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REVIEW ARTICLE

Global Overview of Sars-Cov-2 Induced Covid-19 In 2020: Biological Characterization, Epidemiology with Social, Economic and Environmental Implications

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ABSTRACT

Background: COVID-19 is a global pandemic initiated in January 2020 that caused 79 million cases and more than 1.7 million deaths worldwide. The causative agent of COVID-19 is *Severe Acute Respiratory Syndrome Coronavirus-2*, a member of *Betacoronvirus*. COVID-19 patients are classified into asymptomatic, mild symptomatic, and severe symptomatic cases.

Objectives: To review the prevalence, therapeutic interventions for the treatment, vaccination, and containment of COVID-19 in four quarters of 2020, emphasizing the advancements in biological studies, and the social, economic, and environmental impact of the pandemic.

Methodology: Data of COVID-19 spread, identification, prevention, and control measures was analyzed. The impacts of pandemic on society, economy, and the environment were assessed.

Results: Owing to distinct genome of COVID-19, *de novo* diagnostic tests have been designed, optimized, and carried out in individuals. The specimen for viral detection can be selected from sputum, nasal, and pharyngeal swabs, anal swabs, blood, Bronchoalveolar Lavage Fluid (BLF), and secretions of lower respiratory tract. Primary treatment includes antiviral therapeutic agents, whereas, supplementary treatment includes corticosteroid therapy, antibiotic treatment, and oxygen therapy with the help of non-invasive and invasive mechanical ventilation. The lack of targeted therapeutics failed to induce a 100% mortality rate as recovered patients' immune system produces $CD4^+$ and $CD8^+$ T cell responses and antibodies against the spike protein of the virus. In order to contain the virus spread and build herd immunity in the masses, protein subunit vaccines, RNA-based vaccines, and VLPs were developed.

Conclusion: The social, economic, and environmental impact of COVID-19 has threatened the global community. The novel prevention and control measures offered significant benefits however, an effective treatment will possibly always be required even with the end of pandemic.

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INTRODUCTION

Coronavirus Disease-2019 is a respiratory infection caused by SARS-CoV-2. The first case was reported in December 2019 in Wuhan. Its emergence was associated with the Huanan seafood market, the largest wholesale market for live animals and seafood in the Jiangshan District of Wuhan, China[1]. The first epicenter of the COVID-19 pandemic was also identified in Wuhan, Hubei Province, China[2]. In a period of one month, the respiratory disease and pneumonia of unknown origin and vague diagnostic symptoms significantly spread to other parts of China and rest of the world, and the World Health Organization (WHO) declared the "Global Public Health Emergency" on January 30, 2020[3,4]. The widespread of the pandemic has been fluctuated across the globe, from country to country, and within regions of the same country[5]. On February 11, 2020, the guidelines of the International Committee for the Classification of Viruses, scientifically named the virus "Severe Acute Respiratory Syndrome-related Coronavirus-2", abbreviated as SARS-CoV-2[6]. On December 29, 2020, the WHO reported 79,231,893 cumulative cases of COVID-19, 1,754,574 cumulative deaths, and a mortality rate of 2.2%[7]. The possible identification methods as well as timeline of infection spread has been generated in Fig. **1**.

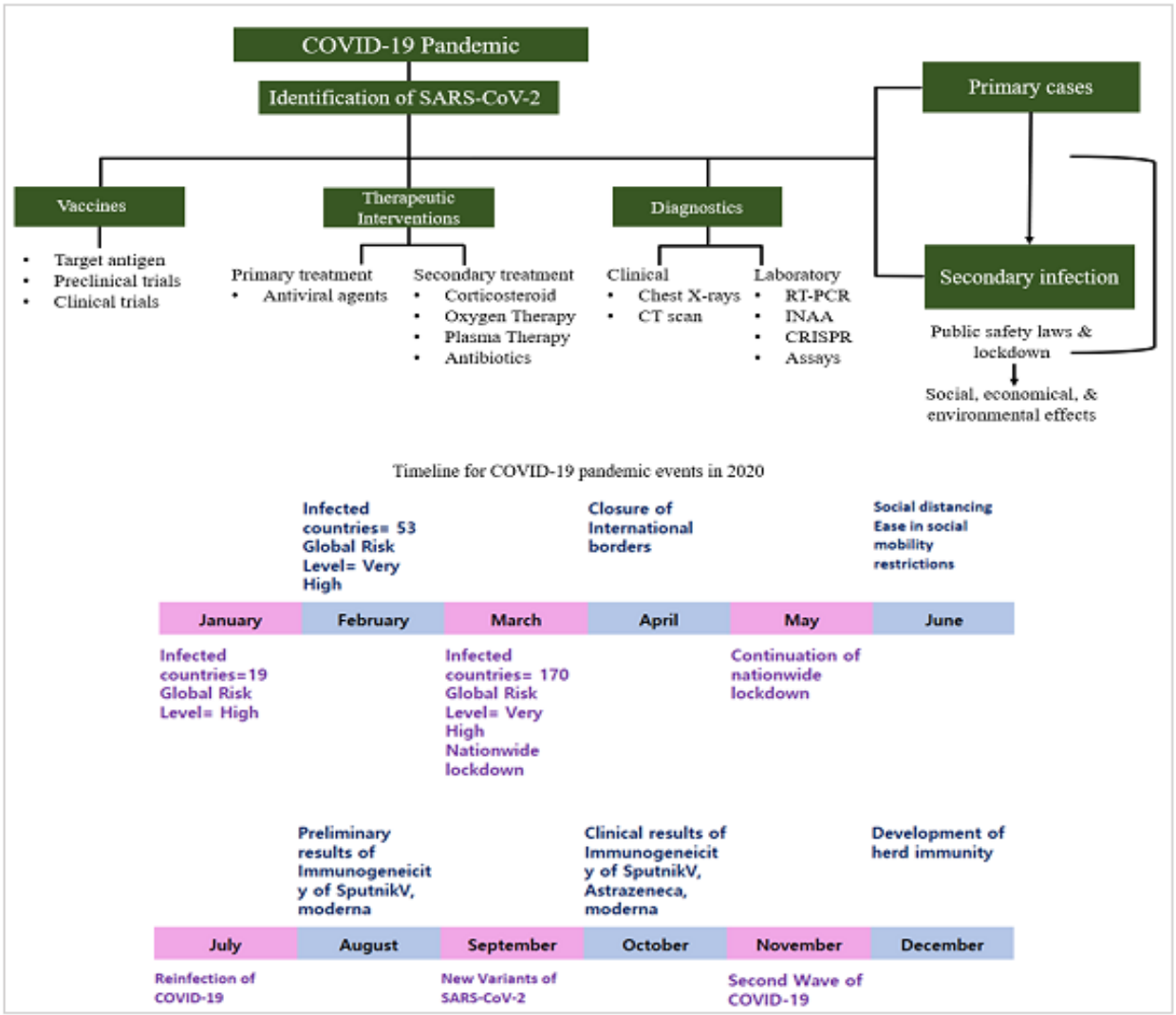


Figure 1. An overview of COVID-19.

COVID-19 cases are classified as asymptomatic, mild symptomatic, and severe symptomatic cases. The signs and symptoms of SARS-CoV-2 are established after 7-14 days of infection, including fever, anorexia, dysplasia, muscular pain, and fatigue[8,9]. The progression of infection severely damages the lower respiratory tract (trachea, bronchoalveolar surfaces, and lungs). The disease is transmitted through both direct and indirect contact with infected individuals. COVID-19 can propagate through sporadic spread, clustered transmission, and community transmission. In order to contain the virus, public safety policies were implemented throughout the world to contain the horizon of SARS-CoV-2 virus; however, most of them compromised mental health and caused social distress among the masses. The lockdown of industries and transnational borders caused an economic downfall in advanced, developing, and underdeveloped nations. The social, economic, and environmental aspects of the COVID-19 pandemic have threatened the survival of the global community. This review summarizes the source, spread, treatment, and development of vaccines in four quarters of 2020, with special attention given to the advancements in biological studies to combat the viral threat and the social, economic, and environmental impact of the COVID-19 pandemic.

BIOLOGICAL CHARACTERIZATION OF NOVEL CORONAVIRUS-2019

Taxonomical Classification

The phylogenetic evidences from genomic studies of the initially unidentified agent revealed sequence homology to the RdRp region of *Betacoronaviruses,* particularly SARS-CoV. Hence, it was named as "2019 novel-Coronavirus" (2019-nCov) by Zhu *et al*.[10] and later termed as SARS-CoV-2 by the *Coronaviridae* Study Group (CSG) of the International Committee on Taxonomy of Viruses (Table **1**)[6]. Taxonomically, SARS-CoV-2 has been assigned to the genus *Betacoronaviruses* of the family *Coronaviridae*[11]. The *Coronaviridae* family consists of three additional genera, *Alphacoronaviruses, Gammacoronaviruses*, and *Deltacoronaviruses*, which are responsible for viral ailments in birds, animals and humans[12,13]. *Alphacoronaviruses* and *Betacoronaviruses* primarily infect mammals, whereas *Gammacoronaviruses* and *Deltacoronaviruses* infect birds[14].

The two distinct members of *Alphacoronaviruses* (HCoV-NL63 and HCoV-229E) and four distinct members of *Betacoronaviruses* (HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV) have been responsible for coronaviruse-induced pathologies in the human population[15]. HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1 account for 15-30% cases of seasonal common cold or mild respiratory infections[16] . However, SARS-CoV causes life-threatening lower respiratory infection and is responsible for Severe Acute Respiratory Syndrome Epidemic during 2002-2003 with 8,096 reported viral infections and a 9.6% mortality rate. The Middle Eastern Respiratory Syndrome (MERS) outbreak 2012 in Saudi Arabia infected 2,494 humans in 27 countries and reported a mortality rate of 34%, corresponding to 858 deaths[17]. SARS-CoV-2 marked the first "Pandemic" of the 21st century.

Table 1. Taxonomical Classification of 2019-Novel Coronavirus.

Scientific	Serial Classification
Order	*Nidoviralis*
Family	*Coronoviridae*
Subfamily	*Orthocoronovirinae*
Genus	*Betacoronavirus*
Sub genus	*Sarbecovirus*
Species	*Severe acute respiratory syndrome coronavirus-2*

Genomic and Proteomic Characterization of Novel Coronavirus-2019

The whole genome sequencing, multiple sequence alignment, and phylogenetic analysis of SARS-CoV-2 exhibited striking sequence homology to bat severe acute respiratory syndrome-related coronaviruses and human coronaviruses[6]. The genetic analysis of SARS-CoV-2 has indicated 75% sequence homology of viral nucleotides to SARS-CoV[18,19]. The whole genome sequencing of SARS-CoV-2 has also revealed 87.9% and 87.3% sequence homology with SARS-like bat coronaviruses, SARS-CoVZC45 and SARS-CoVZXC21, respectively[20]. Moreover, SARS-CoV-2 has also been more closely related to the bat CoV RaTG13 extracted from *Rhinolophus*

affinis. These similarity indices strongly suggest the zoonotic transfer of SARS-CoV-2 and bats as primary hosts of the 2019-novel coronavirus[21,22]. Another candidate for the zoonotic transfer of SARS-CoV-2 is suspected to be pangolins, as phylogenetic studies conducted by Lam *et al*. highlighted 99.9% sequence homology of SARS-CoV-2 with the coronavirus GX/P2V present in *Manis javanica*[23]. However, SARS-CoV-2 has shown the least homology to MERS, with 50% sequence resemblance[24].

Genomic studies of SARS-CoV-2 indicate that it is an enveloped RNA virus, characterized by the presence of positive-sense single stranded RNA molecule[10]. Instead of requiring RNA transcriptase enzyme, positive-sense RNA viruses are capable of using genomic RNA as mRNA for direct protein synthesis. The coronavirus genomic RNA is structurally similar to eukaryotic mRNA with a 5' Cap structure and 3' Poly-A tail, which are essential for durability and the translation of RNA molecules in the cytosolic component of eukaryotic host cells[25]. During the initial phase of the epidemic, Jiang *et al*. successfully provided deep insight into the genomic characterization of SARS-CoV-2. The SARS-CoV-2 genome initiates at the 5' UTR region, followed by the coding region for a set of 15 non-structural proteins, stretching two-thirds in length, and the remaining one-third region being translated into four structural and eight accessory proteins. The RNA genome of novel coronavirus is translated through fourteen Open Reading Frames (ORF) and produces polyproteins. The two polyproteins, pp1ab and pp1a are generated via translation of single ORF at 5' terminus, and collectively generated 15 non-structural proteins. The downstream region contains genes for S, 3a, 3b, E, M, p6, 7a, 7b, 8b, N, 9b, and orf14 proteins, which are synthesized under different ORFs[26]. SARS-CoV-2 lack the Hemagglutinin-esterase (HE) gene, that has been reported in other members of Betacoronavirus[16]. Moreover, mutations and genetic variations at different sites within the genome are responsible for the emergence of various strains of SARS-CoV-2. Phan identified 93 mutations during nucleotide sequence analysis of 86 strains of SARS-CoV-2, from China, Australia, America, South Korea, Singapore, Belgium, and England[27]. Wang *et al*. also reported distinct variations at 13 sites in ORF1a, ORF1b, 3a, M, 8 and N genes of different strains of SARS-CoV-2. In their study, the mutation rate of ORF8 was the highest (30.5%), followed by the mutation rate of ORF1a (29.5%)[28].

