WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 6, 850-890. Review Article ISSN 2277– 7105

CORONA VIRUS: A BRIEF REVIEW ON COVID-19

Atre Omkar*

Pravara Rural College of Pharmacy, Pravaranagar, Dist. Ahmednagar(Maharashtra) 423107 India.

Article Received on
16 April 2021,

Revised on 06 May 2021,
Accepted on 27 May 2021

DOI: 10.20959/wjpr20216-20650

***Corresponding Author**
Atre Omkar
Pravara Rural College of Pharmacy, Pravaranagar, Dist. Ahmednagar (Maharashtra) 423107 India.

ABSTRACT

A novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or (2019-nCoV) with unknown origin spread in Guangdong market province of China. The pandemic was initially caused in local market of Wuhan in dec-19 and thus it was named as coronavirus 19. this infection of covid-19 was soon reached all over the world in no time. Coronavirus causes respiratory infection including pneumonia, cold, sneezing and coughing while in animal it causes diarrhea and upper respiratory diseases. Corona virus enters in human cell through membrane ACE-2 exopeptidase receptor. The presence of COVID-19 was manifested by several symptoms, ranging from asymptomatic/mild symptoms to severe illness and death. However, dueto the worldwide spread of the virus, COVID-19 has become a serious concern in the medical community and was declared as novel covid19 by WHO in2019. Currently some antiviral medications are given as a supportive treatment for covid 19 which gave appreciable results in clinical trials along with some emergency approval of the vaccines for treatment. The number of covid cases now has raised to 15,20,00,000 (march-april). Thus, the main purpose of this review is to provide an overview of covid-19 along with diseases current treatment and future prospects of vaccine development and government`s strategy for management to covid-19.

KEYWORDS: transmembrane protease, covid-19, angiotensin converting enzyme, bat borne virus.

History and origin of disease

In December 2019, an outbreak of pneumonia with unknown origin began in China's wuhan Province, raised global health concerns due to the ease of transmission. Initially it was

stated that the virus arised from the local market of wuhan through some workers around there. All of these workers were said to cause infection in a rapid sense due to the high crowding market. A phylogenetic network analysis of 160 early coronavirus genomes sampled from December 2019 to February 2020 showed that the virus type most closely related to the bat coronavirus was most abundant in Guangdong, China, and designated type "A". Thepredominant type among samples from Wuhan, "B", is more distantly related to the bat coronavirus than the ancestral type "A". Further the strain that was isolated from the infected person was similar to with that of the virus W1V16 that was obtained from the cave of wuhan province of china and thus bats were said to beprimary cause of infection of SARS covid-19. further researchers stated that the virus isolated from pangolin species was only 72% similar to Covid 19 genome sequencing and thus may be said as intermediate of injection of covid 19. Research into the natural reservoir of the virus that caused the 2002–2004 SARS outbreak has resulted in the discovery of many SARS-like bat coronaviruses, most originating in the Rhinolophus genus of horseshoe bats. Phylogenetic analysis indicates that samples taken from Rhinolophus sinicus show a resemblance of 80% to SARS-CoV-2. Phylogenetic analysis also indicates that a virus from Rhinolophus affinis, collected in Yunnan province and designated RaTG13, hasa 96% resemblance to SARS-CoV-2. The RaTG13 virus sequence is the closest known sequence to SARS-CoV-2. All available evidence suggests that SARS-CoV-2 has a natural animal origin and is not genetically engineered. Nevertheless, early in the pandemic, conspiracy theories spread on social media claiming that the virus was bio-engineered by China at the Wuhan Institute of Virology. While some, including former CDC director Robert R. Redfield, have claimed that the virus may have been studied by and escaped from the Institute, virologists who have studied coronaviruses consider the possibility very remote, and the March 2021 WHO report on the joint WHO-China study stated that such an explanation is "extremely unlikely". To quickly diagnose and control the highly infectious disease, suspected people were isolated and diagnostic/ therapeutic procedures were developed via patients' epidemiological and clinical data. After numerous studies, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of the disease, and the disease was dubbed "coronavirus-19″ (COVID 19) by Chinese Scientists. The presence of COVID-19 is manifested by several symptoms, ranging from asymptomatic/mild symptoms to severe illness and death. Common symptoms include cough, fever, and shortness of breath. Other reported symptoms are weakness, malaise, respiratory distress, muscle pain, sorethroat, loss of taste and/or smell. On 11 February 2020, the International Committee on Taxonomy of

Viruses adopted the official name "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). To avoid confusion with the disease SARS, the WHO sometimes refers to SARS-CoV-2 as "the COVID-19 virus" in public health communication.

