Review Article

Covid 19: A Comprehensive Review

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ABSTRACT

There is a new public health crisis threatening the world with the emergency is a novel corona virus (2019-NCOV) or the severe acute respiratory syndrome corona virus (SARS-COV-2). Despite our advances in medicine and research, we continue to be challenged with new pathogens that pose a threat to human lives, global economic security, and the healthcare system. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel corona virus that was first identified in Wuhan, Hubei province, central China, and is responsible for the 2019-20 pandemic. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome corona virus (MERS-CoV), but has lower fatality. The global response to the corona virus disease-2019 (COVID-19) pandemic and provide thoughts regarding lessons for future pandemics. The World Health Organization (WHO) declared a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020. Multiple variants of the virus have emerged and become dominant in many countries since 2021, with the Alpha, Beta, Gamma and Delta variants being the most virulent. As of 23 November 2021, more than 258 million cases and 5.16 million deaths have been confirmed, making the pandemic one of the deadliest in history. This review aimed to discuss the COVID-19 disease beginning from virology, epidemiology and continuing with clinical manifestations, diagnosis, and its complications and to finish with available therapeutic options.

Keywords: Corona virus, Covid 19, Pandemic, SARS, World Health Organization (WHO).

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INTRODUCTION

An ongoing outbreak of pneumonia associated with a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in Wuhan, Hubei province, China in December 2019. On 11 February 2020, the novel virus began to cause pneumonia, and was named as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO).[1-3] In humans and birds, they cause respiratory tract infections that can range from mild to lethal. Mild illnesses in humans include some cases of the common cold while more lethal varieties can cause SARS, MERS and COVID-19. As a number of the initially identified cases had visited a large sea food and live animal market, some investigators were prompted to have an unconfirmed suspicion that this might be initial source of infection. The Chinese Centre for Disease Control and Prevention, along with other related institutions, quickly identified the pathogen as a new type of corona virus.[4-6] India has reported 3.44cr cases and 4.61L of deaths till 08/11/2021. Fortunately so far, children infrequently affected no deaths. But the future course is unknown.[7, 8] Corona virus is a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans.[9, 10]

EPIDEMIOLOGY

Geographic distribution and case counts-Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, cases have been reported in all continents. Globally, over 200 million confirmed cases of COVID-19 have been reported. Updated case counts in English can be found on the World Health Organization and European Centre for Disease Prevention and Control websites.[11, 12] However, by March 2020, the highest prevalence of COVID-19 was recorded in Italy, United States, Spain, France, Iran and Germany. In regards to data on corona virus, the spread of COVID-19 is reported to be basically from individual-to-individual transmission by breathing droplets from coughing and sneezing via close contact.[13] The transmittance of SARS-CoV-2 has been observed to occur with a basic reproduction number (Ro) of 2.2–2.6. This means that on average each infected person can potentially spread SARS-CoV-2 to 2.2–2.6 other persons.[14, 15]During the initial outbreak, in an epidemiological study of 425 corona virus cases in Wuhan, 56% were male, and the median infected individual age was 59 years.[16] In 11 February 2020, 86.6% of infected individuals were between the ages of 30–70 years. The total fatality rate of the cases was 2.3%, and 80.9% of the documented cases were not severe. About 3.8% of the reported cases in hospital were health care workers, and 14.6% of these cases were either chronic or critical. A small

number of cases (2.1%) have been documented for infants infected by the virus. Individuals severely infected by the corona virus were found mostly among patients over 80 years of age, constituting about 14.8% of the total.[17] Death rates have been estimated to be 11–15%.[18,19]In about 22–33% of infected individuals, associated infections are recorded, and these may be higher in individuals with critical conditions.[20, 21]

Table 1: Report on Corona Cases in worldwide[22]

Report on Corona Cases by worldwide Updated on November 26/2021	
ACTIVE CASES	**CLOSED CASES**
9,824,921	240,486,630
Currently Infected Patients	Cases which had an outcome:
19,742,289 (99.6%)	235,287,150 (98%)
in Mild Condition	Recovered / Discharged
82,632 (0.4%)	5,199,480 (2%)
Serious or Critical	Deaths

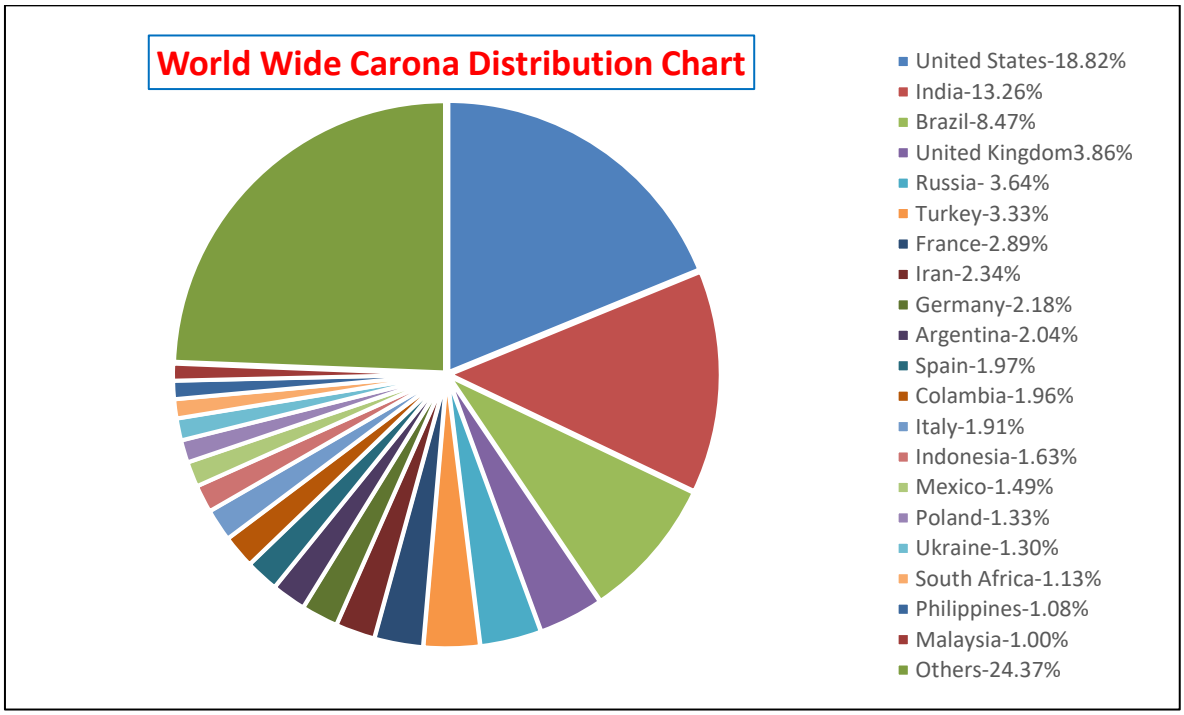

Figure 1: Distribution of Corona Cases in Different countries.[23]

Table 2: List of Active cases of some countries.[22]

Country	Total Cases	New Cases	Total Recovered	Total Deaths	Active Cases
WORLD	260,311,551	+40,657	235,287,150	5,199,480	19,824,921
USA	48,999,737		38,799,986	798,551	9,401,200
India	34,555,431		33,977,830	467,468	110,133
UK	10,021,497		8,874,965	144,433	1,002,099
Russia	9,468,189		8,164,826	269,057	1,034,306
Germany	5,623,047		4,775,300	100,796	746,951
Italy	4,968,341		4,668,257	133,486	166,598
Mexico	3,876,391	+4,128	3,234,360	293,449	348,582
Thailand	2,094,886	+6,559	1,993,964	20,643	80,279
Pakistan	1,283,475	+252	1,241,289	28,697	13,489
Austria	1,108,889		944,173	12,233	152,483
Australia	205,277	+1,627	188,482	1,985	14,810
China	98,583	+13	93,087	4,636	860