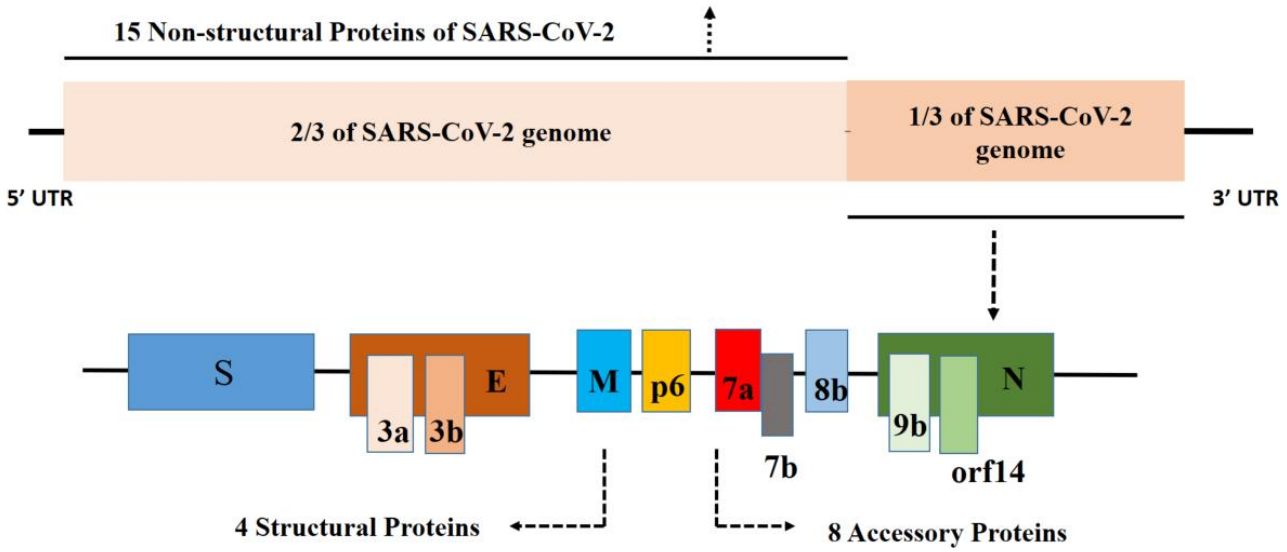
The four structural proteins of SARS-CoV-2 include spike surface glycoprotein (S), small envelope protein (E), membrane protein (M), and nucleocapsid protein (N) (Fig. **2**)[29]. The S glycoprotein contains 1,273 amino acid residues and is made up of two subunits, S1 and S2. The subunit S1 exhibited a structural resemblance to the S1 unit of SARS-CoV. It consists of one Signal Peptide (SP), one N-terminal Domain (NTD), and three C-terminus Domains (CTD1, CTD2, and CTD3). The subunit S2 consists of Fusion Peptide (FP), Heptapeptide Repeat Sequence-1 (HR1), Heptapeptide Repeat Sequence-2 (HR2), Transmembrane Domain (TM) and C-terminal domain[30]. The S-protein is of prime importance since S1 plays a crucial role in interacting with human cell receptor, and S2 plays an important role in membrane fusion during infection[2]. The receptor binding domain (RBD) is located in CTD1 region of SARS-CoV-2 and exhibits 75% amino acid sequence homology to SARS-CoV. This striking resemblance have emphasized the involvement of same host cell receptor during virus-host interaction i.e., Angiotensin Converting Enzyme-2 (ACE-II) and consequently similar clinical manifestations as of SARS-CoV[18]. The binding sites in the RBD of both SARS-CoV and SARS-CoV-2 with 83.3% sequence similarity conserved 13 hydrophobic amino acid residues involved in protein-protein interaction[31]. Moreover, cryo-EM of S-protein indicated that RBD of SARS-CoV-2 has 10 and 20 folds higher affinity to ACE-II receptor of human cells. SARS-CoV-2 binds ACE-II with higher affinity as the binding free energy of the SARS-CoV-2 RBD-ACE2 interaction is -50.43kcal/mol, which is significantly lower than the binding free energy of the SARS-CoV RBD-ACE2 interaction (-36.75kcal/mol)[32]. Moreover, Zhou *et al*. also confirmed the binding affinity of S-protein with ACE-II and non-binding affinity towards dipeptidyl peptidase-IV (receptor of MERS-CoV) and aminopeptidase-N (receptor of other coronaviruses)[33]. The accessory proteins of SARS-CoV-2 also possessed structural variation as compared with SARS-CoV. These include elongated 8b (121 amino acids) and shrunken 3b (22 amino acids) in comparison to SARS-CoV 8b (84 amino acids) and 3b (154 amino acids), whereas the accessory protein 8a was not

found in SARS-CoV-2[26]. This study provides ground for further investigation of the significance of these variations in viral pathogenesis.

PATHOLOGY OF SARS-COV-2

The pathogenesis of coronaviruses involves the interaction of viral surface proteins with the host cell receptor, fusion of viral membrane and host cell membrane, release of viral genome into the intracellular environment of host cell, translation of the viral genome into polypeptides, increase in the copy number of viral genome, assemblage of viral particles in compartmentalized organelles, and release into the extracellular matrix by exocytosis[34]. The presence of S-protein not only imparts unique morphological feature, but also plays a significant role in virus-cell fusion[35]. SARS-CoV-2 interacts with ACE-II present on the surface of cells lining the nasal cavity, epithelial cells of the airways, and alveolar type II cells[36,37]. After binding of RBD to ACE-II, the S-protein is cleaved at Polybasic Furin Cleavage Sites (PRRAR) by host cell's Type II Transmembrane Serine Protease (TMPRSS2) into S1 and S2 subunits[38,39].

nsp	Segment length	Base numbers	nsp	Segment length	Base numbers
nsp1	~181	Not identified	nsp9	4142-4254	112
nsp2	182-819	637	nsp10	4255-4392	137
nsp3	820-2764	1944	nsp11	Absent	0
nsp4	2765-3264	499	nsp12	4393-5325	932
nsp5	3265-3570	305	nsp13	5326-5926	600
nsp6	3571-3850	279	nsp14	5927-6453	526
nsp7	3851-3943	92	nsp15	6454-6799	345
nsp8	3944-4141	197	nsp16	6800-7096	296



Spike surface Glycoprotein (S)	
Envelop Protein (E)	
Membrane Protein (M)	
Nucleocapsid Protein (N)	

3a	7b
3b	8b
p6	9b
7a	orf14

Figure 2. Types of proteins translated from SARS-CoV-2 positive sense RNA genome.

The multiple cleavage sites give distinctive characteristics to SARS-CoV-2 because these are associated with enhanced infectivity and the highly contagious nature of the virus[40]. The exposure of FP in S2 causes conformational changes in the S2 unit[41]. This is followed by folding back of HR1 and HR2 to form a six-helix structure responsible for bringing the viral membrane and host cell membrane close enough to fuse[34]. Like SARS, MERS, and other coronaviruses, the compartmentalization of SARS-CoV-2 occurs via endocytosis [42]. In the double-membrane vesicles, the viral proteins are dissolved and the viral RNA is released in the cytoplasm[43].

The viral genomic RNA (gRNA) is directly translated into pp1a and pp1ab polypeptide. The coronavirus Main Protease (Mpro) cleave the pp1a and pp1ab polypeptide, which results in the release of multisubunit RNA-dependent-RNA-polymerase (nsp12) and other non-structural proteins (nsp1-nsp16). Nsp1/nsp3, nsp2, nsp15, and nsp16 are actively involved in evading the immune response. The coordination of nsp12, nsp13, and nsp14 forms a Replicase-Transcriptase-Complex (RTC), which proceeds RNA synthesis, RNA proofreading, and RNA modification. The RTC is responsible for the transcription of gRNA in three ways. The RTC transcribed gRNA into a nested set of sub genomic RNA (sgRNA), positive-sense single-stranded RNA (+ssRNA), and negative-sense single stranded RNA (-ssRNA)[16,34]. Nested sgRNAs are translated into the structural and accessory proteins, negative-sense RNA strands act as templates to synthesize more complementary positive-sense RNA strands, and positive-sense RNA strands interact with N-protein and form Nucleocapsid in host cytoplasm[44]. The accessory protein nsp8 works as a primase and generate a 7-8 nucleotide short sequence complementary to 3' of gRNA so that new RNA strands can be synthesized. The nsp7- nsp8 complex increases the binding of RdRp (nsp12) to RNA and enhances the enzymatic activity of RdRp[45].

The structural proteins S, M, and E are involved in the formation of the viral coat[16]. These viral proteins are insulated in the endoplasmic reticulum and are released as Endoplasmic Reticulum-Golgi-Intermediate Compartment (ERGIC)[44]. The nucleocapsid is infused with ERGIC, and an assemblage of viral particles take place. During assembly, the nucleocapsid is further stabilized by interactions with the M protein. The M protein also interacts with the S protein and is responsible for its incorporation into the new virion[16]. In coronaviruses, E protein is the outermost protein layer and is involved in several aspects of the virus life cycle and pathogenesis[46]. Once virions are assembled, they are released into the extracellular matrix through exocytosis[47]. In CoVs, the S-protein has also been reported to mediate the fusion of membranes of adjacent normal cells to the infected cell, form multinucleated giant cells, and mechanistically facilitate the rapid spread[43].

DIAGNOSTIC TESTS FOR COVID-19

Specimens for SARS-CoV-2 Detection

The detection of SARS-CoV-2 in humans is correlated with the type of sample, maintenance temperature, isolation techniques, and handling during testing. The specimen for viral detection can be blood, sputum, nasal swabs, pharyngeal swabs, anal swabs, Bronchoalveolar Lavage Fluid (BLF), and secretions of the lower respiratory tract[48]. Nasal swabs and throat swabs have been extensively used for diagnostics owing to simplicity of sampling technique, conventional storage and transfer feasibility of specimens[49]. Collection of BLF had been highly recommended in severe and critical cases as BLF has a rich source of viral particles in comparison to nasal and pharyngeal compartments. Moreover, detection rate of SARS-CoV-2 in BLF has the highest success rate (100%)[50]. The choice of the specimen also correlates to the number of days post-onset of the disease. The maximum viral load in throat swabs can be detected within 4-7 days; in sputum specimens within 7-10 days, and in stool samples within 0-11 days. Precautionary measures and safety are highly emphasized and strictly observed while collecting and processing the samples[51].

Detection of SARS-CoV-2 in Laboratory and Clinical Settings

During the initial days of the COVID-19 outbreak, individuals were suspected as per WHO guidelines based on their exposure to COVID-19 infected areas, and symptoms of fever and cough[52]. For detection of SARS-CoV-2 in the laboratory, Nucleic Acid Amplification Test (NAAT) is conducted either through Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or High Throughput Sequencing (HTS). In case of RT-PCR primers of highly

conserved regions, RdRp gene, S gene, E gene, and N gene were designed, and protocols were optimized. The highest analytical sensitivity for real-time amplification has been observed in the RdRp assay[53]. HTS is extensively used to test the presence of the viral genome of SARS-CoV-2 in test samples. However, large-scale HTS- based testing has not been adapted globally as it is not cost-effective[49]. In clinical settings, primary confirmation is obtained by a Computed TopographyScan (CT-Scan) of the chest, reporting morphological abnormalities of the lungs[54]. Infected patients are reported to suffer from damaged lungs, indicating ground-glass opacity, bilateral patchy shadows, and segmentations of lungs[55,56]. Clinical evidences suggested that it takes almost 10 days for severe lung abnormalities to get noticed after the initial onset of disease[50].

Molecular Techniques for Detection of SARS-CoV-2

Once the extraction procedure is completed, the presence of the SARS-CoV-2 genome is detected in the test samples. For this purpose, the following molecular techniques based on nucleic acid detection have been customized.

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

SARS-CoV-2 is a single-stranded RNA virus. During RT-PCR, ssRNA is firstly converted into a complementary DNA (cDNA) with the help of reverse transcriptase. Reverse transcriptase uses RNA template to synthesize a hybrid DNA molecule by extending the 3´ end of the annealed primer. Once cDNA molecules are synthesized, denaturation takes place and single stranded DNA (ssDNA) molecules are generated, primers are annealed to the template, and elongation takes place by the addition of complementary A, T, C, and G nucleotides to a specific region. Amplification is monitored with the help of a fluorescent dye or sequence-specific DNA probe. Sequence-specific DNA Probe is labeled with a fluorescent molecule and a quencher molecule[57]. Primers are designed complementary to highly conserved region of the genome and are usually 17-22 nucleotides long. Amplification of targeted region is carried out in one step or two steps. During one-step RT-PCR, the amplification process is either carried out in the same vial in which cDNA is synthesized. In two-step RT-PCR, the cDNA template is transferred to a new vial, and the PCR master mix is added to increase the copy number of cDNA. Single-step RT-PCR is time-efficient, whereas, two-step RT-PCR is comparatively sensitive[58]. In the case of RT-PCR for SARS-CoV-2, the genomic regions of ORF1b, ORF8, N, S, RdRp, and E genes were preferred. Based on the urgency of test results, single-step RT-PCR has been extensively used for COVID-19 testing. RT-PCR based commercialized diagnostic kits included COVID-19 RT-PCR (LabCorp), 2019-Novel Coronavirus Real-Time RT-PCR diagnostic panel, TaqPath COVID-19 Combo kit (ThermoFisher Applied Biosystems), Allplex 2019-nCoV Assay (Seegene), and COBAS SARS-CoV-2 (Roche). SimplexaTM COVID-19 direct assay does not require extraction of viral RNA from DNA/RNA sample solution and selectively amplifies only the targeted regions of SARS-CoV-2[58]. RT-PCR diagnostic method is limited as it is sensitive to handle, and time-consuming. The protocol requires RT-PCR thermocycler for temperature variations and is dependent on the sample processing capacity of the thermocycler[57].

Isothermal Nucleic Acid Amplification

Isothermal nucleic acid amplification is a recently developed technique that does not require a variation in temperature as required for RT-PCR. It is the working principle of Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) and Transcription-Mediated Amplification (TMA). SARS-CoV-2 detection kit developed by ID NOW COVID-19 (Abbott Diagnostics) is based on RT-LAMP. The technique takes only 13 minutes per sample to detect viral genome, however, the apparatus is limited to a single tube run[57]. Hologic's Platform has successfully developed high throughput transcription-mediated amplification, which is capable of processing 1,000 samples per day. At the molecular level, hologic panther fusion platform captures the target sequences, amplify specific regions, and detects RNA amplicons transcribed from single-stranded cDNA. The viral RNA fragments are hybridized to oligonucleotides probes and T7 promoter primer[7]. The oligonucleotides contain a complementary sequence of magnetic micro particles, which are separated from an ocean of fragments by applying magnetic field. The captured RNA molecule is reversed transcribed for cDNA and the RNA strand is degraded. The ssDNA molecule is replicated and

denatured to produce templates for RNA amplicons. RNA amplicons are detected with the help of single-stranded torch conjugated to fluorophore and quencher and emit photons upon hybridizing to the RNA amplicon and the signal is read by detectors[36]. The Hologic Panther SARS-CoV-2 has shown greater sensitivity to minute amounts of viral genome present in solution. Gorzalski *et al*., have retested 116 samples of SARS-CoV-2 through TMA and found 98.2% detection accuracy as compared to 96.2% for RT-PCR. TMA has given zero false-positive results with 100% specificity[59]. The platform has been highly recommended by food and drug regulatory authority for testing of large sample size under emergency situation.

CRISPR Assays

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are the nucleic acid sequences present in prokaryotic organisms and are the recognition sites of CRISPR-associated set of enzymes (Cas9, Cas12, and Cas13). Gootenberg *et al*. have previously used Cas13a and combined allele-specific sensing ability of CRISPR and recombinase polymerase amplification to detect RNA fragments of Zika Virus and other pathogens[60]. Cas12 has also been modified to recognize and cut viral RNA of African Swine Fever Virus[61]. CRISPR-based assays have also been established to qualitatively detect SARS-CoV-2. For this purpose, SHERLOCK Biosciences had strategized CRISPR detection technique capable of detecting 10-100 copies per microliter of the sample. Synthetic RNA fragments of COVID-19 were used to perform the test-run. S gene and ORF1ab gene were selected as targeted regions. Isothermal RNA amplification was carried out and amplified fragments were detected through LwaCas13a CRISPR guided RNAs. The qualitative analysis was confirmed by dipstick method and no additional instrument for detection was needed. The breakthrough of CRISPR-based assays had significantly shortened the detection time to 40-60 minutes as compared to 4-6 hours of RT-PCR for detection of SARS-CoV-2 genome[62]. The DETECTR (SARS-CoV-2 DNA endonuclease-targeted CRISPR trans-reporter) have designed RT-LAMP for amplification of extracted RNA from nasopharyngeal and oropharyngeal swabs. The procedure is followed by detection of predefined targeted regions of E gene and N gene by Cas12. The Cas12 fluorescent signal is detectable in <1 min and a visual signal is achieved within 5 mins. The protocol is highly efficient as no cross-reactivity of the N gene of SARS-CoV-2 with other infectious coronaviruses (OC43, HKU1, 229E, and NL63) is noticed. The Cas12a based CRISPR assay needs no special instrument for read-out and takes only 45 minutes. Thus, CRISPR-based assays provide a breakthrough for larger capacity of COVID-19 testing in a limited time duration.