Microbiology of covid virus

SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope. The spike protein, is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell specifically, its S1 subunit catalyzes attachment, the S2 subunit fusion. Protein modeling experiments on the spike protein of the virussoon suggested that SARS-CoV-2 has sufficient affinity to the receptor angiotensin converting enzyme 2 (ANG II) on human cells to use them as a mechanism of cell entry. By 22 January 2020,a group in China working with the full virus genome and a group in the United States using reverse genetics methods independently and experimentally demonstrated that ANG II could act as the receptor for SARS-CoV-2. Studies have shown that SARS-CoV-2 has a higher affinity to humanANG II than the original SARS virus. SARS-CoV-2 may also use basigin to assist in cell entry. Initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2) is essential for entry of SARS-CoV-2. The host protein neuropilin 1 (NRP1) may aid the virus in host cell entry using ANG II. After a SARS-CoV-2 virion attaches to a target cell, thecell's protease TMPRSS2 cuts open the spike protein of the virus, exposing a fusion peptide in theS2 subunit, and the host receptor ANG II. After fusion, an endosome forms around the virion, separating it from the rest of the host cell. The virion escapes when the pH of the endosome drops or when cathepsin, a host cysteine protease, cleaves it. The virion then releases RNA into the cell and forces the cell to produce and disseminate copies of the virus, which infect more cells.

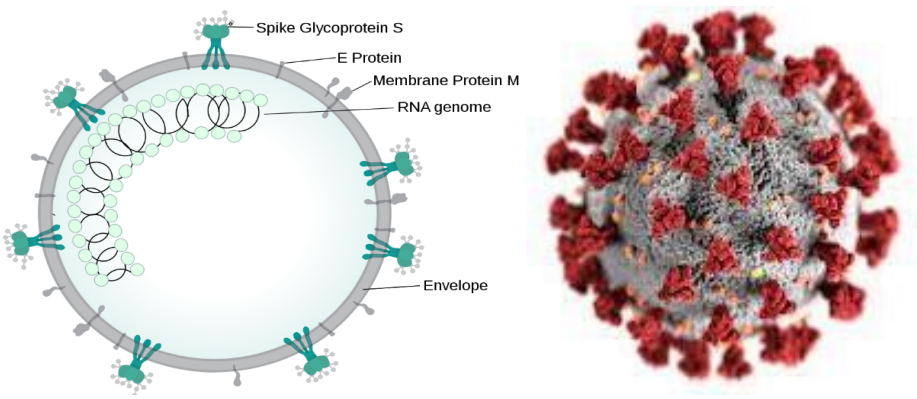

Fig 1: Microbiology of covid virus with spike proteins.

Pathogenesis of the 2019-nCoV

The lungs are the primary site of 2019-nCoV infection. Ang II is found in many types of cells and tissues, including the lungs, blood vessels, heart, liver, kidneys, and gastrointestinal tract. It is also present in the epithelium lining the lung, the nose, and mouth. The chest CT of the infected patients usually shows bilateral ground-glass opacity lesions in the posterior and peripheral lungs that are reported as the characteristic of 2019-nCoV pneumonia. The human angiotensin-converting enzyme 2 (Ang II), known as the major receptor for the viral S protein provides the entry point for 2019-nCoV to capture and infect a wide range of human cells. DC-SIGN (CD209), CD147, and L-SIGN (CD209L) are also other entry receptors for 2019-nCoV. Thus, drugs that interfere with the interactions of the spike protein/ Ang II, CD147, DCSIGN or L-SIGN or with their gene expression may inhibit viral invasion. Occupying the ANG II receptor by SARS-CoV-2 prevents it from performing its normal function, and breaking the Ang I and Ang II peptides. Naturally, there is a high concentration of ACE in the lung tissue. Thus, in ANG II deficiency, ACE will be more active due to more available Ang I which is changed into Ang II. Increased local Ang II levels damage blood vessel linings and cause inflammation and tissue injury. For this reason, it is claimed that the renin-angiotensin- system has a serious role in COVID-19 pathogenesis. So, it can be claimed that the main destructive factor in the patients with severe COVID-19 is abnormal and high activity of local Ang II. Drugs that inhibit ACE or ACE inhibitors (ACEI) such as ramipril, lisinopril, and enalapril may prevent the injuries caused by Ang II via inhibiting its production without blocking the actions of ANG II. In addition to ANG II, there are other enzymes capable to hydrolyse Ang-I or Ang (1–9) to Ang (1–7) such as Neprilysin, Prolylcarboxypeptidase, and Prolylendopeptidase. It appears that if the activity of these enzymes is up-regulated in the lungs of people with COVID-19, the effects of reduced ANG II may be compensated. Among the mentioned enzymes, higher expression levels of Neprilysin have been detected in lung tissue, especially in the membrane of pulmonary epithelial cells. In addition to the negative effect on Ang II production, it cleaves and inactivates some other vasoactive peptides such as substance P, and endothelin. It degrades and inactivates bradykinin. Bradykinin is identified as a potent vasodilator and lowers blood pressure, but causes contraction in the non-vascular smooth muscle of the bronchi and intestines and may play a role in the pain mechanism. So, Neprilysin can be considered as a potential target to control the severity of COVID-19 disease. Both Prolylcarboxypeptidase and Prolylendopeptidase are lysosomal and cytosolic peptidase, respectively, that have been mainly expressed in white blood cells. They have also been detected in lung, liver, and

kidney tissues. In addition to their role in the destruction or maturation of a variety of peptides, both enzymes may be considered as protective agents against AngII induced injuries due to the conversion of AngII to Ang (1–7). Prolylcarboxypeptidase also named angiotensinase C, activates bradykinin, and hydrolyses plasma prekallikrein to active kallikrein. However, some studies have reported an inflammatory role for Prolylcarboxypeptidase in the lungs and other tissues.

