more rapid, precise, and cost-effective designing of protein subunit/peptide vaccines. A technique called 'reverse vaccinology' uses the genome sequences of pathogens rather than organisms to develop novel antigens, which need to be tested by using experimental biology (Bambini and Rappuoli, 2009). Pan-genomic reverse vaccinology, which involves the comparison of genomic data from different strains of SARS-CoV-2, enhances the opportunity of developing novel vaccines (Enayatkhani et al., 2020). Novel epitopes in proteins encoded in the genomes can be predicted in-silico using bioinformatics/immunoinformatics tools based on sequence similarities to previously reported immunogenic motifs or structural approaches such as molecular docking simulations (Ishack and Lipner, 2021). As the genomic and proteomic information of SARS-CoV-2 is rapidly becoming accessible, numerous studies applied reverse vaccinology and machine learning approaches to develop multi-epitope subunit vaccines against SARS-CoV-2 (Enayatkhani et al., 2020; Ong et al., 2020; Sanami et al., 2020; Tahir ul Qamar et al., 2020; Almofti et al., 2021; Saha et al., 2021). Recombinant protein vaccines against SARS-CoV-2 include spike-protein-based, RBD-based, and virus-like particle (VLP)-based vaccines (Krammer, 2020) and 53 of them are in the clinical phase. For example, Novavax's NVX-CoV2373 vaccine is made up of full-length recombinant SARS-CoV-2 spike glycoproteins nanoparticles that have been adjuvanted with Matrix-M1 (Keech et al., 2020). Despite the widespread occurrence of the B.1.1.7 (or alpha) variant, preliminary findings of phase 3 clinical trial in the UK showed an efficacy rate of 86.3% against the alpha variant and 96.4% efficacy against non-alpha variants (Heath et al., 2021). The majority of the recombinant protein subunit vaccines against SARS-CoV-2 have entered the phase 3 clinical trials (Table 4).

Nucleic acid vaccines either RNA or DNA deliver the genetic information of antigen (such as spike glycoprotein) rather than the antigen itself. 15 DNA-based and 21 mRNA-based candidate vaccines against SARS-CoV-2 are in clinical trials. Due to the ease of handling, simple manufacture, and stability of plasmid DNA, DNA-based vaccination methods have become a reality. Of the eleven DNA-based vaccines, only two vaccines, ZyCoV-D (developed by Zydus Cadila) and INO-4800 (by Inovio Pharmaceuticals) have undergone phase 3 clinical trials. ZyCoV-D uses plasmid DNA that contains the genetic information to make the 'spike protein' (Momin et al., 2021). It is the world's first plasmid DNA vaccine for COVID-19 to be approved for emergency use (Mallapaty, 2021). Next to protein vaccines, the majority of the vaccine candidates are mRNA-based which accounts for 16% of all vaccines developed across platforms (Supplementary Table S1). Two mRNA vaccines, Pfizer-BioNTech's BNT162b2 (Comirnaty) and Moderna's mRNA-1273 (Spikevax) were the first to be authorized for use in many countries (Baden et al., 2021; Haas et al., 2021). These vaccines use nucleoside-modified mRNA (modRNA) encoding SARS-CoV-2 spike protein that is encapsulated in lipid nanoparticles (LNP). Other mRNA vaccines, such as CVnCoV (developed by CureVac and CEPI) and ARCoV (developed by Walvax Biotechnology) are in phase 3 clinical trials (Table 4). The mRNA vaccines provide a variety of advantages over other vaccine platforms, including efficient delivery, flexibility, short development time, use of the host's protein translational machinery, and no risk of genome integration (Momin et al., 2021). The era of synthetic genomics led to the development of viral vector-based vaccines that deliver antigen-coding nucleic acid fragments to host cells through viral vectors. Viruses are altered to lower their virulence and their reproduction capability but retaining their ability to infect human cells (Alter et al., 2021). At present, four non-replicating adenovirus-vector vaccines such as Oxford/AstraZeneca's AZD1222, Janssen's Ad26.COV2.S, CanSino's AD5-nCOV (Convidecia), Gamaleya Research Institute's Gam-COVID-Vac (Sputnik V) are now in widespread use (Table 4). All these contain DNA that encodes a SARS-CoV-2 spike protein.

7. Conclusion

The COVID-19 pandemic startled the globe, pushing science to develop new strategies to combat the virus. The availability of genomic data enables a very rapid, thorough, and precise global follow-up of the progression of the COVID-19. Early detection of SARS-CoV-2 variants,

Table 4
List of vaccine candidates in phase 3 or 4 clinical trials.