CLINICAL FEATURES OF SARS-COV-2 INFECTED INDIVIDUALS

Incubation Period and Critical Days

The studies conducted by Xu *et al*., in China have reported incubation period of 3-5 days[63]. Guan *et al*., studied 1,099 patients in China and have reported median incubation period of 4 days. An exceptional incubation period of 24 days had also been observed, which highlighted the importance of quarantine and social distancing to avoid human to human transmission[56]. Pooled analysis of confirmed COVID-19 patients from 4 January, 2020 to 24 February, 2020 has determined incubation period of 5 days[64]. Systematic review and meta-analysis of 18 studies have generated mean incubation period of 6 days with 2 to 14 days critical for onset of illness. Studies concluded by Wang *et al*., have declared 7 to 13 days critical times after the onset of illness and have analyzed clinical parameters including average age, gender ratio, and underlying diseases in COVID-19 patients[65].

Sex-specific and Age-specific Dominance

During 2020, SARS-CoV-2 infection remained dominant in men as compared with women. The mortality rate of COVID-19 was higher in male patients than in female patients[66]. Kopel *et al*., provided a biological explanation for this higher rate of incidence, as kidneys in the male body have more ACEII receptors in comparison to the female body. The immunological mechanism of the female body produces more titer of antibodies[67]. Progesterone and 17 β-estradiol are exclusively produced in females and exhibit immunomodulatory roles. They enhance immune tolerance, deregulate innate immune inflammatory response, and prevent “Cytokine Storm”. These attributes contribute to mild and non-severe progression of COVID-19 in women[68]. The average age of patients was determined 49-70 years[69].

Clinical Manifestations of COVID-19

The clinical manifestations of novel coronavirus have been reported to vary from person to person. The confirmed infected individuals may show no symptoms at all i.e. asymptomatic condition. Common symptoms include fever, dry cough, muscular pain, anorexia, dyspnea, and fatigue [70]. Less common symptoms include headache, sore throat, sputum production, vomiting, and diarrhea. Patients in critical condition suffer from pneumonia, a lower respiratory rate, lymphopenia, and hypoalbuminemia[65]. Sustainment of pathological conditions in patients admitted to Intensive Care Unit (ICU) leads to severe pneumonia, cardiac malfunctioning, shock, Acute Respiratory Distress Syndrome (ARDS), Acute Kidney Injury (AKI), and Multiple Organ Dysfunction Syndrome (MODS)[71]. ARDS is Type-I Respiratory Failure (T1FR) and is marked by the presence of hypoxia (PaO_2 < 8000 Pa), tachypnea, tachycardia, cyanosis, and absence of hypercapnia[72]. Moreover, secondary infection by bacterial sp*. (Staphylococcus caprae,* and *Acinetobacter buamanni)* has also been reported in COVID-19 patients, which insists the compromised immunological setup and multiple culprits for additional severity of pneumonia[65]. Autopsy report of the COVID-19 deceased in China indicated the presence of gray-white patchy lesions in the lungs and alveolar damage with cellular fibromyxoid exudates, bilateral lung tissue damage and ARDS[63]. Barton *et al*., conducted autopsy in the U.S.A. that confirmed the alveolar damage, airway inflammation, and acute bronchopneumonia in non-survivors[73].

SARS-CoV-2 Infection in Pregnant Patients

Changes in the immune system, increase the susceptibility to respiratory infections during pregnancy[74]. The clinical manifestations of COVID-19 are not different in pregnant women when compared to the general population[75]. Fever (36.5°C-38.8°C), cough, shortness of breath and myalgia are the main symptoms reported in SARS-CoV-2 positive pregnant patients. Lymphopenia, elevated levels of C-reactive proteins, aspartate aminotransferase and alanine aminotransferase have also been noticed[76]. Pregnant women have reported pulmonary complications during CT scan, including focal, scattered or bilaterally distributed lesions in the lungs, lymphadenopathy and ground-glass opacity[75]. COVID-19 can also develop complications in the form of fetal distress[77]. Pregnant females developing severe clinical conditions in the old age group, had higher BMI, diabetes and exhibited gastrointestinal disturbances including diarrhea, vomiting, and nausea[78]. In COVID-19 pregnant women, standardized care requires additional protection during the antenatal period, vaginal or cesarean delivery and breastfeeding[74].

A study was conducted on 33 neonates born to COVID-19 mothers under strict preventive infection measures, which indicated positive results for only 3 neonates (9%), confirming vertical transmission of SARS-CoV-2[79]. Viral particles remained unidentified in the breast milk sample of eight patients, however, the possibility of superficial transfer through droplets has not been ruled out, demanding extreme precautions during breastfeeding[80]. The vaginal secretions of pregnant women also reported virus-free suggesting vaginal delivery as safe as cesarean recommended to avoid transfer of infection through any means[81]. COVID-19 is also responsible for the increase in the mortality rate among pregnant women. In non-pregnant females, SARS-CoV-2 infection can cause disturbance in the female reproduction cycle, and the menstrual cycle. It may develop infertility as ACEII are also present on the ovaries, uterus, vagina, and placenta[82]. Children are considered more vulnerable to SARS-CoV-2 Infection, however, clinical manifestations of COVID-19 cases in children are generally less severe than adults[83].

Role of Underlying Diseases and Comorbidities

Hypertension, Cardiovascular Diseases (CVD), and diabetes added additional burden to COVID-19-associated severity and death rate. Hypertensive patients are at greater risk to develop complications during SARS-CoV-2 infection as ACE-II is common to both Renin-Angiotensin-Aldosterone System (RAAS) induced hypertension and COVID-19[84]. Hypertension is the most dominant comorbidity (16.9%), followed by diabetes (8.2%) in Chinese COVID-19 cases[85]. In a study on 212 Chinese patients, pre-existing injuries to kidneys (27.3%), liver (8.7%), and heart (6.1%) have been related to poor prognosis of COVID-19, and patients may encounter life-threatening situation[85]. In New York hypertension is reported in 56.6% of 5700 patients admitted to 12 hospitals around the city. Other underlying conditions, including

Diabetes (33.8%), Coronary Artery Disease (11.1%), Congestive Heart Disease (6.9%), Cancer (6%), Chronic Obstructive Pulmonary Disease (5.4%), Chronic Kidney Disease (5%), and liver disease (0.6%) are also observed[86].

Diabetes is a metabolic condition and is marked by elevated levels of glucose in the blood. Diabetic patients are at a higher risk for SARS-CoV-2 infection as observed in the SARS-2003 and MERS-2012 pandemics[87]. Diabetes also plays an indirect role in viral pathology by facilitating viral entry into cells and impairing the immune system[88]. Guo *et al*., reported that COVID-19 diabetic patients are at a higher risk of developing severe pneumonia, release of tissue injury-related enzymes, hypercoagulable state associated with dysregulation of glucose metabolism and uncontrolled inflammation responses[89]. Moreover, in diabetic patients, therapeutic concern is limited to CQ but not for ACE inhibitors, angiotensin receptor blockers, or thiazolidinediones. Thus, during treatment of SARS-CoV-2 diabetic patients, regular blood glucose monitoring and patient-tailored therapeutic strategies are highly recommended[90].

Patients with chronic obstructive pulmonary disease (COPD) are also at a higher risk of poor prognosis and COVID-19-induced mortality. Alqahtani *et al*., have analyzed the role of "Smoking" and have reported it as a potential risk factor associated with COVID-19 progression, as both active smokers (22%) and ex-smokers (46%) progressed to severe cases[91]. The underlying comorbidities do not confer the same degree of risk; hypertension, CVD, and diabetes significantly assist in the development of complications in COVID-19 patients, whereas, cerebrovascular diseases, chronic liver, and renal disorders have shown non-significant relation to progression of severity in COVID-19 patients[92]. They can also cause therapeutic intervention in COVID-19 treatment, thus limiting the range of therapeutic agents to be used for treatment of SARS-CoV-2 infection[93].

Immunological Assessment of COVID-19

The human body initiates innate immune system upon recognizing foreign antigens displayed on the surface of the infected cells. The innate immune response is followed by an adaptive immune response. Dendritic cells and macrophages initiate a cascade of inflammatory cytokines and chemokines, which attract granulocytes and macrophages[94]. Tumor Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-12 (IL-12), Interferon-α (IFNα), Interferon-β (IFNβ), Interferon-γ (IFNγ), IFN-γ-induced Protein-10 (IP-10), and Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage Colony-Stimulating Factor (GM-CSF) and Granulocyte Colony-Stimulating Factor (G-CSF) act as inflammatory cytokines and promote infiltration of inflammatory cells[95]. CD4+ T cells and CD8+ T cells play a major role in clearance of viral infection[94]. During SARS-CoV-2 infection, activation of the immune system and recruitment of monocytes, dendritic cells, natural killer, T cells and B cells cause fever and mild symptoms of COVID-19[96]. The over-production of inflammatory cytokines during combating the virus, termed as "Cytokine Storm", damages pulmonary tissue at the site of infection. This deterioration of the lungs develops into ARDS and also causes multiple organ failure and death[97]. Asymptomatic individuals have lower levels of pro-inflammatory and anti-inflammatory cytokines, particularly, Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL), Growth-related Oncogene- α (GRO-α). G-CSF and IL-6, indicating a weaker immune response to SARS-CoV-2[98].

During the early phase of pandemic, several studies for immunological characterization of COVID-19 patients were conducted. In Wuhan, the immunological characterization of 107 patients has indicated significant reduction in lymphocytes with severity of clinical conditions[1]. Comparative analysis of clinical and immunological features of moderate cases and severe cases has also reported significant decline in levels of absolute T-lymphocyte, CD4+ T cells, and CD8+ T cell in severe cases as compared to moderate cases[70]. In New York, 90% of hospitalized patients were initially diagnosed with lymphopenia[99]. Chen *et al*., have extensively evaluated cytokine levels in plasma as an immunological indicator and have noticed highly significant values of IL-2R ($P < 0.001$), IL-10 ($P = 0.001$) and significant value for TNF-α ($P = 0.02$). However, no significant differences among severe and moderate patients have been reported for IL-1B ($P= 0.40$), IL-6 ($P= 0.04$), and IL-8 ($P=0.22$). Immune profiling of COVID-19 has revealed heterogeneous immune response with severity of SARS-CoV-2 induced illness. Mathew *et al*., performed High Dimensional Flow

Cytometry of immune components in COVID-19 patients and identified three groups of patients. Patients with severe clinical manifestations of COVID-19 have shown elevated levels of activated CD4+ T cells and lower levels of exhausted CD8+ T cells, and Plasmoblasts. Patients with mild clinical conditions either have reduced CD4+ T cells and elevated level of memory B cells or have highly insignificant levels of activated T cells and memory B cells[100]. In recovered patients, lymphopenia and levels of CD4+ T cells and CD8+ T cells were within normal range[70].

Production of SARS-CoV-2 Specific Antibodies

The time duration of infection to immune response via antibodies production varies from disease to disease and shows variation among patients with the same viral infection. The infected person produces IgM, IgG, and IgA antibodies against N-protein and glycoproteins of S-protein of the enveloped viruses, as observed in the neutralization response to Human Immunodeficiency Virus (HIV)[101]. The serologic studies on SARS and MERS have shown that in patients, virus-specific antibodies are detectable on day 14 after onset of disease[102]. In the case of COVID-19, IgM and IgG antibodies can be detected in one to two weeks of SARS-CoV-2 infection[103]. Hu *et al.,* observed the level of IgM and IgG in COVID-19 patients, which was 73.5% collectively on day 13-15 onset of disease and 97.8% on day 16-18 onset of the disease. Mild and severe patients produced the same amount of IgM, but there was a significant difference in production levels of IgG, as patients with more severity of SARS-CoV-2 infection produced more titer of IgG[104]. The seroconversion of IgM can occur before, simultaneously, or after the seroconversion of IgG[105]. SARS-CoV-2-specific viral antibodies have also been successfully identified in asymptomatic individuals; however, the level of IgG is reported to be lower than in acute symptomatic patients[98].

The titer of antibodies against SARS-CoV-2 infection increases with the severity of disease irrespective of age, gender, and underlying comorbidity[106]. In severe cases of COVID-19, antibodies have failed to generate an effective response against viral particles of SARS-CoV-2. The inefficiency of these antibodies to display significant viral neutralization has been suggested to be associated with cytokine storm, Antibody-Dependent Enhancement (ADE) of viral uptake by macrophages, and enhanced inflammation resulting in immunopathology[107]. In follow-up studies of recovered discharged patients, IgG concentration were reduced by 21% and IgM concentrations declined by 23%[104]. The decline in titer concentrations of SARS-CoV-2 specific antibodies is suggested to provide protection for limited a time period in recovered patients and increases chances of reinfection.

TREATMENT STRATEGIES FOR COVID-19 PATIENTS

In general, COVID-19 patients are treated with antiviral therapy, corticosteroid therapy, intravenous immunoglobulin therapy, and oxygen therapy. During COVID-19 pandemic, randomized and non-randomized clinical trials faced challenges regarding sample size, variation of clinical severity among patients and time constrain for effective treatment yet significant progression to continue or discontinue a particular therapy was reported[108].

Antiviral Treatment of COVID-19 Patients

During the early days of the pandemic, the exact pathogenic pathway of SARS-CoV-2 was not fully understood, thus existing antiviral agents were used for treating COVID-19 patients. In China, Oseltamivir, Ganciclovir, Arbidol, Lopinavir, and Ritonavir have undergone clinical trials for the treatment of the novel coronavirus infection[3]. Lopinavir and Ritonavir are licensed protease inhibitors of HIV, which have shown promising results against SARS-CoV in 2003-2004. These drugs are also recommended for safe treatment of COVID-19 in pregnant women[109]. However, it has been noticed that these drugs failed to reproduce an effective response in other patients as no significant difference in treatment of SARS-CoV-2 infection was obtained in standard care and experimental group[110].

Remdesivir is a nucleotide analog RNA Polymerase Inhibitor with broad-spectrum antiviral activity, and has previously been used for treatment of Ebola virus infection (2014-2016)[111,112]. The preliminary report on a clinical trial of Remdesivir indicated contraction in recovery period of COVID-19 patients to 11 days as compared to 15 days in the control group[113]. Moreover, the final report revealed that Remdesivir had a median recovery time of 10 days as compared to 15 days in the control group. Moreover, patients treated with Remdesivir required a lower

proportion of supplementary oxygen through mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO). During the trail, adverse side-effects common to Remdesivir group and Placebo group were pyrexia, hyperglycemia, anemia, reduced hemoglobin levels and decline in glomerular filtration rate[113].