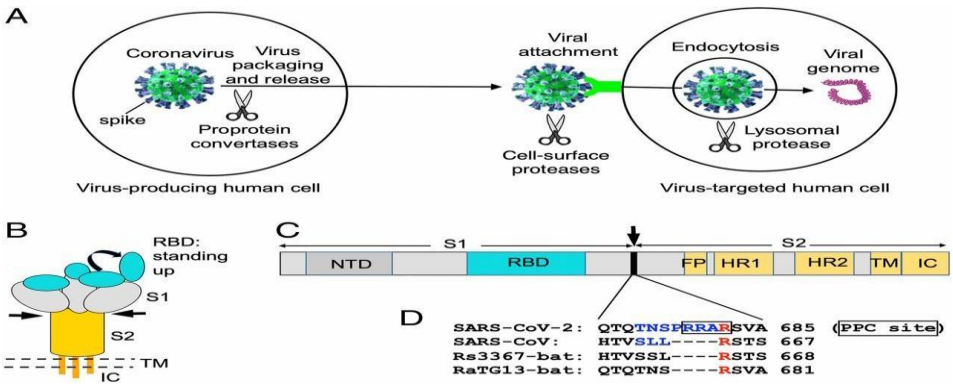

Fig 2: The phylogenetic illustration of the receptor-binding domain (RBD) in various betacoronaviruses a. The structure of RBD in SARS-CoV b. 2019-nCoV c. MERS-CoVd.SARS COVID-19.

Based on the cells that are likely infected, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease.

Stage 1: Asymptomatic state (initial 1–2 days of infection

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ANG II is the main receptor for both SARS-CoV2 and SARS-CoV. In vitro data with SARS-CoV indicate that the ciliated cells are primary cells infected in the conducting airways. However, this concept might need some revision, since single-cell RNA indicates low level of ANG II expression in conducting airway cells and no obvious cell type preference. There is local propagation of the virus but a limited innate immune response. At this stage the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. Perhaps super spreaders could be detected by these studies. For the RT-PCR cycle number to be useful, the sample collection procedure would have to be standardised. Nasal swabs might be more sensitive than throat swabs.

Stage 2: Upper airway and conducting airway response (next few days)

The virus propagates and migrates down the respiratory tract along the conducting airways, and amore robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. At this time, the disease COVID-19 is clinically manifest. The level of CXCL10 (or some other innate response cytokine)may be predictive of the subsequent clinical course. Viral infected epithelial cells are a major source of beta and lambda interferons. CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza.CXCL10 has also been reported to be useful as disease marker in SARS. Determining the host innate immune response might improve predictions on the subsequent course of the disease and need for more aggressive monitoring. For about 80% of the infected patients, the disease will be mild and mostly restricted to the upper and conducting airways. These individuals may be monitored at home with conservative symptomatic therapy.

Stage 3: Hypoxia, ground glass infiltrates, and progression to ARDS

Unfortunately, about 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age. The fatality and morbidity rates maybe revised once the prevalence of mild and asymptomatic cases is better defined. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells. The infected alveolar units tend to be peripheral and subpleural. SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells in adjacent units. I suspect areas of the lung will likely lose most of their type II cells, and secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. This postulated sequence of events has been shown in the murine model of influenza pneumonia. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of ARDS. Recovery will require a vigorous innate and acquired immune response and epithelial regeneration. From my perspective,similar to influenza, administrating epithelial growth factors such as KGF might

be detrimental and might increase the viral load by producing more ANG II expressing cells. Elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also has reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily.