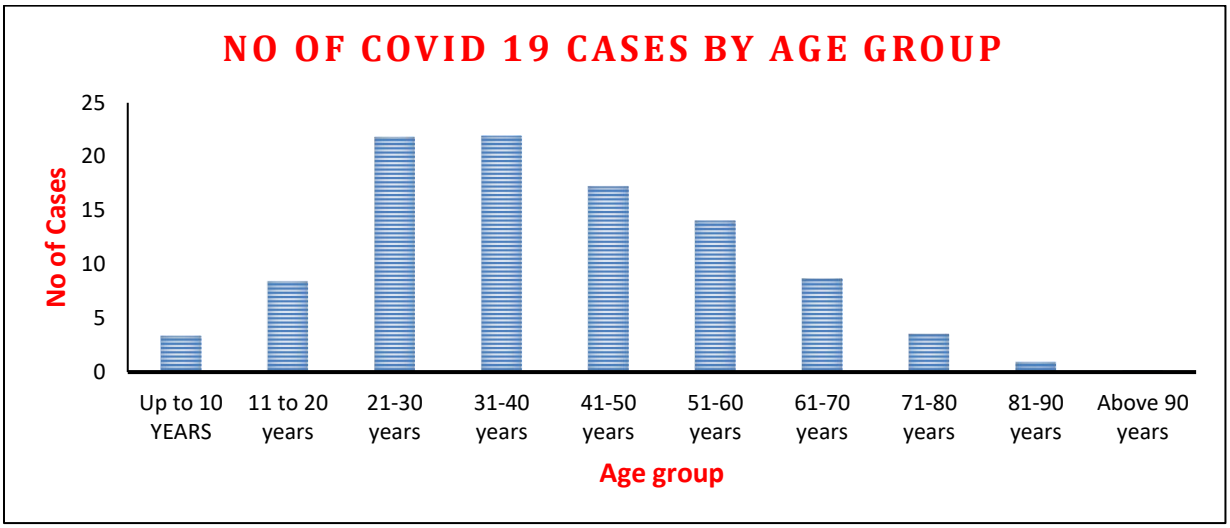

Figure 2: Number of the coronavirus (COVID-19) cases in India as of October 18, 2021, by age group.[22]

ETIOLOGY

Coronavirus virology: Corona viruses are enveloped +ve stranded RNA viruses. Full genome sequencing and phylogenetic analysis indicated that the Corona virus that causes COVID-19 is a beta Coronavirus in the same sub genus as the severe acute respiratory syndrome (SARS) virus, but in a different clade. It is the study group of the International Committee on taxonomy of viruses it has proposed that this virus be designated severe acute respiratory syndrome Corona virus 2 (SARS-COV-2).[24] SARS-COV-2 is a new strain of beta coronavirus from group 2B classified by phylogenetic analysis the genome of SARS-CoV-2 comprises 29,891 nucleotides that encode 9860 amino acids' structural protein (NSPS) are encoded by 5' untranslated region and open reading frame for replication – transcription complex (RTC) formation in double membrane vesicles (DMVs). Structural protein includes spike (S), envelop (E), membrane (M) and Nucleocapsid proteins.[25, 26] The Middle East respiratory syndrome (MERS) virus, another beta coronavirus appears more distantly related.[27, 28]

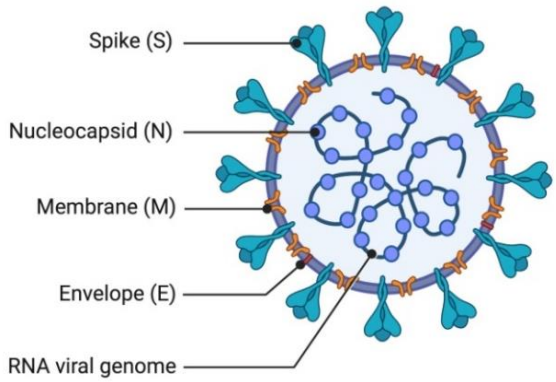

Figure 3: Structural elucidation of Corona Virus

Variants of Viruses: SARS-CoV-2 evolves over time. Most mutations in the SARS-CoV-2 genome have no impact on viral function. Certain variants have garnered widespread attention because of their rapid emergence within populations and evidence for transmission or clinical implications. Each variant has several designations based on the nomenclature used by distinct phylogenetic classification systems; the World Health Organization (WHO) has also designated labels for notable variants based on the Greek alphabet. Early in the pandemic, a study that monitored amino acid changes in the spike protein of SARS-CoV-2 included in a large sequence database identified a D614G (Glycine for aspartic acid) substitution that became the dominant polymorphism globally over time.[29] In animal and in vitro studies, viruses bearing the G614 polymorphism demonstrate higher levels of infectious virus in the respiratory tract, enhanced binding to ACE-2, and increased replication and transmissibility compared with the D614 polymorphism. The G614 variant does not appear to be associated with a higher risk of hospitalization.[30, 31]

As of July 2021, there are four dominant variants of SARS-CoV-2 spreading among global populations: the Alpha Variant (formerly called the UK Variant and officially referred to as **B.1.1.7**), the Beta Variant (formerly called the South Africa Variant and officially referred to as **B.1.351**), the Gamma Variant (formerly called the Brazil Variant and officially referred to as **P.1**), and the Delta Variant (formerly called the India Variant and officially referred to as **B.1.617.2**). Using whole genome sequencing, epidemiology and modelling suggest the Alpha variant VUI-202012/01 (the first variant under investigation in December 2020) in the B.1.1.7 lineage transmits more easily than some other strains.[32]

Alpha (B.1.1.7 lineage): This variant, also known as 20I/501Y.V1, was first identified in the United Kingdom in late 2020 and was temporally associated with an increase in regional infections. Several studies had suggested that Alpha is approximately 50 to 75 percent more transmissible than previously circulating strains and is associated with higher secondary attack rates. A mutation in this variant is a deletion in the spike protein at amino acids 69-70 (del 69-70). Some SARS-CoV-2 molecular tests are unable to detect the S gene (which encodes the spike protein) target when

this deletion is present. These tests would still be able to detect viral RNA since they employ more than one gene target and thus would not result in false-negative results. Nevertheless, S gene target failure has been used as a marker to detect the Alpha variant, with the caveat that del 69-70 has also been reported in other variants.[33-36]

Beta (B.1.351 lineage): This variant, also known as 20H/501Y.V2, was identified in South Africa in late 2020. It is phylogenetically distinct from B.1.1.7 but shares several spike protein mutations. Surveillance data in South Africa indicate that this variant rapidly became the dominant strain there, suggesting that it also has the potential for increased transmissibility.[37]

Gamma (P.1 lineage) – This variant, also known as 20J/501Y.V3, was first identified in Japan in four traveller's from Brazil and was later reported to account for 42 percent of 31 sequenced specimens in the Amazonas state of Brazil in December 2020.[38]

Delta (B.1.617.2 lineage): This lineage, also known as 20A/S: 478K was first identified in India in December 2020 and has become the most prevalent variant there and in several other countries, including the United States and United Kingdom. The Delta variant is highly transmissible, more so than Alpha (B.1.1.7), which was more transmissible than previously circulating SARS-CoV-2 lineages. In reports from the United Kingdom, the proportion of SARS-CoV-2 infections caused by Delta as that caused by Alpha declined, and the secondary household infection rate associated with Delta infection was 13.6 percent compared with 9.0 percent for Alpha.[39]In another report of a small outbreak in the United States, the household attack rate associated with the Delta variant was 53 percent.[40] Infection with Delta may be associated with a higher risk of severe disease and hospitalization than with Alpha.[41]

As long as the coronavirus spreads through the population, mutations will continue to happen, and the delta variant family continues to evolve. New variants of the SARS-CoV-2 virus are detected every week. On 26 November 2021, WHO designated the variant B.1.1.529 a variant of concern, named Omicron, on the advice of WHO's Technical Advisory Group on Virus Evolution (TAG-VE). The B.1.1.529 variant was first reported to WHO from South Africa on 24 November 2021. The epidemiological situation in South Africa has been characterized by three distinct peaks in reported cases, the latest of which was predominantly the Delta variant. In recent weeks, infections have increased steeply, coinciding with the detection of B.1.1.529 variant. The first known confirmed B.1.1.529 infection was from a specimen collected on 9 November 2021.This variant has a large number of mutations, some of which are concerning. Preliminary evidence suggests an increased risk of reinfection with this variant, as compared to other variants of corona virus. The number of cases of this variant appears to be increasing in almost all provinces in South Africa. Current SARS-CoV-2 PCR diagnostics continue to detect this variant.