Favipiravir is an RNA-Dependent RNA Polymerase inhibitor, which is used for treatment of Influenza Viruses A, B and C. Favipiravir has been found effective as etiotropic treatment for SARS-CoV-2 infection. It has been revealed that 62.5% patients treated with Avifavir (Favipiravir) showed viral clearance on day 5 and 92.5% showed viral clearance on day 10 of drug intake. Moreover, it is highly effective in normalizing body temperature in symptomatic COVID-19 patients as early as day 2 of drug intake. The adverse side effects of Avifavir included chest pain, nausea, and gastrointestinal disorders including diarrhea and, vomiting[114]. Cai *et al*., have reported that time duration for viral clearance by Favipiravir is less than that of Lopinavir/Ritonavir in COVID-19 patients[115]. In June 2020, in China randomized controlled trial for testing the therapeutic effectiveness of Favipiravir in patients who, after testing negative once tested positive again for SARS-CoV-2 RNA through reinfection, reactivation of original virus or new infection under NCT04333589[116].

Chloroquine (CQ) and its derivatives are a class of FDA-registered antimalarial drugs which also exhibit antiviral activity. During the SARS epidemic, studies have revealed the antiviral role of CQ as it interfered with glycosylation of ACEII *in vitro.* suggesting the prophylactic and therapeutic use for SARS-CoV infection[117]. The use of CQ in a pilot study of chronic patients possessing Hepatitis-C Virus (HCV) infection also reported significant reductions in viral load of HCV RNA[118]. However, the antiviral property of CQ was also found to be ineffective during *in vivo*. analysis for therapeutic role in HIV infection, highlighting its controversial antiviral role and low safety index[119]. Hydroxychloroquine (HCQ), a derivative of CQ has shown more potency Physiologically Based Pharmacokinetic Models (PBPK) *in vitro.* than CQ[120]. Gautret *et al*., have reported a significant reduction of SARS-CoV-2 viral load in 20 patients treated with HCQ as a primary drug and azithromycin as a reinforcing drug[121]. In U.S.A., an extensive protocol for randomized controlled trial was designed to study the post-exposure prophylaxis role of HCQ in close contact, with results expected in later half of 2020[122]. Another randomized controlled trial was designed in Spain to access prophylactic role of HCQ in pregnant women under NCT04410562[123].

Zinc exhibits antiviral activity through multiple mechanisms. It plays an important role in the immune system through viral recognition, restoration of depleted immune cell function and prevention of cytokine storm[124]. It inhibits viral attachment to host cell receptors and interferes with viral replication by altering the proteolytic processing of replicase polyprotein and RdRp in SARS-CoV, HCV, rhinoviruses and influenza viruses. Zinc showed synergistic effect when co-administered with antiviral therapy in HIV, HCV and SARS-CoV[125]. Zinc is crucial for maintenance of respiratory epithelium and ion-balance system. COVID-19 patients also share risk factors common to zinc deficiency including old age, gender, and diabetes[126]. Case study on four COVID-19 patients reported significant improvement in COVID-19 patients provided with high- dose zinc therapy. Thus, it is highly recommended to further evaluate the association of zinc deficiency with severity of COVID-19 infection[127].

Corticosteroid Treatment of COVID-19 Patients

Therapeutic corticosteroids are administered as an adjuvant therapy for viral infections, particularly influenza and pneumonia. They consist of synthetic Glucocorticoids (GC) and Mineralocorticoids (MC). GC exhibit anti-inflammatory and immunosuppressive properties[128]. GC receptors are located on the surface of epithelial cells and renal cells; upon ligand binding, they enter the nucleus and downregulate genes of pro-inflammatory cytokines and chemokines including AP-1 and NF-kB, and also activate anti-inflammatory genes[129]. However, long-term GC therapy can induce severe side effects, metabolic diseases, cardiovascular anomalies and may attribute to inflammation[128]. Corticosteroid treatment has been associated with sustained viral load in blood, delayed viral clearing, and elongated hospitalization in MERS[130]. Boudreault *et al*., indicated that the adaptation of corticosteroid therapy provides controversial information, as immunomodulation via corticosteroids has varying effects depending upon the specific respiratory virus and rises concern for safety and efficacy of treatment[131]. Based on past clinical evidence, Russell *et al*., also deemed the

treatment as non-beneficial and unqualified to be specifically recommended for SARS-CoV-2[132]. Due to contradictory evidence of corticosteroid therapy in viral infections, the WHO recommended to discontinue by 28 January 2020[7].

Corticosteroid therapy reduced the mortality rates in hematopoietic cell transplant patients infected by seasonal influenza virus[131]. Chen *et al*., reported a reduction in hospitalization period for corticosteroid treatment of SARS-CoV infection and lower mortality rate. These results were contrary to those previously reported by Auyeung *et al*., who reported 20.7-fold increase in ICU administration (severity of clinical conditions) and increased death rate[133,134]. Methylprednisolone has been associated with survival in ARDS patients[135]. During the initial phase of COVID-19 pandemic, corticosteroid therapy was used in 20-44.9% of Chinese severe patients[136]. Low-dose and short-term administration of Methylprednisolone was associated with improvement of oxygen saturation (SpO_2), and better clinical outcomes in COVID-19 patients[134]. Furthermore, corticosteroid treatment also alleviated pulmonary fibrosis and prevented further pathological deterioration in lung injury in COVID-19 patients with ARDS[137]. In June, U.K. reported the clinical trials of Dexamethasone (steroid) under 'recovery' to be effective as one-third reduction in the mortality rate of critical COVID-19 patients was observed[138].

Antibiotic Treatment in COVID-19 Patients

In humans, antibiotic treatment is carried out for illnesses caused by pathogenic bacteria. In COVID-19 patients, a compromised immune system could lead to secondary infection by bacteria. Risk factors for secondary infections include old age, underlying diseases, and a suppressive immune system[139]. The antibiotic treatment was used to cope with such infections[65]. Antimicrobial (antibacterial and antifungal) assessment in sputum is an important indication of superinfection by bacterial and fungal pathogens[140]. *Acinetobacter baumannii, klebsiella pneumoniae, pseudomona aeruginosa, enterobactor cloacae, serratia marcescens, aspergillus fumigatus, aspergillus flavus, candida albicans* and *candida glabrata* were reported as causative agents of secondary infection in various studies[67,92].

In China, intravenous antibiotic treatment was provided to 58% of patients (637/1099), where 78% had mild conditions and 22% exhibited severe clinical manifestations[56]. Huang *et al*., also adapted antibiotic therapy in 81(100%) patients in the study cohort, even though only 10% had secondary bacterial infection[136]. In pregnant patients, administration of intravenous Ceftriaxone was recommended to combat bacterial pneumonia and sepsis[141]. In France, co-administration of azithromycin with HCQ generated better results than HCQ, the significance of azithromycin in the prevention of secondary bacterial infection. Azithromycin also assisted HCQ in the rapid clearance of viral load in 100% of patients as compared to 12.5% of patients in control group[142]. Essential monitoring of immunological parameters in COVID-19 patients is highly recommended to strategize antibiotics use in the treatment of secondary microbial infections[140].

Oxygen Therapy of COVID-19 Patients

For better outcome, therapeutic approach is combined with mechanical medical assistance. Non-invasive ventilation is provided by nasal cannula and an oxygen mask to COVID-19 patients with mild symptoms[66,136]. Mechanical invasive ventilation and Extracorporeal Membrane Oxygenation (ECMO) assist breathing in COVID-19 patients who have developed severe lower respiratory deterioration[143]. The NIV has proved effective in increasing arterial blood gas tensions in patients with impaired central respiratory drive. The NIV is conducted either through Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP). Bi-PAP ventilators and volume-controlled ventilators have been recommended for severe pulmonary injury and ARDS[144]. Moreover, selection between CPAP and High-Flow Nasal Oxygen (HFNO) is based on clinician's choice and depends on airway pressure, O_2 consumption, and patient tolerance. In practice, CPAP is usually preferred to HFNO owing to adjustable airway pressure, provision of 50% Fracture of Inspired Oxygen (FiO_2) at 5-6L/min, patient-ventilator synchrony, and precautions during setting.

Invasive mechanical ventilation is connected to a mechanical ventilator and includes tracheal tube, laryngeal mask, and tracheostomy to bypass the upper respiratory tract. It is used to stabilize patients suffering from

hypoxemia, hypoventilation, hypercapnic respiratory failure, acute lung injury, and ARDS. Mechanical ventilation is guided by clinical condition, comorbidities of patients, optimization of delivered Tidal Volume (TV), and Respiratory Rate (RR). The mechanism of invasive mechanical ventilation is based on trigger, target, and cycle. The trigger is initiated either through a patient's breath or is set as time-triggered in the absence of patient's breath. Target refers to breath delivery strategy and cycle determines how breath is terminated[145]. In patients with severe pneumonia or ARDS, AC-VC ventilators are the best choice as airway pressure is not maintained externally in these ventilators, but is a function of compliance, and resistance of the respiratory system of a patient. AC-PC type ventilators are also proposed for ARDS patients admitted to ICU, however, there is risk of barotrauma formation in some patients. Pressure Regulated Volume Control (PRVC) system does not satisfy ARDS patient's respiratory needs, is only recommended in recovering patients. Walter et al., suggested ideal mechanical conditions for ARDS as RR of 20 breaths per min, inspiratory rate flow of 80 LMP, FiO_2 at 7-8mL/kg IBW, PEEP 5cm H_2O and P_{plt}< 30cm H_2O and PaO_2 55-80mmHg[145]. A detailed precise study focusing on the ventilation system best aligned to patients' respiratory need and survival for COVID-19 is highly recommended to be conducted as oxygen therapy is of prime importance alongside therapeutic treatment.

Synthesis and Production of SARS-CoV-2 Vaccines

The vaccine is a product capable of inducing an immune response by generating antibodies once administered into the body of an organism. Vaccination immunizes that individual or boost pre-existing immunity against specific bacterial or viral infections. Large-scale production of vaccines is an elongated process. It is initiated with the selection of appropriate viral targets, *in vitro* studies, pre-clinical trials in animal models, clinical trials, establishment of pipeline and production of vaccine in large-scale[146]. Once sufficient pre-clinical data is obtained, three phases of clinical trials are conducted. Phase I clinical study is conducted in small sample size, Phase II is done to optimize dosage and Phase III is conducted on larger sample size particularly, a demography at risk. Large-scale production of vaccine requires the approval of FDA, setup of good manufacturing practices, and production platforms[147].

During the early phase of the pandemic, insufficient funding, non-availability of pre-clinical data, non-optimized pipelines, and lack of capacity for mass production of SARS-CoV-2 vaccines resulted in global challenge[146]. In order to develop SARS-CoV-2 vaccines for global population, study, trial was designed, regional, national and international demographics were targeted, rigid and flexible clinical endpoints were determined, traditional and non-traditional technological platforms were adapted, and vaccines were produced in large quantities. Under the umbrella of the Coalition for Epidemic Preparedness and Innovations, and WHO, Vaccine R&D confirmed 115 vaccine candidates initially, and the number was increased to 321 in the latter half of 2020. Pre-clinical studies and clinical trials were initiated by China, USA, Germany, Australia, South Africa, India and South Korea. Human first-line immune response is initiated fully against Spike protein antigen, a primary protein for the interaction of virus-host cell receptor, thus, offering "target antigen" for vaccine development[147].

Based on chemical composition, vaccines for viruses are categorized into protein subunit vaccines, live-attenuated virus vaccines, whole inactivated viral vaccines, viral vector vaccines, Virus-Like Particle (VLP) vaccine, DNA vaccine, and RNA vaccine. SARS-CoV-2 has shown a genomic resemblance to Coronaviruses; however, no FDA approved commercial vaccine is available against Coronaviruses until COVID-19[148]. Protein subunit vaccines comprise of viral antigenic fragments (responsible for generating immune response) and adjuvants (enhance immunogenicity)[149]. S-protein of SARS-CoV and MERS-CoV offer better targets for inducing immune response as compared to N and M structured proteins. Protein subunit vaccines for SARS-CoV and MERS-CoV are based on S-protein targets. During clinical trials, both RBD-based vaccines for SARS-CoV and MERS-CoV induced high-titer neutralizing antibodies without causing pathogenic effect. RBD-based vaccines for SARS-CoV also induced long-lasting neutralizing antibodies for 12 months and that of MERS-CoV for 6 months[150,151]. However, full length S-protein and trimeric S protein (triSpike) of SARS coronavirus also contained non-neutralizing epitopes, and triggered Fcγ Receptor-II (FcγRII)-dependent SARS-CoV

infection *in vitro.* Protein subunit vaccine of SARS-CoV-2 targets full length S protein or RBD of S protein. During 2020, Novavax (SARS-CoV-2 rS/Matrix-M1 adjuvant) entered phase II trial (NCT04533399) in South Africa. Anhui Zhifei Longcoms's recombinant new coronavirus vaccine contains RBD of SARS-CoV-2 (NCT04466085) has also entered phase II clinical trials. These trials were designed to evaluate the efficacy, immunogenicity and safety of SARS-CoV-2 recombinant vaccines[149].

Virus-like Particle (VLP) vaccines present similar conformation of epitopes as in the original virus, but they lack a viral genome. VLP vaccines for Human Papillomavirus (Cervarix and Gardasi) and Hepatitis-B virus (Engerix and Recombinvax HB) have been successfully commercialized[152]. In case of SARS-CoV, chimeric VLP consisting of S protein and influenza virus M1 protein are capable of inducing an immune response against SARS-CoV in the experimental group of mice. The *in vivo* study of mice model also revealed an effective immune response induced by chimeric RBD (MERS-CoV) and VP2 structural protein of Canine Parvovirus[152]. However, VLP vaccines also induce pulmonary immunopathology in preclinical mice models[153]. The evaluation of immunogenicity of SARS-CoV-2 VLP vaccine (NCT04450004) has been registered for clinical trial phase I. In contrast to VLP, DNA vaccines contain genes encoding viral antigen components that are expressed by plasmid vectors. DNA vaccines are administered through electroporation of individual's cells[149]. S-protein based DNA vaccines exhibited the greatest immunogenicity in SARS-CoV and MERS-CoV. GLS-5300 (INO-4800), DNA vaccine of MERS-CoV produced an immune response in 85% participants recruited in the clinical trial registered under NCT04447781 and NCT04336410[154]. Full length DNA vaccine for SARS-CoV-2 designed by Inovio's (INO-4800) has induced T cell immune response in 94% participants with no major adverse effect.

RNA vaccine production platforms are mainstreamed exclusively for COVID-19. RNA vaccines contain mRNA of the antigens that translates inside the human cell and consequently initiates the immune response[149]. Moderna mRNA-1273 vaccine encodes a modified perfusion S-protein, which is more stable and prevents activation of interferons[155]. The Phase III clinical trial (NCT04470427) exhibited 94.5% efficacy with no significant safety concerns. BioNTech and Pfizer's mRNA was initially focused on four candidates BNT162b1 (modified RNA translated into trimer-RBD), BNT162b2 (modified RNA encoding full-length S-protein), BNT162a1 (uridine mRNA-based vaccine), and BNT162c2 (Self-amplifying RNA based vaccine). BNT162b2 exhibited maximum efficiency of 95% against SARS-CoV-2 and least systematic reactogenicity in the old age group[149].