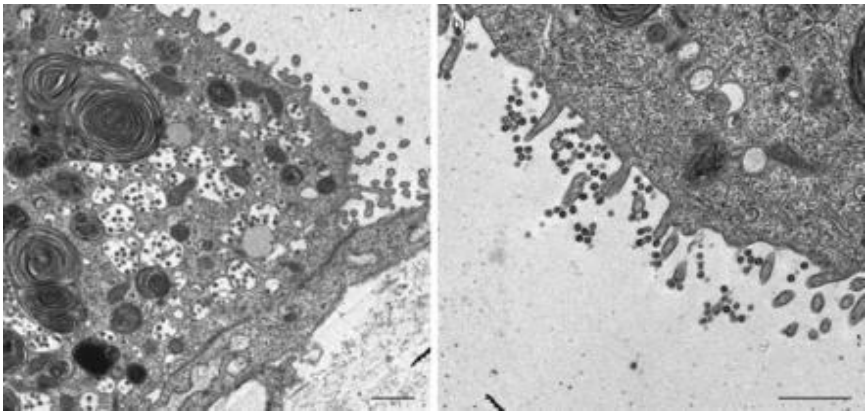

Fig 3: Human alveolar type II cells infected with SARS-CoV. Human type II cells were isolated, cultured in vitro, and then infected with SARS-CoV. Viral particles are seen in double membrane vesicles in the type II cells (a) and along the apical microvilli (b). Reproduced with permission from the American Thoracic Society.

There are significant knowledge gaps in the pathogenesis of COVID-19 that will be filled in over the next few months. We do not know if there are alternate receptors for viral entry. CD209L is an alternative receptor for SARS-CoV. We await detailed studies on infection and the innate immune response of differentiated primary human lung cells. The apical cilia on airway cells and microvilli on type II cells may be important for facilitating viral entry. In conclusion, COVID-19 confined to the conducting airways should be mild and treated symptomatically at home. However, COVID- 19 that has progressed to the gas exchange units of the lung must be monitored carefully and supported to the best of our ability, as we await the development and testing of specific antiviral drugs.

Transmission (Causative agents) of the 2019-nCoV

The first known infections from SARS-CoV-2 were discovered in Wuhan, China. A phylogenetic network analysis of 160 early coronavirus genomes sampled from December 2019 to February 2020 showed that the virus type most closely related to the bat coronavirus was most abundant in Guangdong, China, and designated type "A". The predominant type among samples from Wuhan, "B", is more distantly related to the bat

coronavirus than the ancestral type "A". Research into the natural reservoir of the virus that caused the 2002–2004 SARS outbreak has resulted in the discovery of many SARS-like bat coronaviruses, most originating in the Rhinolophus genus of horseshoe bats. Phylogenetic analysis indicates that samples taken from Rhinolophus sinicus show a resemblance of 80% to SARS-CoV-2. The original source of viral transmission to humans remains unclear, as does whether the virus became pathogenic before or after the spillover event. Because many of the early infectives were workers at the Huanan Seafood Market, it has been suggested that the virus might have originated from the market. However, other research indicates that visitors may have introduced the virus to the market, which then facilitated rapid expansion of the infections.

Fig 4: Samples taken from *Rhinolophus sinicus*, a species of horseshoe bats, show an 80% resemblance to SARS-CoV-2.

Phylogenetic analysis also indicates that a virus from Rhinolophus affinis, collected in Yunnan province and designated RaTG13, has a 96% resemblance to SARS-CoV-2. The RaTG13 virus sequence is the closest known sequence to SARS-CoV-2. Bats are considered the most likely natural reservoir of SARS-CoV-2, but differences between the bat coronavirus and SARS-CoV-2 suggest that humans were infected via an intermediate host. Evidence against this hypothesis includes the fact that pangolin virus samples are too distant to SARS-CoV-2: isolates obtained from pangolins seized in Guangdong were only 92% identical in sequence to the SARS-CoV-2 genome. In addition, despite similarities in a few critical amino acids, pangolin virus samples exhibit poor binding to the human ANG II receptor. The routes of human-to-human transmission of 2019-nCoV among individuals include direct inhalation of contaminated droplets released into the environment by sneezing or coughing, and contact transmission via oral, nasal, and eye mucous. Although a 6-ft distance is emphasized to protect against the spread of the disease, it is not enough. Microbes

in droplets < 5 μm in diameter can stay in the air for a long time and can betransmitted to others over distances of more than 1 m. There is no evidence that 2019-nCoV is spread through water in pools, rivers, lakes. To date, no reports of positive crowns have been received from water play places; however, it cannot be said that it is completely 100% safe. Intestinal infection and the presence of 2019-nCoV in feces have been reported, but there is not enough evidence for fecal-oral transmission of 2019-nCoV. Song et al. examined the presence of 2019-nCoV in testicular biopsy and semen of COVID-19 patients and did not find positive RT- PCR. They stated that 2019-nCov does not infect the testes and the virus may not be sexually transmitted by infected men. Some studies have shown the presence of asymptomatic viral carrierswith normal laboratory and chest CT findings.

Comparison of coronavirus with other 5 class of beta viruses and mode of action in causing viral infection

David Tyrrell who was a british physician insolated and told about coronavirus. Accordingly, there were 6 viruses who belonged to the class of beta coronaviruses which were as following.

- Human coronavirus 229E (HCoV-229E).
- Human coronavirus OC43 (HCoV-OC43).
- Human coronavirus HKU1 (HCoV-HKU1).
- Middle East respiratory syndrome-related coronavirus (MERS-CoV).
- Severe acute respiratory syndrome coronavirus (SARS-CoV-1).
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Human coronavirus 229E (HCoV-229E).