CURRENT KNOWLEDGE ABOUT OMICRON

Researchers in South Africa and around the world are conducting studies to better understand many aspects of Omicron and will continue to share the findings of these studies as they become available.

Transmissibility: It is not yet clear whether Omicron is more transmissible (e.g., more easily spread from person to person) compared to other variants, including Delta. The number of people testing positive has risen in areas of South Africa affected by this variant, but epidemiologic studies are underway to understand if it is because of Omicron or other factors.

Severity of disease: It is not yet clear whether infection with Omicron causes more severe disease compared to infections with other variants, including Delta. Preliminary data suggests that there are increasing rates of hospitalization in South Africa, but this may be due to increasing overall numbers of people becoming infected, rather than a result of specific infection with Omicron. There is currently no information to suggest that symptoms associated with Omicron are different from those from other variants. Initial reported infections were among university students—younger individuals who tend to have more mild disease—but understanding the level of severity of the Omicron variant will take days to several weeks. All variants of COVID-19, including the Delta variant that is dominant worldwide, can cause severe disease or death, in particular for the most vulnerable people, and thus prevention is always key.

Effectiveness of prior SARS-CoV-2 infection: Preliminary evidence suggests there may be an increased risk of reinfection with Omicron (i.e., people who have previously had COVID-19 could become reinfected more easily with Omicron), as compared to other variants of concern, but information is limited. More information on this will become available in the coming days and weeks.

Effectiveness of vaccines: WHO is working with technical partners to understand the potential impact of this variant on our existing countermeasures, including vaccines. Vaccines remain critical to reducing severe disease and death, including against the dominant circulating variant, Delta. Current vaccines remain effective against severe disease and death.

Effectiveness of current tests: The widely used PCR tests continue to detect infection, including infection with Omicron, as we have seen with other variants as well. Studies are ongoing to determine whether there is any impact on other types of tests, including rapid antigen detection tests.

Effectiveness of current treatments: Corticosteroids and IL6 Receptor Blockers will still be effective for managing patients with severe COVID-19. Other treatments will be assessed to see if they are still as effective given the changes to parts of the virus in the Omicron variant.[42, 43]

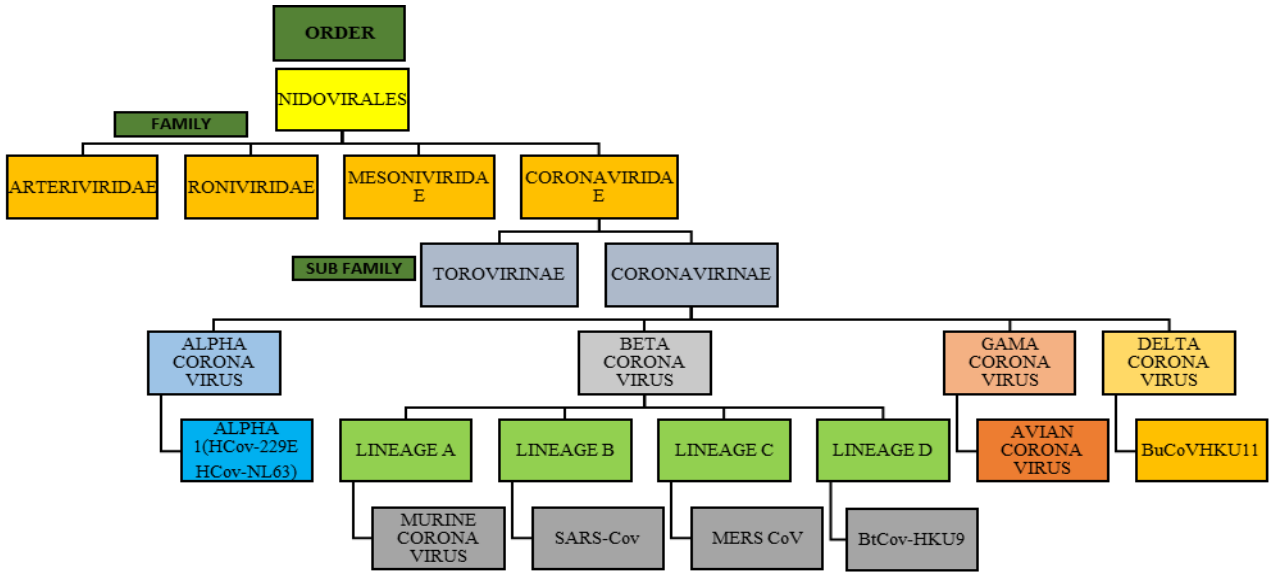

Figure 4: Classification of human corona viruses

PATHOPHYSIOLOGY

First phase (early phase of infection)

During the early phase of infection, SARS-CoV-2 infiltrates the lung parenchyma and starts proliferation. ACE2 and TMPRSS2 play crucial roles in cellular entry of SARS-CoV-2, similar to that of SARS-CoV. The S1 subunit of the spike protein attaches to cellular ligand ACE2 on the host cell surface. Cellular protease priming by TMPRSS2 facilitates S1/S2 subunit cleavage of spike protein and the S2′ subunit allows the fusion of the virus through the host cell membranes. The virus through the host cell membranes Coronavirus genome replication and transcription take place at cytoplasmic membranes after cell entry. The replicas complex mediates the continuous and discontinuous synthesis of RNA, 16 viral subunits and numbers of cellular proteins were then generated. Unlike other RNA viruses, the replicas complex only presented in SARS-CoV-2 for numbers of RNA processing enzymes employment, including putative sequence-specific endoribonuclease, 3′ -to- 5′ exoribonuclease, 2′-O-ribose methyl transferase, ADP ribose 1′- phosphatase etc.[44]

Second phase (pulmonary phase)

Pulmonary phase is characterized by the presence of inflammatory response, tissue damage, and respiratory failure. The viral entry in human lung tissues induced mild upper respiratory tract dysfunction in most cases [18]. Scientists believed that viral replication and budding triggers type 2 alveolar cells to undergo apoptosis and epithelial regeneration of cells, similar to that of SARS-CoV. Although matches the Berlin definitions of serve state, COVID-19 induced respiratory failure showed different features from that of typical ARDS. ARDS is a complex clinical syndrome of acute respiratory failure developed from non-cardiogenic pulmonary edema. Diffuse alveolar damage with fibrin rich hyaline membrane and a few multinucleated giant cells are presented. Reduced ability of epithelium repairing and mucociliary clearance in elderly deteriorate the condition quickly, and eventually death.[45-47]

Third phase (hyper inflammation phase)

Hyper inflammation phase is characterized by the presence of systemic inflammation and damage of distant organs because of the increased host inflammatory response and hypercoagulable state, resulting in multiorgan failure (MOF). High leukocyte number with lymphopenia and increased levels of plasma pro-inflammatory cytokines were observed, especially higher levels of IL-2, IL-6, IL-7, IL-10, C-reactive protein (CRP), granulocyte-colony stimulating factor (G-CSF), interferon-gamma inducible protein (IP) 10, monocyte chemo attractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1α, and tumour necrosis factor (TNF) α in COVID-19 patients with severe condition.[45, 48]

SIGNS AND SYMPTOMS

Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.

Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms may begin one to fourteen days after exposure to the virus. At least a third of people who are infected do not develop noticeable symptoms of those people who develop symptoms noticeable enough to be classed as patients, most (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction). Older people are

at a higher risk of developing severe symptoms. Some people continue to experience a range of effects (long COVID) for months after recovery, and damage to organs has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease.