Viral vector vaccines are recombinant vaccines capable of encoding viral antigens in modified viruses. Viral vector platforms include Adenovirus, Measles virus, Parainfluenza virus, Rabies virus, Modified Vaccinia Virus Ankara (MVA), and Vesicular Stomatitis Virus (VSC). The manufacturing process of these vaccines is complex since it requires custom optimization of cellular systems, exclusion of contaminants, and safety concerns regarding integration of genome into vaccinated human[149]. In the case of SARS-CoV, the adenovirus vector expressing S1 fragment, and MVA expressing S-protein-induced immune response in animal models[156,157]. MERS-CoV S-protein vaccine based chimpanzee adenovirus vector (ChAdOx1) induced high titer of antibodies and was determined safe and well tolerated during clinical trial for MERS-CoV vaccine[149]. COVID-19 viral vector vaccines include AZD1222 (ChAdOx1 nCoV-19), Gam-COV-Vac (rAd26S+rAd5-S), and Ad5. AZD1222 was developed by the collective efforts of Astrazeneca and Oxford University. Gam-CoV-Vac, also known as Sputnik-V is developed by Gamaleya Research Institute, and Ad5 is developed by CanSino Biological Inc. and Beijing Insitute of Biotechnology. AZD1222 (ChAdOx1 nCoV-19), expresses a SARS-CoV-2 S protein. The interim report published in July 2020 stated that it can initiate immune response with no severe adverse side effect[158]. Moreover, the results of Phase II/III clinical trial in UK (2020-0012288-32) reported average efficiency of 70% in participants. Sputnik-V is designed on the recombinant viral vector system in which adenovirus type 26 vector encoding SARS-CoV-2 spike glycoprotein, and adenovirus type 5 vector encoding SAS-CoV-2 S-glycoprotein have been integrated. The Phase I/II trial results for Sputnik-V have revealed the vaccine efficacy after Dose-I is 91.4% and after Dose-II is 95%. Moreover, no adverse effect was noticed in the participants. Ad5 vector COVID-19 vaccine also induces significant immune response after single dose. It has

entered Phase III (NCT04526990 and NCT04540419) at multiple centers around the globe[149].

Live attenuated vaccines are formed after weakening the pathogenicity of viruses by mutations and deletions. These vaccines are commercially available against measles, mumps, polio, and yellow fever. No live attenuated SARS-CoV and MERS-CoV vaccines have undergone clinical trials. Moreover, none of the vaccine candidates for COVID-19 are based on live attenuated vaccine platform as the pathogenesis of disease is still not clear and global incidence of reinfection has been noticed[149]. Whole inactivated viral vaccines are generated by chemical or radiological treatment of virions. Studies indicated that SARS-CoV-inactivated particles by formaldehyde or UV are capable of inducing an immune response[159]. In case of MERS-CoV, γ-irradiated MERS-CoV vaccine adjuvant with MF59 causes eosinophil-induced pulmonary destruction along with generating neutralizing antibodies[160]. SinoVac Inc. have developed CoronaVac by inactivating SARS-CoV-2 after treating it with beta-propiolactone. Phase I and Phase II trials of CoronaVac are registered under NCT04383574 and NCT04352608. Sinopharm Inc. and Wuhan Insitute of Biological Products have collectively introduced inactivated vaccine candidate, which has demonstrated initiation of antibody response with low occurrence of adverse side effects[161].

PREVALENCE OF COVID-19 IN 2020

Epidemiological Parameters of COVID-19

The transmissibility and severity of a pandemic are characterized by epidemiological parameters including Basic reproduction number (R_o), Case-Fatality Rate (CFR) and mortality rate. Basic reproduction numbers (R_o) are an important parameter for determining the expansion potential of an epidemic[162]. It is defined as the number of secondary infections expected to generate from a single patient in a community where the disease has not occurred previously and no herd immunity has been established. The estimated $R_o \geq 1$ in particular demography indicates rapid spread of human-to-human transmissions and infection[162]. R_o values can be estimated by Stochastic Markov Chain Monte Carlo method, Dynamic Compartmental Model, Statistical Exponential Growth Model, Statistical Maximum Likelihood Estimation, Mathematical Transmission Model, stochastic Simulations of Early Outbreak Trajectories, and Mathematical SEIR-type Epidemiological Model[163]. The establishment of an epidemic is dependent on modes and routes of transmission. Transmission of viral particles is initiated through asymptomatic individuals, pre-symptomatic individuals, symptomatic individuals, and the environment. On the basis of origin of COVID-19 transmission, cases were classified into local transmission, community transmission, sporadic cases, imported cases and clusters of cases. The estimated R_o levels of COVID-19 (1.4-5.7) are significantly higher than those for MERS-2012 (0.45-3.9) but have a similar index to SARS-2003 (1.7-3.6). The CFR is another important parameter to understand the seriousness of a pandemic and is defined as the conditional risk of death for patients with the disease[164]. China observed a CFR of 2.3%, whereas Italy reported CFR of 7.2% was during the first half of 2020[165]. Republic of Korea and Germany successfully reduced CFR by 0.7%-1.2% in an infected population by adapting frequent testing equipped with smart lockdown policies, and provision of healthcare facilities[7,166]. Gradual decline in CFR was reported after the first wave of COVID-19 pandemic but it was restored during second wave of pandemic after ease in social restrictions was adapted.

Global Incidence of COVID-19 in 2020

At the beginning of the 21st century, the first coronavirus epidemic broke out in Guangdong, China occurred (2003) by SARS. SARS showed the dominant presence for 8 months in 29 countries with 8,096 cases, 774 deaths, and 9.6% mortality rate. After a decade, the MERS outbreak in the epicenter of Saudi Arabia infected 2,494 humans in 27 countries and reported a mortality rate of 34%, corresponding to 858 deaths[17]. SARS-CoV-2-induced COVID-19 is a large-scale global pandemic that has infected the highest number of people in the history of infectious diseases. Over the span of the year till 29th December 2020, it has infected 72 million people and has induced 17 hundred thousand deaths with the death rate of 2.2%, a number much lower than SARS and MERS, yet a great concern in the global population of 7795 million.

The outbreak of the COVID-19 and its global distribution has been strictly monitored by the government

organization "Center of Disease Control and Prevention", responsible for analyzing incidence rates of diseases and devising preventive measures for national health. "COVID-19" is the first pandemic which has been successfully digitalized in real-time[167]. The Chinese Center for Disease Control and Prevention successfully identified novel coronavirus on 7th January 2020, causative agent of pneumonia infection in Wuhan[10]. In collaboration with internationally recognized states and regions, WHO played a crucial role and successfully generated "Situation Reports" indicating new infections, the total number of cases, and cumulative deaths in COVID-19 patients on a daily and weekly basis. WHO declared very high-risk levels for China and risk alerts for remaining countries, on the 23rd January 2020 as export of novel coronavirus through cross-border travelers became evident[7].

During the first half of 2020, it has been reported that the total number of globally infected individuals was 9,826 in January 2020, whereas, 5,934,936 cases were later confirmed in June, 2020[168]. During February 2020, novel coronavirus spread to 54 countries, causing WHO to declare "High-Risk Levels" for the COVID-19 pandemic as a 769% increase in global cases was observed. Number of cases increased drastically in March by 779% and WHO declared "Global Pandemic". The mitigation of viral spread was carried out by adopting safety measures, and partial or complete lockdown by countries around the globe. This resulted in a relative decline in the percentage of new cases by 467% in April, 220% in May, and 20% in June 2020[169]. China, Republic of Korea, and Japan in Western Pacific; U.S.A in American region; Iran in Eastern Mediterranean and U.K., Spain, Italy, France and Russian Federation in Europe; India in Southeast Asia were highly ranked countries with COVID-19 cases in June 2020. China successfully contained the virus with a few additions of cases per month, whereas the number of cases escalated in other counties, particularly France, Spain, Italy, India, Russia and USA.

In the latter half of 2020, from July 1st to December 29th, 2020, additional cases were reported around the globe. By 30th July, WHO reported an increase of 7 million cases (17, 106,007) and 165 thousand (668,910) COVID-19-induced deaths, proposing a stern need to strictly monitor physical distance and preventive measures. In August, the WHO reported 24,854,840 confirmed cases and 838,924 non-survivors. In September, the global number of COVID-19 confirmed cases infected 0.41 percent of the global population. In October, global cumulative cases were reported as 43,341,451. In November, as escalation of 43% marked in second wave of pandemic. At the end of 2020, 79 million people were infected by SARS-CoV-2 infection, a number of great concern for 7.8 billion people around the world (Fig. **3-4;** Table **2-3**). Throughout the third and fourth trimester, South Africa reported the highest number of cases in the African region. France, Spain, and Italy reported peak infections in the European region for COVID-19, a resurgence owing to enhanced social interactions during vacations and ease of social restrictive measures. USA and India reported the highest number of COVID-19 cases in 2020, highlighting challenges faced in the world's most populated countries.

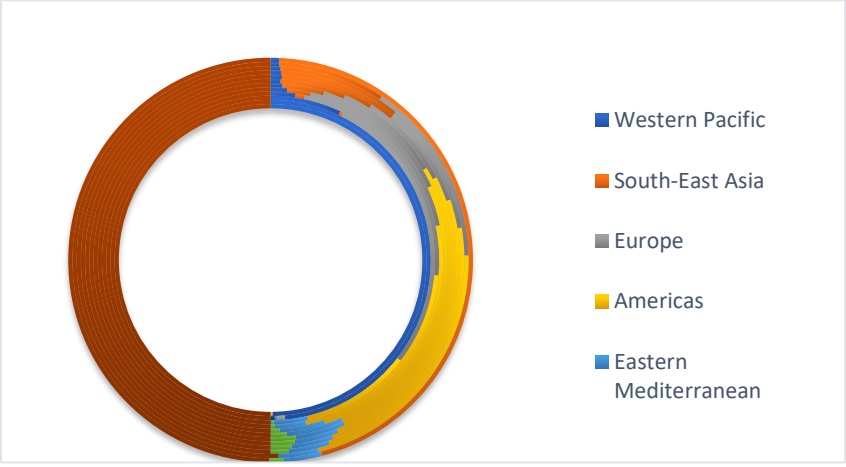


Figure 3. Distribution of COVID-19 cases from January 2020 to December 2020[7].

Table 2. Detailed Epidemiological Presence in WHO Distributed Regions in the Months of January 2020 to December 2020.

	Jan 2020	Feb 2020	Mar 2020	Apr 2020	May 2020	Jun 2020
Western Pacific	9782	82,941	104,686	147,743	181,665	215,566
South-East Asia	17	47	4,215	54,021	260,579	784,931
Europe	14	1119	423,946	1,434,649	2,142,547	2,692,086
America	9	79	163,014	1,246,190	2,743,793	5,136,705
Eastern Mediterranean	4	510	50,349	182,417	505,001	1,058,055
Africa	0	2	3,786	24,713	100,610	297,290
Other	0	705	712	712	741	741
Worldwide	9826	85,403	750,890	3,090,445	5,934,936	10,185,374
	Jul 2020	**Aug 2020**	**Sep 2020**	**Oct 2020**	**Nov 2020**	**Dec 2020**
Western Pacific	306,052	487,571	600,891	715,300	874,705	1,059,751
South-East Asia	2,009,963	4,073,148	6,720771	8,969,707	10,738,733	71,842,422
Europe	3,333,300	4,205,708	5,662,875	9,664,042	18,495,511	25,271.220
America	9,152173	13,138912	16,233,110	19,737,794	26,216,515	34,403.371
Eastern Mediterranean	1,533,357	1,903,547	2,340,215	2,955,552	4,045,906	4,823,157
Africa	770,421	1,044,513	1,172,342	1,298,315	1,49,524	1,831,277
Other	741	741	741	741	-	-
Worldwide	17,106,007	24,854,140	32,730,945	43,341,451	61,866,635	79,231,893

Table 3. Differential Percentage Increase in the Number of Cumulative Cases in Consecutive Months from January 2020 to December 2020.

Months-2020	Total Number of Cases	Cases in Previous Month	New Cases each Month	Percentage Increase
January	9,826	-	-	-
February	85,403	9,826	75,577	769%
March	750,890	85,403	665487	779%
April	3,090,445	750, 890	2,339,555	312%
May	5,934,936	3,090,445	2,844,491	92%
June	10,185,374	5,934,936	4,250,411	72%
July	17,106,007	10,185,374	6,920,633	68%
August	24,854,140	17,106,007	7,748,133	45%
September	32,730,945	24,854,140	7,876,805	32%
October	43,341,451	32,730,945	10,610,506	32%
November	61,866,635	43,341,451	18,525,184	43%
December	79,231,893	61,866,635	17,365,258	-6%

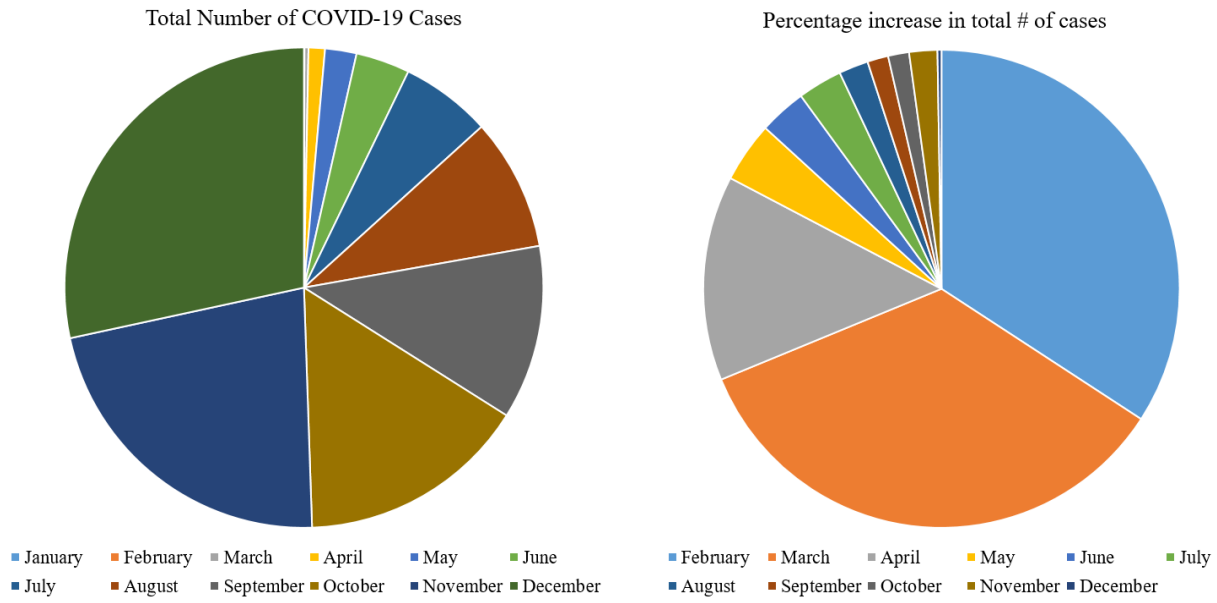


Figure 4. Total number of SARS-CoV-2 positive cases in each month and relative percentage increase from January 2020 to December 2020[7].