Vaccine platform	Vaccine name	Type of candidate vaccine	Developer/manufacturer	Clinical stage	Reference
DNA based vaccine	ZyCoV-D	Plasmid DNA Covid-19 vaccine	Zydus Cadila	Phase 3	Momin et al., 2021
	INO-4800 COVID-19 Vaccine	Plasmid DNA Covid-19 vaccine	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	Phase 3	Andrade et al., 2021
Inactivated virus	CoronaVac*	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Sinovac Biotech	Phase 4	Tanriover et al., 2021
	WIBP-CorV	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products (WIBP)	Phase 3	Al Kaabi et al., 2021
	BBIBP-CorV*	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products (BIBP)	Phase 4	Xia et al., 2021
	Covidful or IMBCAMS COVID-19 vaccine	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Institute of Medical Biology (IMB) + Chinese Academy of Medical Sciences (CAMS)	Phase 3	Huang et al., 2021
	QazVac or QazCovid-in	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Research Institute for Biological Safety Problems, Kazakhstan	Phase 3	Zakarya et al., 2021
	Covaxin (BBV152)*	Whole-virion Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Bharat Biotech International Limited + Indian Council of Medical Research (ICMR)	Phase 3	Ganneru et al., 2021
	KCONVAC or Minhai COVID-19 vaccine	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Shenzhen Kangtai Biological Products Co., Ltd. + Beijing Minhai Biotechnology	Phase 3	https://en.biokangtai.com/
	VLA2001 or Valneva COVID-19 vaccine	Inactivated SARS-CoV-2 vaccine, produced in Vero cells	Valneva, National Institute for Health Research, United Kingdom	Phase 3	https://valneva.com/research-development/covid-19-vla2001/
	ERUCOV-VAC or TURKOVAC	Inactivated SARS-CoV-2 vaccine (Vero cell)	Health Institutes of Turkey + Erciyes University.	Phase 3	http://www.erciyes.edu.tr/
Protein subunit	NVX-CoV2373	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full-length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)	Novavax + Coalition for Epidemic Preparedness Innovations (CEPI)	Phase 3	Heath et al., 2021
	ZIFIVAX or ZF2001	Recombinant SARS-CoV-2 (CHO Cell) – RBD-based protein subunit vaccine	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Phase 3	Yang et al., 2021
	VAT00002	SARS-CoV-2 S protein with adjuvant	Sanofi Pasteur + GSK	Phase 3	https://www.sanofi.com/en/our-covid-19-vaccine-candidates
	SCB-2019	Trimeric subunit Spike Protein vaccine + CpG 1018 adjuvant plus Alum adjuvant	Clover Biopharmaceuticals Inc./GSK/ Dynavax	Phase 3	Richmond et al., 2021
	COVAX-19 (or SpikoGen)	Recombinant spike protein + adjuvant	Vaxine + CinnaGen Co.	Phase 3	https://vaxine.net/
	MVC-COV1901	Spike-2P protein + adjuvant CpG 1018	Medigen Vaccine Biologics Corporation + Dynavax Technologies + National Institute of Health	Phase 4	Hsieh et al., 2021
	FINLAY-FR-2 or Soberana 2	RBD chemically conjugated to tetanus toxoid plus adjuvant	Instituto Finlay de Vacunas Cuba	Phase 3	Chang-Monteagudo et al., 2021
	EpiVacCorona	Based on peptide antigens	Federal Budgetary Research Institution (FBRI) State Research Center of Virology and Biotechnology VECTOR,	Phase 3	Ryzhikov et al., 2021
	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	RBD (baculovirus production expressed in Sf9 cells)	West China Hospital + Sichuan University	Phase 3	Meng et al., 2021
	CIGB-66 (or Abdala)	RBD + aluminium hydroxide	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 3	http://www.cigb.edu.cu/
	BECOV2A (Corbevax)	RBD + aluminium hydroxide + CpG 1018	Biological E. Limited	Phase 3	https://www.biologicale.com/Vaccines_Biologics/products.html
	Nanocovax	Recombinant Sars-CoV-2 Spike protein, Aluminum adjuvanted	Nanogen Pharmaceutical Biotechnology JSC	Phase 3	https://nanogenpharma.com/products/nanocovax-141.html
	GBP510	Recombinant surface protein vaccine with adjuvant AS03 (Aluminium hydroxide)	SK Bioscience Co., Ltd. and Coalition for Epidemic Preparedness Innovations (CEPI)	Phase 3	https://www.skbioscience.co.kr/
	Razi Cov Pars	Recombinant spike protein	Iranian Razi Vaccine and Serum Research Institute	Phase 3	http://www.rvsri.ac.ir/
RNA based vaccine	mRNA-1273 (Spikevax)*	Nucleoside-modified mRNA (modRNA) encoding a spike protein, encapsulated in lipid nanoparticles	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4	Baden et al., 2021
	BNT162b2/ Comirnaty	Nucleoside-modified mRNA encapsulated in a lipid nanoparticle (LNP)	Pfizer/BioNTech + Fosun Pharma	Phase 4	Haas et al., 2021