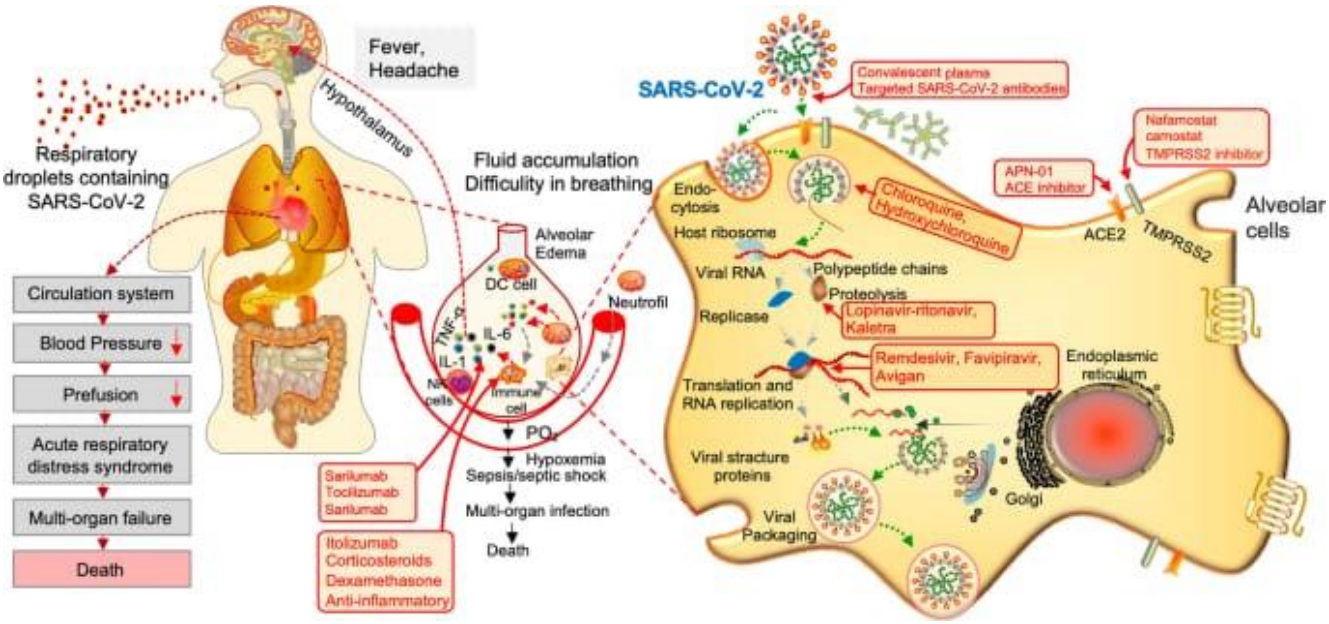

Figure 5: Pathophysiology and treatment strategies for COVID-19

Common symptoms include headache, loss of smell and taste, nasal congestion and runny nose, cough, muscle pain, sore throat, fever, diarrhoea, and breathing difficulties. People with the same infection may have different symptoms, and their symptoms may change over time. Three common clusters of symptoms have been identified: one respiratory symptom cluster with cough, sputum, shortness of breath, and fever; a musculoskeletal symptom cluster with muscle and joint pain, headache, and fatigue; a cluster of digestive symptoms with abdominal pain, vomiting, and diarrhoea. In people without prior ear, nose, and throat disorders, loss of taste combined with loss of smell is associated with COVID-19 and is reported in as many as 88% of cases.[49-53]

TRANSMISSION

The disease is mainly transmitted via the respiratory route when people inhale droplets and small airborne particles (that form an aerosol) that infected people exhale as they breathe, talk, cough, sneeze, or sing. Infected people are more likely to transmit COVID-19 when they are physically close. However, infection can occur over longer distances, particularly indoors. Infectivity can occur 1-3 days before the onset of symptoms. Infected persons can spread the disease even if they are pre-symptomatic or asymptomatic. Most commonly, the peak viral load in upper respiratory tract samples occurs close to the time of symptom onset and declines after the first week after symptoms begin. Person-to-person spread is the main mode of SARS-CoV-2 transmission.[54-56]

Route of person-to-person transmission- Direct person to person respiratory transmission is the essential method for transmission of severe acute respiratory syndrome Covid 2 (SARS-CoV-2).[57] It is thought to happen essentially through short close contact (i.e., inside roughly six feet or two meters) by means of respiratory particles; infection delivered in the respiratory secretions when an individual with contamination hacks, sniffles, cough, sneeze, or talks can infect someone else in case it is breathed in or connects with the mucous membranes. Disease may likewise happen in case an individual's hands are polluted by these discharges or by contacting surfaces and afterward they contact their eyes, nose, or mouth, surfaces are not idea to be a significant course of transmission.[58, 59]

SARS-CoV-2 has been detected in non-respiratory specimens, including stool, blood, ocular secretions, and semen, but the role of these sites in transmission is uncertain.[60-62] Several reports have described detection of SARS-CoV-2 RNA from stool specimens, even after viral RNA could no longer be detected from upper respiratory specimens, and replicative virus has been cultured from stool in rare cases.[63] Scattered reports of clusters in a residential building and in a dense urban community with poor sanitation have suggested the possibility of transmission through aerosolization of virus from sewage drainage. However, according to a joint WHO-China report, transmission through the fecal-oral route did not appear to be a significant factor in the spread of infection.[64, 65]

Recognition of SARS-CoV-2 RNA in blood has additionally been accounted for in some however not all investigations that have tried for it. There is also no evidence that SARS-CoV-2 can be transmitted through contact with non-mucous membrane sites (e.g., abraded skin). [66, 67]

Viral shedding and period of infectiousness - The exact span during which a person with SARS-CoV-2 disease can

transmit contamination to others is questionable. The possibility to communicate SARS-CoV-2 starts preceding the advancement of indications and is most elevated right off the bat throughout sickness; the danger of transmission diminishes from there on. Transmission after 7 to 10 days of illness is unlikely, particularly for otherwise immune competent patients with no severe infection.[66]

Period of greatest infectiousness - Infected individuals are more likely to be in the earlier stages of illness when viral RNA levels from upper respiratory specimens are the highest. One modeling study, in which the mean serial interval between the onset of symptoms among 77 transmission pairs in China was 5.8 days, estimated that infectiousness peaked between two days before and one day after symptom onset and declined within seven days.[68-70]

Risk of transmission depends on exposure type - The risk of transmission from a person with SARS-CoV-2 disease differs by the sort and length of openness, utilization of preventive measures, and reasonable individual elements (e.g., the measure of infection in respiratory discharges).[71] Numerous people don't send SARS-CoV-2 to any other individual, and epidemiologic information recommends that the minority of list cases bring about most of auxiliary diseases.[72-74]

In health care settings when personal protective equipment was not used (including hospitals and long-term care facilities).[75,76] In other congregate settings where individuals are residing or working in close quarters (e.g., cruise ships, homeless shelters, detention facilities, college dormitories and food processing facilities).[77-80]

The risk of transmission in outside settings seems, by all accounts, to be generously lower than inside, even though information is restricted. In any case, close contact with a person with COVID-19 remaining parts a danger outside.[81]

Asymptomatic or presymptomatic transmission- Transmission of SARS-CoV-2 from individuals with infection but no symptoms (including those who later developed symptoms and thus were considered presymptomatic) has been well documented.[82-84] The biologic reason for this is upheld by a study of a SARS-CoV-2 episode in a drawn-out care office, in which irresistible infection was refined from RT-PCR-positive upper respiratory lot examples in presymptomatic and asymptomatic patients as ahead of schedule as six days preceding the improvement of common manifestations.[85] The levels and length of viral RNA in the upper respiratory parcel of asymptomatic patients are likewise like those of suggestive patients.[86]

In any case, asymptomatic or presymptomatic people are more averse to segregate themselves from others, and the degree to which transmission from such people adds to the pandemic is questionable. A CDC displaying concentrate on assessed that 59% of transmission could be credited to people without manifestations: 35% from presymptomatic people, and 24 percent from the individuals who stayed asymptomatic.[87]

Environmental contamination - Virus present on contaminated surfaces may be another source of infection if susceptible individuals touch these surfaces and then transfer infectious virus to mucous membranes in the mouth, eyes, or nose. The recurrence and relative significance of this kind of transmission are dubious, albeit polluted surfaces are not idea to be a significant wellspring of transmission. It very well might be almost certain a possible wellspring of disease in settings where there is substantial viral tainting (e.g., in a contaminated person's family or in medical care settings).[88]

Risk of animal contact- SARS-CoV-2 infection is thought to have initially been communicated to people from a creature have, yet the continuous danger of transmission through creature contact is dubious. There are no proofs recommending creatures (counting tamed creatures) are a significant wellspring of disease in people.[89]

IMMUNE RESPONSES FOLLOWING INFECTION

Protective SARS-CoV-2-specific antibodies and cell-mediated responses are induced following infection. Evidence suggests that some of these responses can be detected for at least a year following infection.