Table 4. Percentage Increase in the Number of Deaths Indicating a Rise in Mortality Rate with the Spread of COVID-19 from January 2020 to December 2020[7].

Months-2020	Total Number of Deaths	No. of Deaths in Previous Month	Percentage Increase w.r.t Previous Month
January	213	-	-
February	2,924	213	1264%
March	36,405	2,924	1011%
April	217,769	36,405	498%
May	367,166	217,769	67%
June	503,862	367,166	37%
July	668,910	503,862	33%
August	838,924	668,910	25%
September	991,224	838,924	18%
October	1,157,509	991,224	17%
November	1,448,990	1,157,509	25%
December	1,754,574	1,448,990	21%

COVID-19 Induced Deaths in 2020

In the early phase of the pandemic, the disease was concentrated in mainland China and a total number of COVID-19-induced deaths on 31st January were reported 213. However, with the spread of the disease to other countries, the number of non-survivals also increased drastically, making COVID-19 a highly deadly pandemic. In February, 3,924 deaths were reported, with a maximum number of non-survivals (72%) belonging to China. During March, the European region marked the highest death rate of 73% for COVID-19 patients; the highest number of deaths being reported in Italy (11,591) and Spain (7,340)[7]. In the situation report for 30th April, 2020, it was recorded that 62% COVID-19 induced deaths occurred in Europe

where Spain, Italy, United Kingdom, and France were among the top four. In May, the highest number of deaths were noticed in 21% in the U.K. (21%), Italy (18%), and France (16%) and Spain (16%). In June, the number of deaths in the American region contributed to 49% of global COVID-19-induced deaths and was followed by 39% European.

In the third trimester, the highest number of death rate was observed in the USA (1,414), Brazil (1,595), India (779), and Russia (161). In August, COVID-19 produced 170,014 non-survivors and in October the death toll crossed 1.1 million (Table **4**). COVID-19 induced 187,251 in October in WHO classified seven regions[169]. Due to variants of SARS-CoV-2 and the second wave of pandemic across the world, a 25% increase in death rate was observed and 291,481 deaths were reported. An additional 21% rise in the number of deaths were reported in December 2020 and total number COVID-19 induced deaths reached 1.7 million. During the third quarter of 2020, the highest number of deaths were reported in America, European and Southeast Asian Regions, particularly, U.S.A., U.K., and India[7].

Prevalence of COVID-19 in China during 2020

Ferretti et al. has estimated R_o=2 in the epicenter of COVID-19 disease. Most transmissions are conducted through pre-symptomatic individuals (46%), in comparison to symptomatic individuals (38%), asymptomatic individuals (10%) and environmental contamination (6%). The pre-symptomatic condition was case-specific and distinguished from the asymptomatic condition in which no signs and symptoms of viral infection were noticed at all[89]. Read *et al*., provided a comprehensive estimation of infected individuals in Wuhan before 23rd January, 2020 and estimated average 6,510-25,095 new cases and maximum increase of 33,490 cases in Chinese population[168]. Mizumoto *et al*., applied statistical analysis, and estimated R_o= 3.49 with dataset available till 11 February 2020. The estimated number of infections were 18,967 and COVID-19 induced deaths were 821. The estimation was close to officially record, positive cases of 19,559 COVID-19 infection and 821 COVID-19 induced deaths[170]. The pooled R_o value of COVID-19 epidemic in China was estimated to be 3.32, indicating an infected person can transmit disease to at least four other persons. Sanche *et al*., adopted case count approach and estimated R_o between 4.7-6.6[171]. Mathematical modelling of R_o estimation provided a range of 1.4-6.49 indicating the exponential role of human-to-human transmissions[172,173], highlighting underestimation of the COVID-19 spread and the importance of strict social preventive measures.

In China, the outbreak of respiratory novel infection of unknown etiology was officially confirmed on 31st December 2019. By 21st January, 278 cases were reported, and 93% were concentrated in Wuhan, Hubei province. On January 31st, the number of SARS-CoV-2 positive cases reached 9,720. The cases were initially studied with respect to the exposure to the Hunan Seafood market, but later drastic increases confirmed spread through human contacts. China reported 50,580 laboratory confirmed cases on 15th February and 157% increase till 29th February, 2020[7]. In March, 3,151 new confirmed cases were reported as a result of implementation of restriction policies in Hubei province and Chinese region. Moreover, in the first half of 2020, an additional 2,682 cases were reported in China, highlighting the importance of non-pharmaceutical measures for containment of the virus in the world's highest populated country[162]. In the third trimester of 2020, China reported a 3% increase in COVID-19 infections. However, the number of cases reached 96,324 on December 29th, 2020, and a 6% increase was noticed during last trimester of 2020.

Prevalence of COVID-19 in American Region

WHO defines American region as North America (United States of America) and South America. In the region, local transmissions through community interactions and cluster cases have extensively been reported, and SARS-CoV-2 viral containment has proved challenging. The epidemiological incidence of COVID-19 was highest in USA, followed by Brazil, Mexico, and Canada. In U.S.A, six imported cases from China were confirmed in January and the number of confirmed positive cases increased to 62 in February[7]. However, the incidence rate escalated in March when a 236,416% increase was noticed, resulting in 146,640 infections. Implementation of preventive measures and an increase in lockdown duration could not significantly contain the virus in a population of 331 million. With rapid and enhanced testing facilities, U.S.A. reported 1,003,974 cases in April, 1,716,078 cases in May, and 2,537,636 cases in June 2020. The escalation listed USA

as the most infected country in the world, with the highest number of COVID-19 individuals in the first half of 2020[7]. The trend was sustained during the latter half of 2020 and USA noticed 18 million COVID-19 infections in December. During June to July, COVID-19 cases increased by 73%. The following months of August and September reported a reduction of 20% and 25% in COVID-19 cases. During the second wave of pandemic, initiated in October, COVID-19 incidence rates increased by 44%. It reached peak value of 177% during November and an increment of 30% during December. The cumulative cases of COVID-19 in December 2020 were 18,648,989, contributing 54% of infections in American region. In U.S.A, community transmissions were the major reason for the escalation of COVID-19 positive cases.

Canada reported 3 infections in January, whereas, Brazil reported only 1 infection, and Mexico reported only 2 infections in February. Canada confirmed the first COVID-19 imported case in January 2020 and only 14 on 29th February, 2020. International and national transmissions established an epidemic in Canada, reporting 6,303 new infections in March. The epidemic sustained throughout 2020, with new infections rising each month, April (44,046), May (39,108), June (13,509), July (11,920), August (11,888), September (23,098), October (65,648), November (142,960) and December (180,234). Gradual reductions in the relative number of confirmed cases were observed in May, June, July, and August as strict lockdown was implemented. The escalation in October, November and December correlated to the second wave of pandemic and the evolution of virulent strains of SARS-CoV-2. The average number of new cases per day also increased in Brazil, March (137), April (2,254), May (12,686), June (29,299), July (38,972), August (40,404), September (29,493), October (23,484), November (28,141) and December (39,039). Mexico observed relative percentage increases in April (697%), May (405%), June (156%), July (88%), August (43%), September (23%), October (24%), November (22%) and December (26%). On December 29th, Mexico reported 1,372,243 cumulative cases of COVID-19. Overall, no country in the region was included in COVID-19 free zone[7].

Prevalence of COVID-19 in Europe

United Kingdom, France, Finland, Germany and Italy imported COVID-19 infection in January, 2020[5]. SEIR mathematical models indicated R_o= 6.94 with 95% CI, 475,000 expected cases, and 50,000 cumulative deaths in the absence of preventive measures and lockdown policy for the public in European countries[174]. Linka et al., also estimated R_o= 4.22 ± 1.69 for European region and the highest R_o was estimated in the cases of Germany (6.33) and Netherlands (5.88)[175]. SARS-CoV-2 positive confirmed cases escalated by local, community and clustered patterns of transmissions. Italy reported 888 infections, Germany and France reported 57 infections, Spain reported 32 infections and U.K. reported 20 infections in February. Italy, Germany, France, Spain and UK reported a rapid increase in the number of SARS-CoV-2 positive cases in March and April (Italy=2,035,059, Germany=195,062, France=1,277,009, Spain=212,885, UK=165,205). The relative decrease in subsequent number of new cases were observed in Germany (35,140), Spain (36,053), France (29,864) and Italy (7,772) as time transitioned from 1st May to 30th June. Contrary to this, U.K. reported 146,744 new cases of COVID-19 in June. In the second half of 2020, Italy and Spain reported peak infections in September, U.K. reported peak infections in October, Germany and Russian Federation reported peak infections in November, France and Turkey reported peak infections in December. The variation in peak infections highlights the fact that the start of the second wave of COVID-19 varied in different countries. These rises in the number of new cases were the manifestation of ease in social restrictions, and virulent strains of SARS-CoV-2.

Russian Federation and Turkey are assigned to Europe under WHO Regional Distribution. Russian Federation reported only 2 imported cases in February; however, the number of COVID-19 cases increased drastically in a population of 143 million. In March 1,837 cases were confirmed and the number increased to 647,849 in June 2020. The highest number of new cases were reported in April (5697%). Russian Federation noticed a rise in the number of new infections in July (30%), August (18%), September (16%), October (35%), November (47%), and December (35%). The rapid surge was associated with delayed adaptation of restriction policies by the public. Turkey was among the first European countries to report an escalation of COVID-19 cases after the first infection. During March 10,827 COVID-19 cases were reported and a drastic increase of 986% was observed in the following

month. The spread of disease in May (39%), June (22%), July (16%), August (16%), September (17%), October (16%), November (35%), and December (170%), indicated that the second wave of the pandemic was initiated in November in the country.

Prevalence of COVID-19 in Western Pacific Region

WHO classified China, Republic of Korea, Japan, Vietnam, Singapore, New Zealand, Australia, Malaysia, Cambodia, Philippines, Mongolia, Republic of Fiji, Brunei Darussalam and Papua New Guinea in Western Pacific region? Republic of Korea and Japan were on the list of countries which confirmed presence of imported cases on 20th January, 2020[7]. Philippines reported the highest number of cumulative cases, reporting 469,005 infections in the region. Philippines reported only 3 cases in January; 2020 however, rapid increase in the number of cases was noticed each month, March (1,543), April (6,666), May (9,012), June (19,214), July (52,936), August (123,757), September (88,125), October (70,274), November (56,167) and December (75,659). The ease of preventive measures by authorities and neglect on the part of the population were related to emergence of new cases during the first and second wave of pandemic. Japan reported only 230 cases of COVID-19 in February. During the first wave of pandemic, peak infections were observed during April (12,135). During the second wave of pandemic, Japan reported peak infections in November (47,155) and December (72,659). South Korea reported 11 cases on 31st January 2020. Local transmissions and clustered infections were the cause of more cases in February (3,150), March (6,636), April (979), May (1,132), and June (1,332), July (1,505), August (5,394), September (3,912), October (2,432), November (7,740), and December (23,109). Throughout the year, Korea reported a higher number of cases per day in August, November and December.

Australia also observed a continuous rise in the number of COVID-19 cases; however, it was not as high as in Philippines, Japan, and Korea. In Australia, the highest number of CVOID-19 cases were confirmed in August (9,244). In contrast to these three countries, it reported only 511 new SARS-CoV-2 infections in October, 358 in November and 411 in December. These results are the manifestations of a complete shutdown of cross-border traveling of people. New Zealand reported 1 case of COVID-19 in February. The adaptation of lockdown policies during earlier stages of the pandemic was responsible for only 529 cases in April 25 in May, 24 in June and 32 in July. Unlike other countries, peak infections of COVID-19 were reported in August (168) and no exponential rise was noticed in the following months September (99), October (108). November (111) and December (92). In the region, Viet Nam noticed more cases in March (187), August (531) and November (172) and reported 1440 cumulative cases on 29th December, 2020[7]. In these countries, strict lockdown policies, non-pharmaceutical interventions, contact tracing, and shutdown of borders limited the spread of COVID-19.

Prevalence of COVID-19 in Eastern Mediterranean

The Eastern Mediterranean region comprises 23 countries. Iran, Pakistan, Saudi Arabia, United Arab Emirates, Egypt and Qatar collectively reported 764,330 cumulative cases in June and 2,370,306 cumulative cases in December 2020. Iran confirmed 338 infections in February and sustained the highest number of cases in the region throughout the year. The percentage increase in the number of cases per month was as high as 12177% in March and as low as 19% in September 2020. Pakistan confirmed 2 imported cases of COVID-19 in February. Pakistan observed a continuous surge of infections through pilgrims from Iran, and local transmissions. The estimated R_o for COVID-19 cases in Pakistan from 1st March to 28th May, 2020 was approximated to 1.87[176]. Pakistan reported a percentage increase of COVID-19 cases in April (754%), May (341%), June (201%), July (33%), August (6%), September (5%), October (6%), November (63%) and December (20%). The second wave of COVID-19 was initiated in November 2020 as new strains of SARS-CoV-2 were reported.

Saudi Arabia reported a percentage increase of 1373% in April, followed by 290% in May, 124% in June and 33% in July. The rise was mitigated by closing borders for International visitors to the state. Consequently, a percentage increase as low as 4% was reported in the months of October and November. U.A.E. is an international hub of business and tourism. U.A.E. confirmed 611 infections with COVID-19 in March and 11,929 in April. U.A.E reported a 184% increase in May

and 42% in June. COVID-19 infections drastically increased 39% in October, marking the start of the second wave of COVID-19 pandemic. Iraq, Yemen, Syrian Arab Republic, and Afghanistan reported 14% cumulative cases of COVID-19 in the region, a number too high for the poverty and hunger-driven population of these countries.

Prevalence of COVID-19 in Southeast Asia

The Southeast Asian region comprises India, Bangladesh, Thailand, Sri Lanka, Nepal, Indonesia, Myanmar, Maldives, Bhutan and Timor-Leste. Early prediction of COVID-19 outbreak in India estimated R_o=1.41, a number of concern in world, the second largest populated country [177]. India confirmed 1,071 COVID-19 cases in March 2020. However, the rapid spread of SARS-CoV-2 reported the second highest number of infections in the world after U.S.A. The COVID-19 cases increased every month, April (31,979), May (140,093), June (384,697), July (1,072,030), August (1,903,863), September (2,449,799), October (1,953,897), November (1,446,490), and December (794,931). India contributed to 86% of the cumulative cases in the Southeast Asian Region.

Bangladesh reported its first case of COVID-19 on March 8, 2020, and later confirmed 49 cases on 31st March 2020. The estimated R_o was equivalent to 1.82 for a duration of 65 days[178]. It contributed to the second highest number of COVID-19 cases in the region, preceded by India. The number of new cases per month increased in April (7,054), May (37,505), June (97,193), July (93,088), August (74,036), September (48,948), October (42,378), November (60,368), and December (47,480). In the region, Thailand was the first state to report 14 imported cases on 31st January 2020. The number of new cases per month increased in February (42), March (1,482), April (1,430), May (127), June (90), July (139), August (101), September (112), October (0), November (520), and December (2054). During July to November, Thailand only reported 3,966 infections. The number of COVID-19 cases dramatically increased to 6,020 in December, coinciding with the second wave of the pandemic.