Identified in late 2004 in a small child of age 7 years who had bronchiolitis in netherlands.this virus was originated from palm civets and bats with same binding to the ACE-2 as likecovid-19. Entry mechanism was same as like the COVID-19 strain along with additional endocytosis and plasma membrane cell fusion. Treatment for the HCoV-NL63 virus was dependent on the severity of associated symptomology. Most mild to moderate infections had gone away on their own. Symptoms was relieved by taking a pain reliever or fever medication, taking a hot shower, or using a humidifier. Antiviral treatment was necessaryfor infected patients that end up in the intensive care unit (ICU)due to acute respiratory infection. Intravenous immunoglobulin was FDA approved HCoV-NL63 inhibitor that is also used to treat primary immune deficiency, RSV, and Kawasaki disease.

- Human coronavirus OC43 (HCoV-OC43).

The morphology was same as COVID-19 virus with positive sense single strained,enveloped with binding to N-Acetyl neuraminic acid receptor. in 1889-1890 the Russian flu caused same pandemic as like covid 19 with the killing about 1 million population worldwide. the causative agent for this was not known. Some stated that it was Influenza virus of H2N3 or H3N3 strain. Further in Nov-2020 Danish researcher stated that symptoms was similar to that of COVID-19. In 2002-2004 SARS outbreak which was stated to have same common ancestor as like the Russian flu in late 19s. orifin of these strains was said to be most likely from rodents and then to cattle and then towards the host i.e. humans.

- Human coronavirus HKU1 (HCoV-HKU1).

Discovered in Jan 2004 from one of man from hongkong the structure is same with enveloped and ssRNA but the binding is towards 9-O Acetylnueromінic acid receptor. It also has an additional hemagglutinin esterase binding ability which make it different from other class of viruses. These viruses were seen in a man who returned from Shenzhen china. These viruses were not isolated but was genetically sequenced from the virus with similar structure with mouse hepatitis virus. It was said to arise from rodents.

- Middle East respiratory syndrome-related coronavirus (MERS-CoV).

It is single strained positive spiked ssRNA with binding ability to DPP4 receptor. First casewas identified on April 2002 in Jeddah, Saudi Arabia. Evolution was said to be from the bats of species Tylonycteris bat coronavirus and Pipisterellus bat covid HKU5 and HKU4. First source of covid in human of these type was due to the initial contact from quatar and dromedary camels from south Africa where it as source of infection in human beings beforebat coronavirus. The person who got infected died in Nov 2013. later on, June 2014 around 689 cases were found with 283 death number.

- Severe acute respiratory syndrome coronavirus (SARS-CoV-1).

Said to have originated from wuhan market as majority of initial cases was found over there. the virus was closely resembeled the structure as like SARS covid 19 where it infected only epithelial cells of lungs who binds to ACE-2 who infects human bats and plam civets. The host viral genome was isolated by university of hong kong. the two species of rhinophus were closely related to covid 19 strain.

1. Rhinolophus Sinicus- about 80% resembalace.

2. Rhinolophus affinis -96% similar to SARS covid 2.

Until now RaTG13 virus sequence is the closest resembalace of covid 19 strain.

Total variants for covid up to date

- **Notable variants**

In early November 2020, Cluster 5, also referred to as FVI-spike by the Danish State Serum Institute (SSI), was discovered in Northern Jutland, Denmark, and is believed to have been spread from minks to humans via mink farms. On 4 November 2020, it was announced that the mink population in Denmark would be culled to prevent the possible spread of this mutation and reduce the risk of new mutations happening. A lockdown and travel restrictions were introduced in seven municipalities of Northern Jutland to prevent the mutation from spreading, which could compromise national or international responses to the COVID-19 pandemic. By 5 November 2020, some 214 mink-related human cases had been detected. The World Health Organization (WHO) has stated that cluster 5 has a "moderately decreased sensitivity to neutralizing antibodies". SSI warned that the mutation could reduce the effect of COVID-19 vaccines under development, although it was unlikely to render them useless. Following the lockdown and mass-testing, SSI announced on 19 November 2020 that cluster 5 in all probability had become extinct. As of 1 February 2021, authors to a peer-reviewed paper, all of whom were from the SSI, assessed that cluster 5 was not in circulation in the human population.

1. Lineage B.1.1.7 / Variant of Concern 20DEC-01

First detected in October 2020 during the COVID-19 pandemic in the United Kingdom from a sample taken the previous month in Kent, Lineage B.1.1.7, was previously known as the first Variant Under Investigation in December 2020 and later notated as VOC-202012/01. It is also known as lineage B.1.1.7 or 20I/501Y.V1 (formerly 20B/501Y.V1). Since then, its prevalence odds have doubled every 6.5 days, the presumed generational interval. It is correlated with a significant increase in the rate of COVID-19 infection in United Kingdom, associated partly withthe N501Y mutation. There is some evidence that this variant has 40%–80% increased transmissibility (with most estimates lying around the middle to higher end of this range), and early analyses suggest an increase in lethality. More recent work has found no evidence of increased virulence.