Humoral immunity- Following infection with SARS-CoV-2, most of patients foster recognizable serum antibodies to the receptor-restricting area of the viral spike protein and related killing action.[90, 91] Nonetheless, the greatness of counter acting agent reaction might be related with seriousness of sickness, and patients with gentle disease may not mount noticeable killing antibodies. Killing movement has been related with assurance from ensuing disease.[92] perceptible restricting antibodies, which by and large connect with killing movement, are additionally connected with a diminished danger of SARS-CoV-2 reinfection.[93]

Cell-mediated immunity –Studies have additionally distinguished SARS-CoV-2-explicit CD4 and CD8 T cell reactions in patients who had recuperated from COVID-19 and in people who had gotten COVID-19 inoculation, which propose the potential for a solid T cell invulnerable reaction.[94] Studies have additionally distinguished SARS-CoV-2-explicit CD4 and CD8 T cell reactions in patients who had recuperated from COVID-19 and in people who had gotten COVID-19 inoculation, which propose the potential for a solid T cell invulnerable reaction.[95] Antibodies that neutralize SARS-CoV-2 and SARS-CoV-2-responsive CD4 T cells have been distinguished in certain people without known openness to SARS-CoV-2, and a portion of these give off an impression of being cross-receptive with antigens from normal cold Covid's.[96] Regardless of whether these prior invulnerable reactions sway the danger or the seriousness of COVID-19 and whether they will impact COVID-19 antibody reactions stay obscure.

Risk of reinfection- The short-term risk of reinfection (e.g., within the first several months after initial infection) is low. Prior infection reduces the risk of infection in the subsequent six to seven months by 80 to 85 percent.[97]

Reinfection with variations of concern (like B.1.351, which is less defenceless to killing antibodies created against wild-type infection) has been archived following disease with wild-type infection, yet the general risk of reinfection with such variations is dubious.[98] Irregular instances of affirmed reinfection utilizing sequencing information have been depicted all through the world.[99] In a portion of these cases, the subsequent disease was asymptomatic or milder than the main, raising the likelihood that insusceptibility from an underlying contamination may lessen the seriousness of a reinfection regardless of whether it forestall it. Nonetheless, not all instances of implied reinfection have been less serious than the underlying disease, and something like one lethal reinfection has been accounted for in a patient going through B cell-draining treatment and chemotherapy.[100]

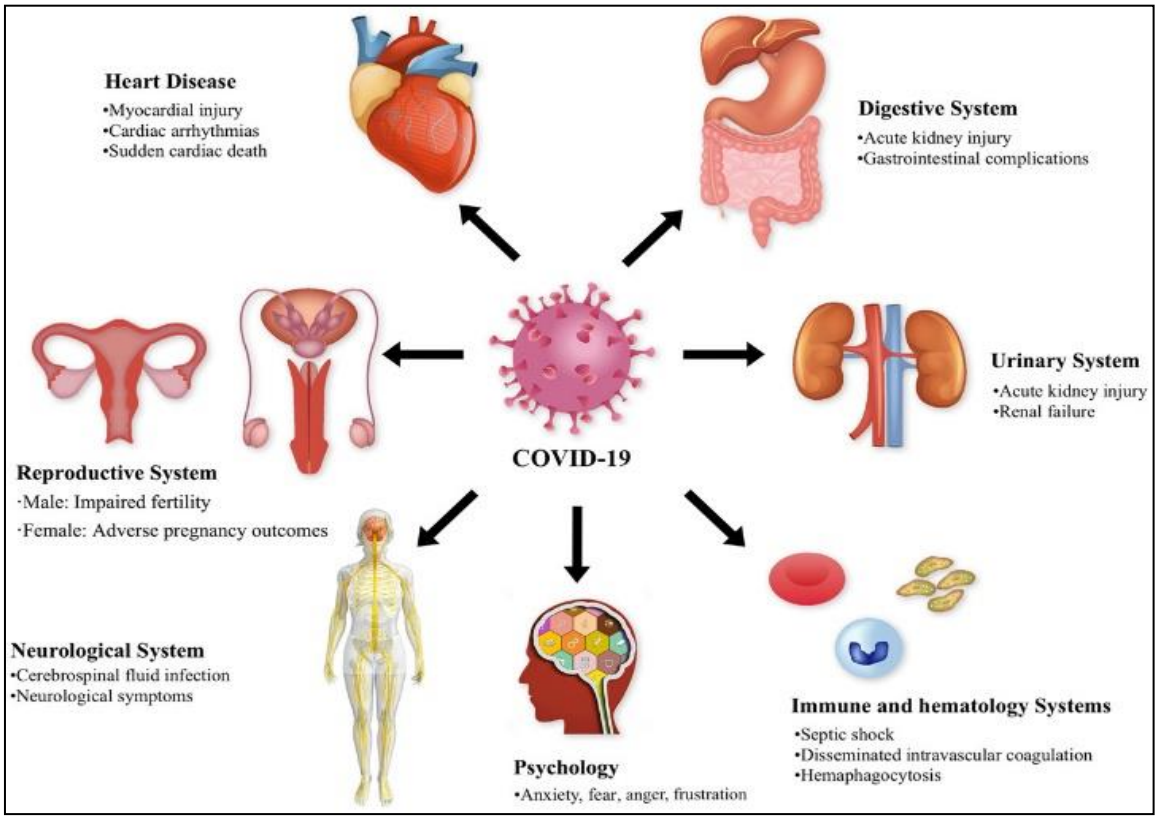

Figure 6: A potential complications of COVID-19 on other organ systems

PREVENTION

To prevent the spread of COVID-19:

- Maintain a safe distance from others (at least 1 metre), even if they don't appear to be sick.
- Wear a mask in public, especially indoors or when physical distancing is not possible.
- Choose open, well-ventilated spaces over closed ones. Open a window if indoors.
- Clean your hands often. Use soap and water, or an alcohol-based hand rub.
- Get vaccinated when it's your turn. Follow local guidance about vaccination.
- Cover your nose and mouth with your bent elbow or a tissue when you cough or sneeze. Stay home if you feel unwell.
- If you have a fever, cough and difficulty breathing, seek medical attention. Call in advance so your healthcare provider can direct you to the right health facility. This protects you and prevents the spread of viruses and other infections.
- Masks properly fitted masks can help prevent the spread of the virus from the person wearing the mask to others. Masks alone do not protect against COVID-19 and should be combined with physical distancing and hand hygiene.

If people group transmission of serious intense respiratory disorder Covid 2 (SARS-CoV-2) is available, occupants are by and large urged to rehearse social removing by staying away from swarms and keeping a separation of six feet (two meters) from others when in open. Specifically, people ought to keep away from close contact with sick people. People are likewise urged to wear covers when out openly. Tenacious hand washing, especially in the wake of contacting surfaces out in the open, utilization of hand sanitizer that contains essentially 60% liquor is a sensible other option if the hands are not apparently filthy. The significance of hand cleanliness was outlined by a review wherein bodily fluid examples immunized with refined SARS-CoV-2 infection were applied to human skin gathered

from examination. SARS-CoV-2 stayed reasonable on the skin for around nine hours yet was totally inactivated inside 15 seconds of openness to 80% alcohol. Respiratory hygiene (e.g., covering the cough or sneeze), avoiding touching the face (eyes, nose, and mouth) is another measure.[101]

The American Academy of Ophthalmology suggests that people not wear contact lenses, because they make people touch their eyes more frequently.[102] cleaning and sanitizing articles and surfaces that are as often as possible contacted. The United States Centres for Disease Control and Prevention (CDC) has given direction on sanitization in the home setting; a rundown of Environmental Protection Agency-enrolled items can be viewed as here. These measures should be followed by all individuals when there is community transmission of SARS-CoV-2 but should be emphasized for older adults and individuals with chronic medical conditions. While educating patients on the utilization with respect to veils, clinicians should advise them to try not to contact the eyes, nose, and mouth when putting on luminating the cover, to rehearse hand cleanliness previously, then after the fact taking care of the veil, and to wash material covers regularly. Clinicians ought to likewise accentuate that the veil doesn't decrease the significance of other preventive measures, for example, social separating and hand cleanliness. Patients can likewise be advised that covers have not been related with hindrance in gas trade, incorporating among patients with basic lung sickness.[103, 104]

Source control – A few examinations support the utilization of covers to give source control and lessen transmission locally.[105-107] In a review investigation of 124 patients with affirmed COVID-19 and their families in Beijing, China, optional transmission happened in 41 families; utilization of veils by relatives (counting the list patient) before sickness beginning in the record patient was freely connected with a decreased danger of disease.[108] The kind of veil utilized (clinical or material) was not indicated.