Prevalence of COVID-19 in African Region

African region was marked COVID-19 free zone until 29th February, when Nigeria and Algeria confirmed the presence of the first imported case. COVID-19 spread rapidly through local, clustered, and community transmissions. The estimation of R_o provided a value of 2.37 (CI 95%, 2.2-2.5). South Africa ranked first in Africa for reporting the highest number of SARS-CoV-2 infections during the first and second half of 2020. In June, South Africa confirmed 144,264 cumulative cases, Nigeria 25,133, Algeria 25,133, Ghana 17,351. Democratic Republic of Congo, the hub of an Ebola virus outbreak in 2009, reported 98 cases in March and 6,938 by the end of June 2020[7]. During the second half of 2020, Algeria reported a 228% increase, South Africa reported 106% cases, Nigeria reported a 96% rise in the number of COVID-19 cases. Democratic Republic of Congo reported an increase of 80% and Ghana reported an increase of 55% in COVID-19 cases. The relative percentage increase was the highest in December, 2020 and correlated to a second wave of COVID-19 pandemic[7].

PRECAUTIONARY MEASURES AGAINST COVID-19 AND SOCIAL IMPACT

COVID-19 has a significant impact on the socio-economic life of mankind. The pandemic has challenged human interactions, which form the basic network of a dynamic society, and has threatened the existence of a global community. Cultural and societal norms are the backbone of any nation, whereas education and industrial setup strengthen the socio-economic dimensions of nations. COVID-19 is a communicable disease which spreads through viral droplets in the air. The virus enters the body of a healthy person through inhalation of contaminated air or land onto the body's surface[19]. It is also transmitted through fomites, and contaminated water [7]. Direct contact with COVID-19 positive individuals enhanced rates of transmission and SARS-CoV-2 infection[179].

Precautionary Measures and Non-Pharmaceutical Interventions

After the announcement of " Global High-Risk Level" of COVID-19 by WHO in March, countries adapted precautionary measures, and non-pharmaceutical interventions to combat the larger-scale community spread, and cope with demanding medical equipment and the healthcare facilities[180,181]. These include frequent cleaning of hands with alcohol-based sanitizers, washing of hands with soap underwater for at least 20 seconds,

avoiding hand-shakes during greetings, following social distancing, avoiding unnecessary traveling, and community activities, and taking precautionary measures for religious gatherings[182]. The use of mask was made mandatory. Cloth masks were used by the general public to commute, and they provided efficient protection against SARS-CoV-2 and other viral droplets. Protection from viral droplets is dependent on the type of fabric used and the number of layers of clothing. The implementation of regional lockdown by government authorities significantly declined real-time infections as compared to the estimated rise in curves for COVID-19 cases in China, Europe, UK, and India[175,183].

In China, public gatherings and activities have been banned since January. The global community observed 13% reduction in expected global cases of COVID-19 by imposing strict lockdown policies and limiting community transmissions[184]. Moreover, China also closed schools and workplaces, and expected delay of the succeeding waves of pandemic[185]. High values of estimated R_o for COVID-19 in European region correlated to the social infrastructure and characterization of European nations[175]. Germany, U.K., and India officially implemented lockdown policies on March 24, 2020[174]. Restrictive movement of the masses, social distancing and contact tracing in India were adapted to mitigate the transmission rates of COVID-19[183]. Some countries adopted strict lockdown policies, including Pakistan, Iran, and Italy, whereas, South Korea implemented soft lockdown and adapted a widespread testing strategy[180]. Air travel restrictions from China were implemented to combat high-risk levels for USA, Taiwan, Hong Kong, Singapore, South Korea, Japan, and Vietnam[169].

Impact of COVID-19 on Vulnerable population

The shutdown of outdoor activities, quarantine, social isolation of the masses and unemployment have increased depression, stress-related gender violence, and abuse in vulnerable children and women[176,186]. The underprivileged class of society living in poor-sanitary and unstable residences faced insufficient primary health care before the pandemic, and the situation became worse during the pandemic. Vulnerable people in society, including retarded individuals, homeless people, internally displaced persons, and low-class migrants, have been devastated by COVID-19 closures and restrictions [187]. COVID-19 has a direct impact on children of low and middle-income countries, as it interrupted administration of vaccines of other diseases, and lacks access to food during school hours[188]. Closure of educational institutions and day-care centers in Italy still protected majority of children from SAS=RS-CoV-2 infection as only 1.5% pediatric COVID-19 cases were reported[189].

The R_o estimations for COVID-19 have declared the people of Africa vulnerable as most countries have under-developed health care systems[190]. The lack of proper infrastructure, meager access to national health facilities, and congested residential units make “Refugees” a high-risk population for SARS-CoV-2 infection. In Bangladesh, one million Rohingyan refugees, staying at Kutupalong-Balukhali Expansion site and vicinities, were highly prone to COVID-19 throughout the year[191]. In Lebanon, Syrian refugee settlements reported poor access to clean water and sanitation. Contaminated water and untreated sewage materials can induce self-inoculated infection in masses[192]. In a framed time, radical decisions for the development of special health care facilities are needed to reduce infectious contacts in these societies.

Psychological Impact of COVID-19

Natural disasters, terror attacks, and pandemics of the past have shown associations to anxiety, depression, drug addiction, and Post-traumatic Stress Syndrome (PTSD)[78]. People also suffered anxiety, depression, and fear of stigmatization after the SARS and Ebola pandemics. Cooke *et al*., reported that one in four adults suffered from COVID-19-induced stress. Pooled data indicated 23.8% world population-developed PTSD and 24.8% adults suffered from COVID-19-associated stress[193]. The high-stress levels were concentrated in epidemiologically infection-dominant countries[194,195]. Patients suffering from COVID-19-developed depression, whereas healthy population developed fear of getting sick and suffocated from long-term homestays. Hage *et al*. reported increased risks of mental stress in health care professionals regarding their performance under limited medical resources and transfer of SARS-CoV-2 infection from hospitals[196].

The coverage of COVID-19 pandemic by media outlets provided by the real-time situation and management of international health crisis. However, the pandemic was

either understated or exaggerated on social media platforms, which escalated waves of fear among the general public[197]. On social platforms, the pandemic was followed by infodemic, a situation of prime misinformation and fake news on social media platforms. The situation jeopardized the efforts of national health institutions and induced mental distress in communities[198]. Efforts were made to create awareness for public health and safety regarding social consciousness, and psychological pressure induced by COVID-19 in every age group of all countries[199].

Educational Impact of COVID-19

COVID-19 has also put pressure on educational institutions. In order to prevent the transmission of disease in children, public and private schools around the world started offering online classes[200]. During the initial phase of the pandemic, schools and institutions readily adapted distant teaching and learning mechanisms by offering online classes through google classrooms, zoom, and learning management system (LMS)[201]. During March-August, the tech industry played a crucial role in aiding to the online educational activities, yet regional, national, and international communities faced several challenges during the pandemic. The several unresolved hindrances include non-availability of electricity, distorted internet connections, and deprivation of computers and electronic gadgets in low-income families and people living in remote areas. The deprivation of on-campus study has rendered girls' education inaccessible and created difficulties in achieving sustainable developmental goals of gender equality and women empowerment in developing countries[202].

A plethora of international students also developed financial and psychological stress in the pandemic. The problems were primarily caused by the cancelation of on-campus classes, restricted movements in the hostel's accommodation, quarantine, and uncertainty of return to and from their homeland[203]. In July, international students who resumed research-based studies had shown higher productivity and prioritization of research activities as they had restricted access to available funding[186]. Countries including Northern Ireland and Pakistan postponed examinations[204,205]. In the third trimester, Pakistan reopened schools by adapting strict preventive measures and SOPs. However, due to a second wave of the pandemic, the shutdown was implemented again to prevent a hike in the number of COVID-19 cases in children.

Provision of Basic Healthcare facilities and Management of Outpatients

Owing to its distinctive origin, exponential transmissions, and rapid spread the focus of medical professionals and researchers shifted to the study of COVID-19. During the pandemic, most hospitals restricted visiting hours or completely closed facilities for outpatients. Moreover, mental health care facilities were also partially or completely closed. In USA, the cancelation of non-urgent outpatient activities, follow-ups, and operations of cancer patients gave rise to problems regarding management of prior health services[166]. The decision of closure was also finalized by the managing authorities of the public and private health sectors in infection-prominent regions of France in Europe and Pakistan in Asia[206].

COVID-19 situation has been associated with worse outcomes for diabetes due to the disruptions caused by the pandemic in the diet, care routine, and lifestyle during social restrictions[207]. In Pakistan, Italy, and France, physical access to outpatient departments (OPD) of hospitals was not approved by authorities. In order to cope with the situation, telemedicine was emphasized, and distant communication between doctors and patients through video-conferencing was held[208].

COVID-19 and Healthcare Professionals

While handling the pandemic, health care providers and medical staff were obligated to wear Personal Protective Equipment (PPE), masks, and gloves to protect themselves from viral transmission through the coughing or sneezing of patients[209]. In health care professionals, N95 respirators were extensively used to avoid any contamination while providing health care services[210]. Surgical masks have previously successfully hindered the transmission of respiratory viruses, including influenza virus and rhinovirus. They also proved effective as they reduced aerosol and droplet viral contamination of area[211]. Initially, the selection of facial masks (medical or/and surgical) and respirators (N95, P2, and FFP2) aroused concerns regarding maximum protection of healthcare workers, medical and non-medical hospital staffs. The type of mask to be used primarily depended upon the availability

of stock and preferred choice of workers[212]. The constant use of N95 respirators by health care professionals, assigned to COVID-19 patients provided benefit against COVID-19[213]. However, SARS-CoV-2-induced healthcare-associated infection in nurses and doctors[214]. Throughout the sustained crisis, inadequate supply of PPE put doctors and nurses at higher risks of contamination and viral threat.

IMPACT OF COVID-19 ON INTEGRATED GLOBAL ECONOMY

COVID-19 Induced Economic Downfall

The 20th century marked the era of globalization, which transvers into the 21st century. In the neo-liberal contemporary period, the world economy was highly intercalated and interdependent[215,216]. The economic repercussions of COVID-19 have encompassed the whole world[217]. The infectious spread of COVID-19 has disturbed the businesses, industries, and financial structure of the entire world. Economists have declared that the virus is as contagious economically as it is medically. In the first half of 2020, strict national and international policies, including the shutdown of industrial and economic sectors, closed international borders, and delayed trade gave birth to a global financial crisis close to a recession. The global shutdown rendered people jobless increasing the burden on domestic and international economic growth indicators including Gross Domestic Product (GDP), consumer spending and income, industrial production, labor market, inflation, and balance of trade. The disturbance in the export-import cycle has caused inflation in prices of basic commodities like food and medicines[217]. The pandemic also incurred a burden on the global healthcare sector. In U.S.A., the cost to fight the pandemic for two months was estimated 2.14 trillion dollars[218]. During SARS (2003), global economic loss was estimated 30-100 billion USD[219]. The initial loss associated with COVID-19 has been estimated to $1.1 trillion, compared to $25.2 billion loss in 2014 during Ebola virus epidemic.

Estrada mathematical modeling of economic indicators has concluded that the world economy will eventually be restored by 2025. During the first trimester, in January and February, China reported a peak number of cases of COVID-19, resulting in decline of the Chinese economy which led to the distortion of global supply chain. In March, the economic recession was shifted to Europe and U.S.A., which reported the highest COVID-19 cases, and adapted lockdown policies, and shutdown businesses. The second trimester of 2020 sustained the crippled economic events giving rise to inflation, the rise in unemployment rate, and shut down of national revenues across the globe. The Chinese authorities eased the lockdown for businesses and industries to recuperate the economic losses. During the third and fourth trimester, countries adapted Standard Operating Procedures (SOPs) specifically designed for the pandemic and reopened revenue- generating national sectors including restaurants, recreational places, road and rail transportation, and aviation. Irrespective of social distancing measures and SOPs, a fluctuation in the number of new cases per day was observed in the second half of 2020. Overall, COVID-19 has put pressure on advanced, developed, developing, and under-developing nations of the world.

Reduction in National and Global GDP

The national economy is an important component of the financial growth of a state. Stock markets, manufacturing capacity, unemployment rate, Consumer Price Index (CPI), currency strength, Gross Domestic Product (GDP), and trade are important indicators extensively studied to determine the economic standing of a nation and its contribution towards global GDP. Thus, Global GDP is an economic indicator of world economic progress which is created by the national GDP of the countries across the world. International Monetary Fund (IMF) has estimated a reduction of 3.5% to 4.8% in global GDP in 2020 and an expected rise of 4.9% in 2021 (Fig. **5**). The top hit countries of the COVID-19 pandemic have contributed to 55% global GDP in 2019. These include U.S.A. (24%), China (16%), Japan (6%), Germany (5%), France, India, U.K. (3%), Italy, Brazil, and Canada (2%). Clark has estimated that the growth rate in the GDP of EU may decrease by 7.4% and a forecasted economic recovery in 2021 will be unable to balance the present economic recession created by COVID-19 situation[220]. World Economic Outlook (WEO) have reported a reduction of 3.5% global GDP as compared to pre-pandemic GDP of 2.8%. Moreover, the advanced economies U.S.A (-4.9%), Canada (-5.5%), Spain (-11.1%), U.K. (-10%), Italy (-9.2%), France (-9%), Germany (-5.4%), Japan (-5.1%) contributed significantly

to the decline in global GDP. The emerging markets and economies India (-8.0%), Brazil (-4.5%), and ASEAN (-3.7%) also faced challenges during the pandemic. The economic downfall was prominent in the second quarter of 2020, as states followed lockdown policies across the globe.

In U.S.A, during the first quarter of 2020, stalled manufacturing operations resulted in -1.3% GDP. During the second quarter, GDP hit the lowest with -9.0% downfall. In the third quarter, after ease of restrictions and booming of the industrial sector, a positive rise of 7.5% was observed, and in the fourth quarter, additional GDP growth of 1.1% was noticed[221]. Following U.S.A., India reported the highest number of cases in the world. The GDP growth of India observed a rise of 3.1% in the first quarter; however, the country noticed a decline of -23.9% in the second quarter, and -7.5% in third quarter of 2020. The abrupt decline was the manifestation of a nationwide lockdown to control the surge of COVID-19 pandemic. India observed positive growth of 0.4% during the fourth quarter of 2020. The economy of Japan primarily relies on the manufacturing units, private consumption sector and exports. Japan was among the first few countries that reported imported cases of COVID-19 in January 2020. The growth of Japanese economy contracted in the first quarter (GDP= -0.9%) and the second quarter (GDP= -27.8%) in second quarter of 2020. However, with the growth of private consumption and increased exports, Japan regained its economic strength reporting a 21.4% rise in GDP during the third quarter and 9% GDP during the fourth quarter of 2020.