2. Variant of Concern 21FEB-02

Variant of Concern 21FEB-02 (previously written as VOC-202102/02), described by Public Health England (PHE) as "B.1.1.7 with E484K"is of the same lineage in the Pango nomenclature system, but has an additional E484K mutation. As of 17 March 2021, there are 39 confirmed cases of VOC-21FEB-02 in the UK. On 4th march scientists reported B.1.1.7 with E484K mutations in the state of Oregon. In 13 test samples analysed, one had this combination, which appeared to have arisen spontaneously and locally, rather than being imported.

3. Lineage B.1.1.207

First sequenced in August 2020 in Nigeria,[80] the implications for transmission and virulence are unclear but it has been listed as an emerging variant by the US Centers for Disease Control. Sequenced by the African Centre of Excellence for Genomics of Infectious Diseases in Nigeria, this variant has a P681H mutation, shared in common with UK's Lineage B.1.1.7. It shares no other mutations with Lineage B.1.1.7 and as of late December 2020 this variant accounts for around 1% of viral genomes sequenced in Nigeria, though this may rise. By March 2021, Lineage B.1.1.207 had been detected in Peru, Germany, Singapore, Hong Kong, Vietnam, Costa Rica, South Korea, Canada, Australia, Japan, France, Italy, Ecuador, Mexico, UK and the USA.

4. Lineage B.1.1.317

While B.1.1.317 is not considered a variant of concern, Queensland Health forced 2 people undertaking hotel quarantine in Brisbane, Australia to undergo an additional 5 days quarantine ontop of the mandatory 14 days after it was confirmed they were infected with this variant.

5. Lineage B.1.1.318

Lineage B.1.1.318 was designated by PHE as a VUI (VUI-21FEB-04, previously VUI-202102/04)on 24 February 2021. 16 cases of it have been detected in the UK.

6. Lineage B.1.351

On 18 December 2020, the 501.V2 variant, also known as 501.V2, 20H/501Y.V2 (formerly 20C/501Y.V2), VOC-20DEC-02 (formerly VOC-202012/02), or lineage B.1.351, was first detected in South Africa and reported by the country's health department. Researchers and officials reported that the prevalence of the variant was higher among young people with no

underlying health conditions, and by comparison with other variants it is more frequently resulting in serious illness in those cases. The South African health department also indicated that the variantmay be driving the second wave of the COVID-19 epidemic in the country due to the variant spreading at a more rapid pace than other earlier variants of the virus. Scientists noted that the variant contains several mutations that allow it to attach more easily to human cells because of the following three mutations in the receptor-binding domain (RBD) in the spike glycoprotein of the virus: N501Y, K417N, and E484K. The N501Y mutation has also been detected in the United Kingdom.

CDC has listed B.1.429 and the related B.1.427 as "variants of concern," and cites a preprint for saying that they exhibit a ~20% increase in viral transmissibility, have a "Significant impacton neutralization by some, but not all," therapeutics that have been given Emergency Use Authorization (EUA) by FDA for treatment or prevention of COVID-19, and moderately reduce neutralization by plasma collected by people who have previously infected by the virus or who have received a vaccine against the virus. B.1.429 was first observed in July 2020 by researchers at the Cedars-Sinai Medical Center, California, in one of 1,230 virus samples collected in Los Angeles County since the start of the COVID-19 epidemic. It was not detected again until September when it reappeared among samples in California, but numbers remained very low until November. In November 2020, the CAL. Europe, Asia and Australia.

7. Lineage B.1.525

B.1.525, also called VUI-21FEB-03 (previously VUI-202102/03) by Public Health England (PHE) and formerly known as UK1188, does not carry the same N501Y mutation found in B.1.1.7, 501.V2 and P.1, but carries the same E484K-mutation as found in the P.1, P.2, and 501.V2 variants, and also carries the same H69/V70 deletion (a deletion of the amino acids histidine and valine in positions 69 and 70) as found in B.1.1.7, N439K variant (B.1.141 and B.1.258) and Y453F variant (Cluster 5). B.1.525 differs from all other variants by having both the E484K-mutation and a new F888L mutation (a substitution of phenylalanine (F) with leucine (L) in the S2 domain of the spike protein). As of March 5, it had been detected in UK, Denmark, Finland, Norway, Netherlands, Belgium, France, Spain, Nigeria, Ghana, Jordan, Japan, Singapore, Australia, Canada, Germany, Italy, Slovenia, Austria, Malaysia, Switzerland , the Republic of Ireland and the US. It has also been reported in Mayotte, the overseas department/region of France. The first cases were detected in December 2020 in the

UK and Nigeria, and as of 15 February, it had occurred in the highest frequency among samples in the latter country. As of 24 February, 56 cases were found in the UK. Denmark, which sequence all their COVID-19 cases, found 113 cases of this variant from January 14 to February 21, of which seven were directly related to foreign travels to Nigeria. UK experts are studying it to understand how much of a risk it could be. It is currently regarded as a "variant under investigation", but pending further study, it may become a "variant of concern". Prof Ravi Gupta, from the University of Cambridge spoke to the BBC and said B.1.525 appeared to have "significant mutations" already seen in some of the other newer variants, which is partly reassuring as their likely effect is to someextent more predictable.