Prevent exposure - Mask wearing locally may likewise be related with assurance for the wearer. In a report of 382 help individuals who were reviewed about close to home preventive procedures in the setting of a SARS-CoV-2 flare-up on a United States Navy plane carrying warship, self-report of wearing a face cover was freely connected with a lower probability of disease (chances proportion [OR] 0.3), as were keeping away from normal regions (OR 0.6) and noticing social removing (OR 0.5).[109]

Filtration efficacy - Filtering facepiece respirators (FFR) have the most noteworthy filtration adequacy. In the United States, the prototypical FFR is the N95 respirator, which channels somewhere around 95% of 0.3 micrometre particles. Clinical covers have lower filtration viability, which relies upon how intently the veil lies against the face. In one review, clinical covers with ties versus ear circles sifted 72 and 38 percent of particles, individually (around 0.02 to 3.00 micrometres).[110] Despite the variability in filtration efficacy of different masks (respirators, medical masks, cloth masks) in experimental settings, data on clinical efficacy differences in preventing transmission of SARS-CoV-2 are lacking.

Other face protection- Despite the fact that eye assurance is suggested in medical services settings, the job of face safeguards or goggles notwithstanding veils to additionally diminish the danger of contamination locally is dubious.[111] Albeit one review recommended that the extent of hospitalized patients with COVID-19 who utilized eyeglasses every day was lower than that assessed for everyone, eyeglasses are by and large thought to be inadequate for eye security.[112]

Social/physical distancing- In locations where there is community transmission of SARS-CoV-2 (including throughout the United States), individuals are advised to practice social or physical distancing in both indoor and outdoor spaces by maintaining a minimum distance from other people outside their household. Physical distancing is likely independently associated with a reduced risk of SARS-CoV-2 transmission.[113, 114]

Screening in high-risk settings - Screening for SARS-CoV-2 disease with sequential viral testing is prescribed in long haul care offices to rapidly distinguish cases so that tainted people can be separated, contacts can be isolated, and flare-ups can be forestalled.[115]

Other public health measures - On January 30, 2020, the WHO announced the COVID-19 flare-up a general wellbeing crisis of worldwide concern and, in March 2020, started to portray it as a pandemic to underline the weightiness of the circumstance and urge all nations to make a move in distinguishing disease and forestalling spread.[115]

- Social/physical distancing orders
- Stay-at-home orders
- School, venue, and nonessential business closure
- Bans on public gatherings
- Travel restriction with exit and/or entry screening
- Aggressive case identification and isolation (separating individuals with infection from others)
- Contact tracing and quarantine (separating individuals who have been exposed from others)

Post-exposure management- In region where SARS-CoV-2 is predominant, all inhabitants ought to be urged to remain alert for side effects and practice proper preventive measures to decrease the danger of disease.

Testing and quarantine-Testing and quarantine is strategies to quickly identify secondary infections in an exposed individual and reduce the risk of that individual exposing others before an infection is recognized**.**

For unvaccinated individuals: ***Every day checking for fever, hack, or dyspnoea for 14 days. People who foster such signs or indications should remain at home and avoid***

others, remembering those for their family, in case they are not doing as such as of now (as underneath), and contact their clinical suppliers.

Self-quarantine at home, with maintenance of at least six feet (two meters) from others always. They should avoid contact with individuals at high risk for severe illness. The preferred quarantine period is 14 days following the date of the keep going openness (since the singular remaining parts asymptomatic) and depends on the brooding time frame for SARS-CoV-2 contamination. A seven-day quarantine period, provided that the individual remained asymptomatic throughout and has a negative NAAT or antigen SARS-CoV-2 test within 48 hours of the planned end of quarantine.[116]

For vaccinated individuals: Completely immunized people are excluded from oneself quarantine ideas above however ought to get tried 3 to 5 days following openness and wear a veil in broad daylight for 14 days or until the test is contrary. They ought to likewise proceed to self-screen for fever and indications for 14 days following openness and go through assessment if highlights of COVID-19 create.[117]

Post-exposure prophylaxis for select: In the United States, the FDA has given a crisis use approval (EUA) to utilize the monoclonal counter acting agent mixes casirivimab-imdevimab or bamlanivimab-etesevimab to forestall SARS-CoV-2 disease in select people more than 12 years old.[118, 119]

The doses for post-exposure prophylaxis are:

Casirivimab (600mg) - imdevimab (600mg) as a single subcutaneous injection or intravenous infusion.

Bamlanivimab 700 mg plus etesevimab 1400 mg administered together as a single intravenous infusion.[120]

Table 3: Vaccination Status of some countries by worldwide.[22, 23]

Country	Doses given	Fully vaccinated	% Of population fully vaccinated
India	**121Cr**	**43Cr**	**31.2%**
China (Mainland)	233Cr	107Cr	74.30%
United States	45.4Cr	19.5Cr	59.1%
Brazil	29.8Cr	12.8Cr	60.4%
Indonesia	23.1Cr	9.31Cr	34.0%
Japan	19.7Cr	9.69Cr	77.0%
Mexico	13.2Cr	6.46Cr	50.1%
Russia	12.4Cr	5.55Cr	38.5%
Pakistan	12.2Cr	4.98Cr	22.6%
Germany	12Cr	5.68Cr	68.2%
Turkey	12Cr	5.03Cr	59.6%
United Kingdom	11.4Cr	4.63Cr	68.8%
France	10.4Cr	4.69Cr	69.6%
Iran	10.2Cr	4.47Cr	53.2%
Italy	9.51Cr	4.4Cr	73.8%
Bangladesh	9.27Cr	3.57Cr	21.7%
Philippines	7.85Cr	4.39Cr	40.0%
Argentina	6.71Cr	2.9Cr	63.9%