Crash of Stock Markets

The stock market is one of the leading indicators of the future economic direction of a state. The strength of the stock market provides information about the growth potential and thriving capability of companies and economies[222]. In the long run, a strong market is associated with high earnings and a prosperous economic situation, whereas a weak market is an indication of future economic decline. The exponential spread of SARS-CoV-2, lack of knowledge, and treatment facilities, and uncertainties associated with the COVID-19 sustained during the first quarter of 2020. In order to reduce the transmission of the virus, governments enforced lockdown of commercial markets, macro-businesses and micro-businesses. In the first and second quarter, the fluctuating interests of investors led to COVID-19 induced stock market shocks. Owing to the demanding needs of technology during the lockdown, global hike in investment in tech companies was observed. However, the stock markets of U.S.A, U.K, Japan, and Italy disproportionately suffered, and manufacturing companies met aggressive recession.

American, European, and Asian stock markets plunged with the implementation of strict preventive measures. Gormsen and Koijen reported a rise in risk levels from 0.0071 to 0.0196 from February to March, establishing a severe negative impact on the global stock market [223]. During the pandemic industrial setups, crude oil, and cooperate sector markets generated more loss for investors, whereas gold and food commodities proved safe-haven assets. In the initial days of February, the index points of Chinese stock market hit low. During March, the stock market of U.S.A. hit circuit breaker mechanism and Chicago stock market hit its lowest peak during 9th to 16th March, 2020[222]. U.S.A. stock market reported an intense reduction in equity values of petroleum, real-estate, entertainment, and hospitality divisions, while it noticed high returns for natural gas, food, healthcare, and software stocks[221]. Following U.S.A., U.K. also reported a 10% decline in index points on March 12, 2020. The Japanese stock market recorded a 20% loss in March. During the lockdown period, the Asian stock markets of Singapore and South Korea did not report such fluctuations as compared to American and European stock markets[221]. COVID-19 had a short-term negative impact on stock markets of countries marked by advanced and progressive industrial sectors such as China, Italy, South Korea, Spain, Germany, Japan, and U.S.A[224]. In the third quarter of 2020, Japanese stock markets reported 71% stock returns, strengthening its position as a major economic center[225]. These stock markets gradually revived after the uplift of the lockdown and ease in social parameters for the containment of the virus.

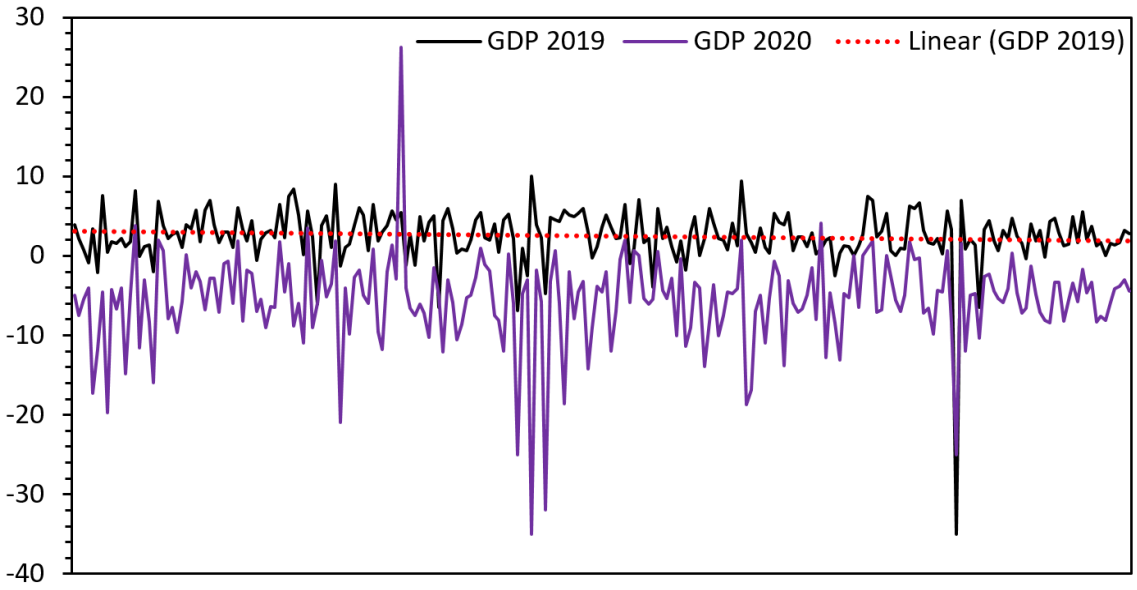


Figure 5. Reduction in GDP of 227 countries reported by IMF.

Impact on International Supply Chain Contagion and Market Disruption

The manufacturing sector of any state is an indicator of a flourishing economy. This establishment plays a significant role in providing services and products to the customers. It is also associated with the rate of employment; the bigger the manufacturing capacity is, the more workers will be required to operate it successfully. The financial impact of the reduced or stalled manufacturing sector is amplified globally through international supply chain contagion. Supply shocks in one industry of a country are transmitted to another industry of another country when the output of the first is an input of the latter. In addition to the stalled manufacturing process, the non-interest of investors and compromised purchasing power of domestic and international customers affect the production sector severely when compared to the service sector[226].

The impact of COVID-19 on the production sector differentiates itself from other natural disasters (earthquakes, tsunamis, and flooding) where loss incurred can be estimated by analyzing physical damage[227]. U.S.A., China, Germany, Japan, Britain, India, France, and Italy have been responsible for 65% of the world's manufacturing in 2019 and are important members of the international supply chain[228]. In the first quarter of 2020, the shutdown of Chinese industrial sector created a void in the global supply chain, which was filled by India, Vietnam, South Korea, and Japan. During January to February 2020, Chinese industrial production reported a decline of 13.5%. The most negatively impacted production sectors included transport equipment (-28%), general equipment (-28%), textiles (-27%), and machinery (25%)[229]. During January-February, the Purchasing Managers Index (PMI) of the Chinese manufacturing department declined significantly, whereas, during March-May the PMI of other dominant manufacturing countries reported significant reduction as the production sector was shuttered down[226].

The hyper-specialization of the European industrial sector faced the challenges of domestic production of medical equipment, as the shortage from Chinese suppliers intensified during the pandemic[229]. The automobile industry of Italy specializes in the production of automobile parts, suffered financial losses during the pandemic from foreign purchases that were interrupted due to trans-national borders shut down. The loss of active income impacted domestic household incomes and the healthcare system of Italy, reducing GDP to -9%. Japan, China, South Korea and Taiwan are the major exporters in the Information and Technology Communication Industries and collectively contribute to 50% of imports of U.S.A. Hubei province is the hub of electronics and optical fiber industry, caused a global reduction of 10% in smartphones production and shippment[226]. During the pandemic, researchers and policy makers supported the strengthening of resilience, and

sustainability of supply chains in domestic and international arena to cope with COVID-19-induced disruptions in the markets[228].

Impact of COVID-19 on Global Oil and Petroleum Demand

Owing to the COVID-19 mitigation policies, shutdown of production units, manufacturing industries reduced global demand for oil. This incurred economic loss of oil and petroleum exporting countries, particularly Saudi Arabia, Kuwait. Initially, the Brent oil prices dropped to $20 per barrel to the previous rate of $69 in 2019[226]. The reduced oil demand directly impacts the industrial and aviation sector, it also affects the value of the stock market. The crude oil supply and demand shocks to affect the stock market sector and energy-intensive sectors. The restricted international travels and closure of the aviation industry further reduced the extraction of oil and refining activity. Before COVID-19 the economic boom in China made it the largest importer of crude oil. The pandemic had risen the risk of spillover between Global and Chinese Crude oil futures[230]. Prior to the widespread SARS-CoV-2 infection, the US was already facing an oil price slump. The COVID-19 situation further added to the oil price shocks and sent a blow to the USA economy[231]. Arezki and Nguyen highlighted the fact that the export and recovery of global oil prices in the international market depending on the control of pandemic in China, USA, and Germany.

Impact of COVID-19 on Other Sectors of Revenue

COVID-19 induced a negative impact on the tourism and transport industry[232]. Albulescu proved that the sustainment of the COVID-19 situation in the first half of 2020 had a negative impact on US financial volatility and disturbed global financial cycle, as US is the biggest economy in the world[232]. During the first wave of COVID-19, the sales of agricultural commodities reduced by 20% because of implementation of public safety laws. Panic buying and mismanagement of food sources caused non-availability of vegetables, fruits, and meat[233]. The tourism sector reported increased revenue after the rise of globalization and became a significant sector of economic growth. According to the 2016 statistical data, 9.5% of the European workforce has been in earning through the tourism sector and generated revenue of 2.4 million dollars. They faced challenges of sustenance of businesses during COVID-19 Pandemic owing to national and international travel restrictions. Tourism contributed to 4.2% of the GDP of USA in 2019 and 1.9% of the GDP of Egypt in 2019. COVID-19 incurred irreversible revenue losses to Egyptian Peninsula. The impact of restrictions on air travels and International Air Transport Association has been estimated to reduce global revenue by 44%. The Global Travel Business Association reported that the business travel sector would lose $820 billion in revenue due to the coronavirus pandemic. The airline business hit the lowest during March, when sudden flights cancellation was devised by authorities and some businesses reported to exist on the verge of bankruptcy including U.K airline Flybe.

The global film industry incurred a $5 billion loss during the coronavirus outbreak. The US higher education sector reported a loss of $600billion, with the closure of on-campus activities. The fear of lack of investments in non-banking firms leading to insolvencies and bankruptcies was significantly mitigated by the country's government policies for economic emergencies and relief packages. Foreign Direct Investment (FDI) is an important indicator of economic development. Before the global recession of 2008, an FDI influx US $ 1971 billion in 2007 was reported, the highest amount of last decade, was hit hard as most funds were utilized to assist health care programs and vaccine development against SARS-CoV-2. Goodell further elaborated the eminent economic consequences of COVID-19 on domestic banks, health care management finances, and financial markets[227]. Overall, the diversion of funds for the management of health care facilities and resources during highly prevalent infections have burdened the economic capacity of middle, low-middle, and low-income countries, as was observed in the case of HIV[227 234].

IMPACT OF COVID-19 ON ENVIRONMENT

Positive Impact of COVID-19 on Environment

Most countries tried to control the expansion of SARS CoV-2 by implementing lockdown, social distancing measures, strict traffic restrictions, and self-quarantine measures. These measures reduced air pollution in Brazil and lowered the concentrations of nitrogen dioxide, carbon dioxide, carbon monoxide, and particulate matter that have a

diameter of less than 2.5µm or less than 10µm[235]. The lockdown in China also caused 30% to 50% reduction in the levels of air pollutants NO_x, $PM_{2.5}$, $PM_{10,}$ and SO_2[236]. The study of Tropospheric NO_2 in East China using Ozone Monitoring Instrument (OMI) and Tropospheric Monitoring Instrument (TROPOMI) revealed significant reduction in concentration of NO_2[237]. Lockdown during COVID-19 caused a great drop in the global consumption of oil and coal, and subsequent decrease in air pollution. The air quality of cities improved due to limited use of vehicles. New York reported 50% and China observed a decrease of 25% in the emission of Greenhouse gases[238]. European countries, including Spain, Italy and U.K. reported decreased emissions of Nitrogen dioxide[239]. The lockdown also resulted noticeable reduction in water bodies, canals, and rivers in urban areas.

Harmful Impact of COVID-19 on Environment

The adverse effect of COVID-19 on the environment is also a major concern. The healthy and safe air and water environment are of great importance for life on earth[239, 240]. SARS-CoV-2 resulted in an increased load of medical, inorganic, and plastic waste[241]. Extensive use of face masks generated 129 billion waste face masks that are the most noticeable item responsible for polluting ocean water and threatening the life of marine animals[241]. The disposal of medical waste gave rise to a challenging problem as transport and disposal infrastructure needed to incorporate large quantities of waste in China, Italy, France, and Netherlands. On February 2020, Wuhan produced 200 tons of medical waste which were four times the waste it produced in pre-pandemic situation[238]. The use of biocidal agents, soaps and simple water used in washing of contamination material possessed threat to the sanitation system. Several treatment technologies have been introduced for pharmaceutical, domestic and industrial wastewater[242]. The European Union classified healthcare waste generated during the pandemic as highly infectious and Philippines built a disposal facility on the island of Luzon to handle COVID-19 induced medical waste[238]. PPE waste in Bangladesh reported disastrous and its management was very challenging[243]. Moreover, in order to manage medical waste in China, U.S.A and South Korea, on-site incinerators, mobile incinerators, and autoclave systems had been provided to manage health care waste and ensure safety of health care professionals[238].

CONCLUSIONS

SARS-CoV-2, with a zoonotic lineage and transmission ability via human contact, and environmental contamination, causes respiratory ailments in humans. Infected individuals may stay asymptomatic or show mild and severe symptoms with disease progression. The first wave of COVID-19 was successfully mitigated by adaptation of social distancing, quarantine, strict lockdown, and non-pharmaceutical hygienic measures, contact tracing and regular temperature checkups. The economic fatality of the SARS-CoV-2 induced pandemic could not be denied and its impact on the financial burden of advanced, middle-income, lower-middle-income, and low-income countries was handled through the respective government's preparedness and management policies. During the first half of the 2020, ongoing therapeutic clinical trials and production of vaccine pipelines were the main events. During the second half of the 2020, the ease of lockdown policies alleviated the social and economic stress, and establishment of herd immunity in masses, and functioning of industrial sectors under SOPs were the main events. The second wave of COVID-19 pandemic and new variants of SARS-CoV-2 which were initiated during October and November resurfaced the global concern against the COVID-19. During the year, international organizations, WHO, World Trade Organization, International Monetary Fund, G20, and Asia Development Bank provided monetary packages. The assistance provided by a health care professional, researchers, testing facilities, and governments' policies helped combating the second wave of pandemic observed with ease of restrictions globally. Overall, the challenges posed by COVID-19 have been so far and could only be handled through public awareness, public safety measures, and sufficient allocation of funding for vaccine development. The progression of a pandemic will persist in the following year, and the productivity of the global community will highly depend on vaccines-driven social and economic makeup.

CONFLICT OF 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 article.

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LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
BLF	Bronchoalveolar lavage fluid
CRISPR	Clustered regularly interspaced short palindromic repeats
CTD	C-terminus Domain
CPAP	Continuous positive airway pressure
COVID-19	Coronavirus Disease-2019
CQ	Chloroquine
GC	Glucocorticoids
DDP	Gross domestic product
HCV	Hepatitis-C Virus
HE	Hemagglutinin-esterase
IMF	International Monetary Fund
MERS	Middle Eastern Respiratory Syndrome
Nsps	Non-structural proteins
NTD	N-terminal Domain
OPD	Outpatient department
ORF	Open Reading Frames
PCR	Polymerase chain reaction
PTSD	Post-traumatic Stress Syndrome
SARD-CoV-2	Severe Acute Respiratory Syndrome-related Coronavirus-2
SP	Signal Peptide
WHO	World Health Organization

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