8. Lineage B.1.526

In November 2020, a mutant variant was discovered in New York City, which was named B.1.526. As of April 11, 2021, the variant has been detected in at least 48 U.S. states and 18 countries.

9. Lineage B.1.617

In October 2020, a new variant was discovered in India, which was named B.1.617. There werevery few detections until January 2021 and by April it had spread to at least 20 countries in all continents except Antarctica and South America. Among some 15 defining mutations, it has spike mutations D111D (synonymous), G142D, P681R, E484Q and L452R, the latter two of which may cause it to easily avoid antibodies. In an update on 15 April 2021, PHE designated B.1.617 as a 'Variant under investigation', VUI-21APR-01. On 29 April 2021, PHE added two further variants, VUI-21APR-02 and VUI-21APR-03, effectively B.1.617.2 and B.1.617.3.

10. Lineage B.1.618

In October 2020, this variant was first isolated. It has a mutation called E484K which is the samemutation which South African variant has. It is growing significantly in recent months in West Bengal. As of 23 April 2021, the CoV-Lineages database showed 135 sequences detected in India, with single-figure numbers in each of eight other countries worldwide.

11. Lineage P.3

On 18 February 2021, the Department of Health of the Philippines confirmed the detection of two mutations of COVID-19 in Central Visayas after samples from patients were sent to undergo genome sequencing. The mutations were later named as E484K and N501Y, which

were detected in 37 out of 50 samples, with both mutations co-occurrent in 29 out of these. There were no official names for the variants and the full sequence was yet to be identified. On 13 March, the Department of Health confirmed the mutations constitutes a variant which was designated as lineage P.3. On the same day, it also confirmed the first Lineage P.1 COVID-19 case in the country. Although the P.1 and P.3 variants stem from the same lineage B.1.1.28, the department said that P.3 variant's impact on vaccine efficacy and transmissibility is yet to be ascertained. The Philippines had 98 cases of P.3 variant on 13 March. On 12 March it was announced that P.3had also been detected in Japan. On 17 March, the United Kingdom confirmed its first two cases, where PHE termed it VUI-21MAR-02. On 30 April 2021, Malaysia detected 8 cases of P.3variant in Sarawak.

- **Notable missense mutations1. D614G**

D614G is a missense mutation that affects the spike protein of SARS-CoV-2. The frequency of this mutation in the viral population has increased during the pandemic. G (glycine) has replaced D (aspartic acid) at position 614 in many countries, especially in Europe though more slowly in China and the rest of East Asia, supporting the hypothesis that G increases the transmission rate, which is consistent with higher viral titers and infectivity in vitro. Researchers with the PANGOLIN tool nicknamed this mutation "Doug". In July 2020, it was reported that the moreinfectious D614G SARS-CoV-2 variant had become the dominant form in the pandemic. PHE confirmed that the D614G mutation had a "moderate effect on transmissibility" and was being tracked internationally. The global prevalence of D614G correlates with the prevalence of loss of smell (anosmia) as a symptom of COVID-19, possibly mediated by higher binding of the RBD to the ANG II receptor or higher protein stability and hence higher infectivity of the olfactory epithelium. Variants containing the D614G mutation are found in the G clade by GISAID[4] and the B.1 clade by the PANGOLIN tool.

2. E484K

The name of the mutation, E484K, refers to an exchange whereby the glutamic acid (E) is replacedby lysine (K) at position 484. is nicknamed "Eeek".E484K has been reported to be an escape mutation (i.e., a mutation that improves a virus's ability to evade the host's immune system) fromat least one form of monoclonal antibody against SARS-CoV-2, indicating there may be a "possible change in antigenicity". The P.1. lineage described in Japan and Manaus, the P.2 lineage(also known as B.1.1.28.2 lineage, Brazil) and 501.V2 (South Africa) exhibit

this mutation. A limited number of B.1.1.7 genomes with E484K mutation have also been detected. Monoclonal and serum-derived antibodies are reported to be from 10 to 60 times less effective in neutralizing virus bearing the E484K mutation. On 2 February 2021, medical scientists in the United Kingdom reported the detection of E484K in 11 samples (out of 214,000 samples), a mutation that may compromise current vaccine effectiveness.