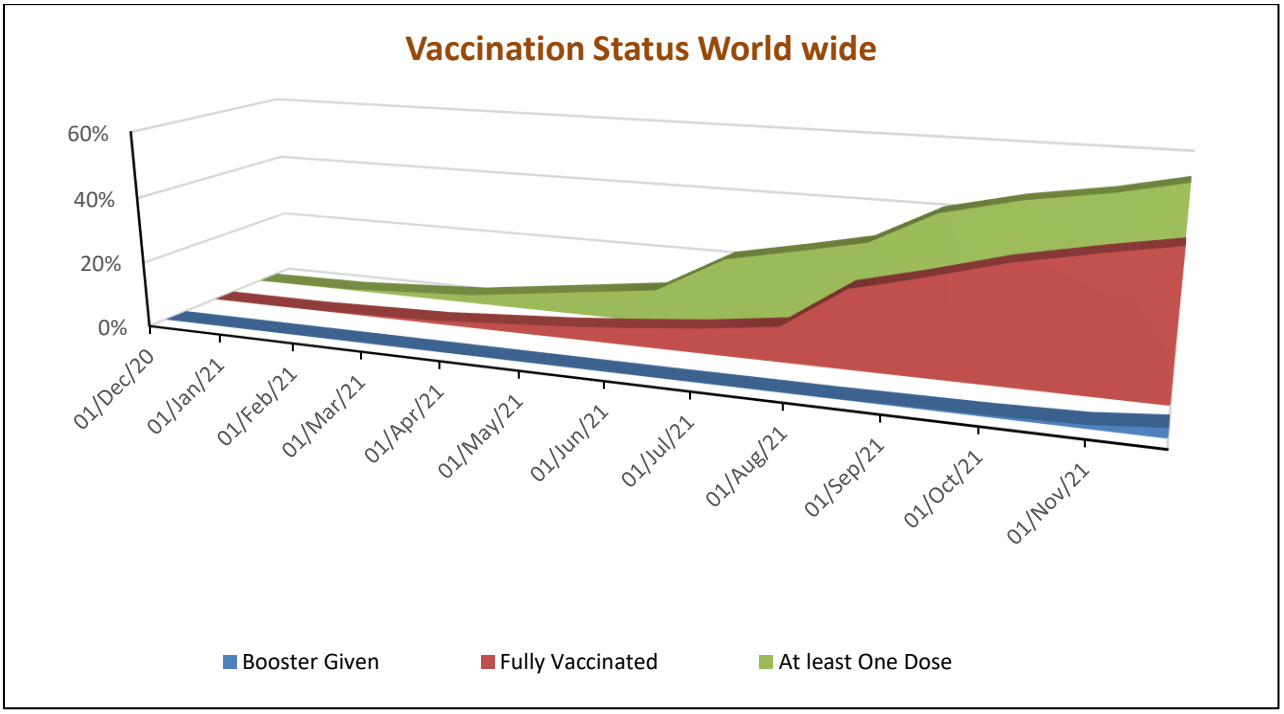

Figure 7: The Percentage of Vaccination by worldwide population.[22, 23]

DIAGNOSTIC TESTS

There are different types of coronavirus tests that can be done:

Swab Test – In this case, a special swab is used to take a sample from your nose or throat.[121]

Nasal aspirate – In this case, a saline solution will be injected into your nose and, then a sample is taken with a light suction

Tracheal aspirate – In this case, a thin tube with a torch, also known as a bronchoscope, is put into your mouth to reach your lungs from where a sample is collected.

Sputum Test – Sputum is thick mucus that gets accumulated in the lungs and comes out with a cough. During this test, you're required to cough up sputum in a special cup or a swab is used to take a sample from your nose.

Blood test – In this case, a blood sample is taken from a vein in the arm.[122]

Rapid diagnostic tests based on antigen detection- A rapid test has also been started for the COVID-19, which involves taking samples from the nose, throat, and lungs. A rapid diagnostic test (RDT) of a sample of the respiratory tract of a person helps to detect the viral proteins (antigens) related to the COVID-19 virus. This ensures a speedy and accurate diagnosis, and its usage is CDC-approved.[123]

Rapid diagnostic tests based on host antibody detection- This test detects the presence of antibodies in the blood of COVID-19 infected people. The strength of antibody response depends on several factors like age, medications, infections, and severity of disease etc. Before the test, the concerned health professionals may request you to wear a mask during the test. In case there are any other steps that need to be taken, the healthcare professional can communicate that to you.[124]

Some other tests for corona virus:

- Polymerase chain reaction (PCR) tests are sent away to a lab to diagnose disease
- Lateral flow tests (LFTs) can diagnose Covid-19 on the spot, but aren't as accurate as PCR tests
- Antibody (or serology) tests can't diagnose active infection, but they can help to tell if a person has immunity to Covid-19

RT-PCR TEST

PCR tests are used to directly screen for the presence of viral RNA, which will be detectable in the body before antibodies form or symptoms of the disease are present. This means the tests can tell whether someone has the virus very early on in their illness. During Covid-19 PCR testing, substances known as reverse transcriptase or DNA polymerase are added to a nasopharyngeal sample in a lab. These substances work to make numerous copies of any viral RNA that may be present. This is so that enough copies of the RNA are present to signal a positive result, as specifically designed primers and probes attach themselves to sequences of the genetic code of the virus to signal that a pathogen has been found. "PCR gives us a good indication of who is infected," says University of Sussex senior lecturer in microbiology Dr Edward Wright. "They can be isolated and get in contact with people they've been in touch with so they can be quarantined too, just in case. That's the true advantage of the current major diagnostic tests; you can break that transmission chain and get a clearer picture of what's happening. "By scaling PCR testing to screen vast swathes of nasopharyngeal swab samples from within a population, public health officials can get a clearer picture of the spread of a disease like Covid-19. However, PCR still has its caveats. These types of Covid-19 test need to be sent away to a laboratory for analysis, meaning it can take days for people to find out their results.[125, 126]

LFT TEST

LFTs are like PCR tests, in that they're both types of antigen test, designed to pick up active Covid-19 infection rather than antibodies to the disease. With a Covid-19 LFT, a nasopharyngeal sample is placed on a small absorbent pad, which is then drawn along the pad via a capillary line to a strip coated in antibodies, which bind to SARS-Cov-2 proteins. If these proteins are present, this will show as a coloured line on the test, indicating infection. The major benefit of LFTs over PCRs is that they do not need to be sent away for confirmation, and instead provide results within 15 to 30 minutes. However, what they gain in speed they sacrifice in accuracy.

A review of 64 studies from Europe and the US showed a wide variance in accuracy between different brands of LFT. The review also found that the tests were far better at identifying Covid-19 in people who had symptoms than those who did not. LFT sensitivity in symptomatic people ranged from 34% to 88%, with an average accuracy of 72%. In people without symptoms the LFTs correctly identified an average of 58% of those who were infected. While the use of LFTs for mass asymptomatic screening has been encouraged in countries like the UK, experts have cast doubt on how useful these types of Covid-19 test really are in this context.[127, 128]

ANTIBODY TEST

"An antibody test tells us what proportion of the population has been infected. It won't tell you who is infected, because the antibodies are generated after a week or two, after which time the virus should have been cleared from the system. But it tells you who's been infected and who should be immune to the virus." A study published in the journal Immunity has found that people who recover from even mild cases of Covid-19 produce antibodies for at least five to seven months and could do so for much longer. Historical studies have indicated that people who survived the sudden acute respiratory syndrome (SARS) outbreak in the early 2000s had antibodies in their blood for years after recovery. Both SARS and Covid-19 are caused by similar

corona viruses, so it's not unreasonable to think that Covid-19 could have a similar effect. "If there's a high enough level of people in the population who have immunity, they will then stop this virus from circulating within the population, which is known as herd immunity," says Wright. "If someone is infected, as long as the people around them have immunity the virus won't be able to spread."

Unlike PCR tests, which commonly use swabs to detect Covid-19, blood samples are usually used for antibody tests. This is because there will be a very small amount of Covid-19 circulating in the blood compared to the respiratory tract, but a significant and measurable antibody presence in the blood following infection. Antibody tests are being used to evaluate the immune responses in people who have been vaccinated against Covid-19. Researchers don't yet know how long vaccine-induced immunity will last or if booster shots will be needed. There has been some indication that Covid-19 variants are making certain vaccines less effective, but thus far they still appear to generally provide enough protection to guard against severe or fatal disease.[129]

TREATMENT MEASURES

Unfortunately, up until this point, there has yet to be a vaccine or proven effective therapy against SARS-CoV-2 infection. While many trials, including much needed randomized controlled trials (RCTs), are currently underway, the main stay of therapy remains supportive care. This ranges from symptomatic treatment to ventilator support for patients with ARDS depending on illness severity. This also includes recognizing and treating super imposed bacterial infections and/or sepsis early on. Many of the current clinical trials are investigating drugs that were previously used to treat SARS-CoV and MERS-CoV. These will be discussed further below.

Chloroquine/Hydroxychloroquine: Chloroquine and hydroxychloroquine are widely used antimalarial drugs. Hydroxychloroquine is a Chloroquine analogue with less drug-to-drug interaction and a better safety profile. Both Chloroquine and hydroxychloroquine are shown to inhibit the growth of SARS-CoV-2 *in vitro* and decrease viral replication in a concentration-dependent manner. Hydroxychloroquine was found to be more potent. It has been hypothesized that both Chloroquine and hydroxychloroquine may inhibit SARS-CoV-2 replication. They may do this by changing the pH at the surface of the cell membrane thereby inhibiting fusion in addition to inhibiting nucleic acid replication, glycosylation, and viral assembly and release.[130]

Azithromycin: Azithromycin is a macrolide antibiotic that has been widely used in patients with chronic pulmonary inflammatory disorders and/or community acquired pneumonia for its anti-inflammatory effect.[131] However, there is limited data suggesting the beneficial effect of Azithromycin in combination with Chloroquine/ hydroxychloroquine in the treatment of ARDS in patients with SARS-CoV-2 infection.