(*continued on next page*)

Table 4 (*continued*)

Vaccine platform	Vaccine name	Type of candidate vaccine	Developer/manufacturer	Clinical stage	Reference
	Tozinameran (INN)*				
	CVnCoV	Unmodified mRNA that encodes the full-length, pre-fusion stabilized coronavirus spike protein	CureVac N.V. and the Coalition for Epidemic Preparedness Innovations (CEPI)	Phase 3	https://www.curevac.com/en/covid-19/
	ARCoV (Walvax COVID-19 vaccine)	Lipid nanoparticle (LNP)-encapsulated mRNA encoding the Receptor Binding Domain of SARS-CoV-2	Walvax Biotechnology, Suzhou Abogen Biosciences, and PLA Academy of Military Science.	Phase 3	Zhang et al., 2020b
	mRNA-1273.351	LNP-encapsulated mRNA- vaccine encoding full-length, prefusion stabilized S protein of the SARS-CoV-2B.1.351 variant	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4	Choi et al., 2021
	ARCT-154 (VBC-COV19-154)	Nucleoside-modified mRNA encapsulated in a lipid nanoparticle (LNP)	Vinbiocare Biotechnology + Arcturus Therapeutics, Inc.	Phase 3	https://arcturusrx.com/mrna-medicines-pipeline/#pipelineGroup_lunarCovid
Viral vector (Non-replicating)	AZD1222 (Vaxzevria)* Covishield*	ChAdOx1 replication-deficient simian adenovirus vector, containing the full-length codon-optimized coding sequence of SARS-CoV-2 spike protein	AstraZeneca + University of Oxford; Serum Institute of India	Phase 4	Knoll and Wonodi, 2021
	AD5-nCOV (Convidecia)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 4	Zhu et al., 2020
	Ad5-nCoV-IH (Convidecia)	Recombinant COVID-19 vaccine (adenovirus type 5 vector) for Inhalation (Ad5-nCoV-IH)	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 3	Wu et al., 2021
	Gam-COVID-Vac (Sputnik V)	Adenovirus viral vector vaccine – based on rAd26-S + rAd5-S	Gamaleya Research Institute, Health Ministry of the Russian Federation	Phase 3	Logunov et al., 2021
	Ad26.COV2.S (Janssen COVID-19 Vaccine)*	Recombinant adenovirus type 26 (Ad26) vector expressing SARS-CoV-2 spike (S) protein	Janssen Pharmaceuticals	Phase 4	Alter et al., 2021
Viral vector (Replicating)	DelNS1-nCoV-RBD LAIV	Comprises weakened flu viruses, such as H1N1, H3N2, and B, with genetic segments of the S-protein (Intranasal flu-based-RBD)	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	Phase 3	https://clinicaltrials.gov/ct2/show/NCT05200741
Virus like particle	CoVLP	Plant-produced virus-like particle (VLP) vaccine	Medicago Inc. + GlaxoSmithKline (GSK)	Phase 3	Ward et al., 2021
Live attenuated virus	COVI-VAC (CDX-005)	Intranasal live attenuated vaccine	Codagenix/Serum Institute of India	Phase 3	https://codagenix.com/vaccine-programs/covid-19/

* World Health Organization (WHO) Emergency Use Authorization (EUA) qualified COVID-19 vaccines (as of December 3, 2021). (https://covid19.trackvaccines.org/agency/who/).

along with a better knowledge of the mutational processes behind shifting patterns of virulence, transmissibility, and antigenicity, have greatly aided in making timely public health decisions. It is critical to emphasize that genomic information must be utilized with caution while taking public health decisions. The use of improper bioinformatics tools, sampling bias, sequencing errors, and misinterpretation of findings may all lead to wrong conclusions. The genomic sequence of SARS-CoV-2 also enabled the cloning and synthesis of specific viral proteins, which aided in the development of rapid diagnostic tests for SARS-CoV-2 screening. In order to understand SARS-CoV-2 variant spread in different countries, it is essential to integrate genomic and epidemiological data. The increased adoption of genomic technologies in various facets of the worldwide response to the COVID-19 pandemic is major evidence of the role of genomics in modern medicine. Furthermore, the tremendous advances in genomics and lessons learnt from the battle against SARS-CoV-2 offer a great potential to reduce the future threats to mankind and bolster preparedness for future outbreaks.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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