An open-label non-randomized clinical trial of 36 patients done in China showed a synergistic effect combining hydroxychloroquine and Azithromycin in treatment of SARSCoV-2 infection by reducing the detection of SARS-CoV-2 RNA in specimens from the upper respiratory tract.[132] However, this study did not comment on the clinical benefit of this combination. Another small observational study in China showed that combining hydroxychloroquine and Azithromycin for the treatment of SARS-CoV-2 in hospitalized patients had no clinical benefit and no evidence of rapid viral RNA clearance (97). Hydroxychloroquine and Azithromycin can both lead to corrected QT (QTc) prolongation, which can lead to fatal arrhythmias. Therefore, they should be used with caution in patients with prolonged QTc and those with certain medical conditions such as hepatic or renal disease.[133]

Remdesivir: Remdesivir is a novel nucleotide analogue that incorporates into nascent viral RNA chains and causes premature termination inhibiting viral replication. Remdesivir has been shown to be an effective antiviral agent against beta-corona viruses such as SARS-CoV and SARS-MERS in mice, non-human primates and *in vitro*, and is currently in clinical trials for the treatment of Ebola virus.[134] A study in China showed that remdesivir is highly effective in controlling SARS-CoV-2 infection *in vitro*. Another study that was recently published involving compassionate-use of remdesivir showed clinical improvement in 68% of patient (36 out of 53) who had severe SARS-CoV-2 infection; 57% were extubated and 47% were discharged.[135]

Despite its promising results *invitro*, *invivo* in animal models, and in compassionate-use studies in humans, remdesivir is still not approved by the FDA for use as a standard of care therapy due to lack of established data on safety and efficacy in humans. The biopharmaceutical company Giliad has initiated two phase 3 clinical trials to evaluate the safety and efficacy of this drug in COVID-19 patients.

Lopinavir-Ritonavir: Lopinavir-ritonavir is a protease inhibitor combination that has been used against human immunodeficiency virus (HIV) infection. This drug was proven to have *in vitro* activity against SARS-CoV; however, it does not seem to have a clear benefit during the current outbreak.[136] A randomized, controlled, open-label trial that included 199 patients assessed the use of lopinavir–ritonavir treatment in patients with SARS-CoV-2 and showed no benefit with administration of the drug compared to standard care alone, which comprised of antibiotics, vasopressors, renal replacement therapy, extracorporeal membrane oxygenation (ECMO) and/or supplemental oxygen/invasive ventilation if needed. Gastrointestinal adverse events were higher in the lopinavir– ritonavir group compared to those receiving standard-care alone; however, adverse events were higher in the standard-care group overall.[137]

Favipiravir: Favipiravir is an RNA polymerase inhibitor that is used for the treatment of influenza in China. Favipiravir is able to block the replication of RNA viruses by blocking the

RNA-dependent RNA polymerase (RdRp) enzyme. Therefore, favipiravir may have antiviral activity against SARS-CoV-2, which is also an RNA virus. Clinic trials involving the use of this drug in treating SARS-CoV-2 infection are currently ongoing.[138]

Ivermectin: Ivermectin is an FDA-approved medication for the treatment of various parasites and has an established safety profile in humans. Ivermectin has been shown to inhibit *in vitro* replication of various positive single stranded RNA viruses such as dengue and west Nile (104, 105). This drug has recently demonstrated *in vitro* activity against SARS-CoV-2 when a single dose was able to control viral replication within 24–48 h. It is hypothesized that this is likely through the inhibition of importin α/β1 heterodimer, which mediates nuclear import of viral proteins, a process that many RNA viruses rely on during infection (105, 106). The FDA has not yet approved ivermectin for the prevention or treatment of SARS-CoV-2 infection. RCTs studying the efficacy and safety of this drug in COVID-19 are still lacking.[139, 140]

Heparin

As more studies emerge linking coagulopathies to COVID-19 including systemic thrombosis and DIC, this raises the question whether heparin should be used in hospitalized patients to prevent these complications. In a retrospective study in China that included 449 patients, patients who received a prophylactic dose of heparin when they had sepsis-induced coagulopathy (SIC) score ≥ 6 and a d-dimer level >6-fold of upper limit of normal had decreased mortality . Based on the limited available data, the International Society of Thrombosis and Hemostasis (ISTH) recommend the measurement of d-dimer, PT, and platelet count for all patients with COVID-19 infection to help with risk stratification. The society also recommends the administration of low molecular weight heparin at prophylactic dose to all hospitalized patients with no contraindications. RCTs examining the use of heparin in COVID-19 patients are required to make appropriate recommendations.[141, 142]

Vitamin C: Vitamin C, also known as ascorbic acid, has antioxidant properties and plays a significant role in reducing inflammatory response. Studies have shown that ascorbic acid down-regulates the production of pro-inflammatory cytokines. These concepts have generated interest in the use of ascorbic acid in the management of inflammatory conditions. In a recent randomized clinical trial involving 167 patients in the intensive care unit, intravenous infusion of high-dose ascorbic acid compared to placebo did not significantly reduce organ dysfunction scores or improve levels of biomarkers indicating inflammation among patients with sepsis and ARDS, two disease processes heavily associated with inflammation. A randomized controlled trial is currently underway and in phase 2 to study the clinical efficacy and safety of vitamin C infusion for treatment of COVID-19 pneumonia.[143-145]

Zinc: It has been shown that increased zinc concentration inside the cell can effectively impair replication of several RNA viruses such as influenza and polioviruses. A study showed that zinc in combination with zinc-ionophores like pyrithione inhibited the replication of SARS-CoV in cell cultures. Therefore, zinc supplementation may be of potential benefit for prophylaxis and treatment of COVID-19 and it is currently under investigation in multiple clinical trials in combination with other agents including hydroxychloroquine, vitamin C, and vitamin D.[146, 147]

Montelukast: Montelukast has been shown to suppress oxidative stress and have anti-inflammatory effects. Use of high dose montelukast has been effective in the treatment of acute asthma. Because much of the morbidity and mortality from COVID-19 infection is due to excessive inflammatory processes, it is thought that montelukast may play a role in limiting the progression of disease. One of the protein complexes involved in cytokine production and inflammatory responses is NF-B (nuclear factor kappa-light chain-enhancer of activated B cells). Therefore, inhibition of the NF-B signalizing pathway has been investigated for potential therapeutic options in inflammatory diseases. Montelukast inhibits the signalling of NF-B and other proinflammatory mediators. Its use in COVID-19 infection is currently being studied in a large clinical trial, which is in phase 3, compared with placebo.[148, 149]

FUTURE ASPECTS

Preventive measures include physical or social distancing, quarantining, and ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. This recommendation is meant to reduce the spread of the disease by asymptomatic and pre-symptomatic individuals and is complementary to established preventive measures such as social distancing. Face coverings limit the volume and travel distance of expiratory droplets dispersed when talking, breathing, and coughing. A face covering without vents or holes will also filter out particles containing the virus from inhaled and exhaled air, reducing the chances of infection. Thorough hand hygiene after any cough or sneeze is required. The WHO also recommends that individuals wash hands often with soap and water for at least twenty seconds, especially after going to the toilet or when hands are visibly dirty, before eating and after blowing one's nose.

CONCLUSION

The COVID-19 pandemic has challenged the world not just in the global health but also the global psychosocial and economic health. This pandemic is testing our resolve to solve challenging situation together. The scientific world has taken on this challenge and is investigating this virus, the COVID-19 disease, and pathogenesis, and has developed systems in epidemiology, diagnosis, clinical management, and development of vaccines in a timeline that is unprecedented (all within 1 year). This brief

summary tried to describe some of the development and also the unanswered questions, with an attempt to use this information to allow us to look forward. Management basically consists of palliative care. Home care may be likely for cases with a mild disease that can be sufficiently isolated. To decrease the danger of spread in society, people should be advised to wash hands assiduously, carry out respiratory hygiene, and keep away from crowds and close contact with sick individuals. Facemasks are not regularly suggested for asymptomatic cases, but social distancing is advised in every place that has society spread.

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