3. N501Y

N501Y denotes a change from asparagine (N) to tyrosine (Y) in amino-acid position 501. N501Y has been nicknamed "Nelly". This change is believed by PHE to increase binding affinity becauseof its position inside the spike glycoprotein's receptor-binding domain, which binds ANG II in human cells; data also support the hypothesis of increased binding affinity from this change. Molecular interaction modeling and the free energy of binding calculations has demonstrated thatthe mutation N501Y has the highest binding affinity in variants of concern RBD to hANG II. Variants with N501Y include P.1 (Brazil/Japan), Variant of Concern 20DEC-01 (UK), 501.V2 (South Africa), and COH.20G/501Y (Columbus, Ohio). This last became the dominant form of the virus in Columbus in late December 2020 and January and appears to have evolved independently of other variants.

4. S477G/N

A highly flexible region in the receptor binding domain (RBD) of SARS-CoV-2, starting from residue 475 and continuing up to residue 485, was identified using bioinformatics and statistical methods in several studies. The University of Graz and the Biotech Company Innophore have shown in a recent publication that structurally, the position S477 shows the highest flexibility among them.

At the same time, S477 is hitherto the most frequently exchanged amino acid residue in the RBDsof SARS-CoV-2 mutants. By using molecular dynamics simulations of RBD during the binding process to hANG II, it has been shown that both S477G and S477N strengthen the binding of the SARS-COV-2 spike with the hANG II receptor. The vaccine developer BioNTech referenced thisamino acid exchange as relevant regarding future vaccine design in a preprint published in February 2021.

5. P681H

In January 2021, scientists reported in a preprint that the mutation 'P681H', a characteristic feature of the significant novel SARS-CoV-2 variants detected in the U.K. (B.1.1.7) and

Nigeria (B.1.1.207), is showing a significant exponential increase in worldwide frequency, similar to the now globally prevalent 'D614G'.

6. E484Q

The name of the mutation, E484Q, refers to an exchange whereby the glutamic acid (E) is replaced by glutamine (Q) at position 484. India is seeing a significant surge of COVID-19 starting 2021 caused by a "double mutant". This "double mutant" strain has been named B.1.617. E484Q is a key mutation in this strain that enhances ANG II receptor binding ability and reduces existing antibodies from attaching to this mutated, hence differently folded, spike protein.

7. L452R

The name of the mutation, L452R, refers to an exchange whereby the leucine (L) is replaced by arginine (R) at position 452. There has been a significant surge of COVID-19 starting 2021 all across India caused by a "double mutant". This "double mutant" strain has been named B.1.617. L452R is a relevant mutation in this strain that enhances ANG II receptor binding ability and reduces existing antibodies from attaching to this mutated, hence differently folded, spike protein.L452R, some studies show, could even make the coronavirus resistant to T cells, that are class of cells necessary to target and destroy virus-infected cells. They are different from antibodies that are useful in blocking coronavirus particles and preventing it from proliferating.

8. P681R

The name of the mutation, P681R, refers to an exchange whereby the proline (P) is replaced by arginine (R) at position 681. Indian SARS-CoV-2 Genomics Consortium (**INSACOG**) foundthat other than the two mutations E484Q and L452R, there is also a third significant mutation, P681R in B.1.617. All three concerning mutations are on the spike protein, the operative part of the coronavirus that binds to receptor cells of the body.

9. N440K

This mutation is said to increase infectivity of virus by 10 to 1000 times than current circulating strains. It is involved in current rapid surge of Covid cases in India. India has largest proportion ofN440K mutated variants followed by the US and Germany.

Mode of Spreading

Peoples can get the infection through close contact with a person who has symptoms from the virus includes cough and sneezing. Generally, corona virus was spread via airborne zoonotic droplets. Virus was replicated in ciliated epithelium that caused cellular damage and infection at infection site. According to a study published in 2019. Angiotensin converting enzyme 2 (ACE.2), a membrane exopeptidase in the receptor used by corona virus in entry to human cell. Respiratory infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when then are <5μm in diameter, they are referred to as droplet nuclei.1 According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes. In an analysis of 75,465 COVID-19 cases in China, airborne transmission was not reported.Droplet transmission occurs when a person is in in close contact (within 1 m) with someone who has respiratory symptoms (e.g., coughing or sneezing) and is therefore at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infective respiratory droplets. Transmission may also occur through fomites in the immediate environment around the infected person.8 Therefore, transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer). Airborne transmission is different from droplet transmission as it refers to the presence of microbes within droplet nuclei, which are generally considered to be particles <5μm in diameter, can remain in the air for long periods of time and be transmitted to others over distances greater than 1 m. In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment,manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation. There is some evidence that COVID-19 infection may lead to intestinal infection and be present in faeces. However, to date only one study has cultured the COVID-19 virus from a single stool specimen. There have been no reports of faecal−oral transmission of the COVID-19 virus to date.

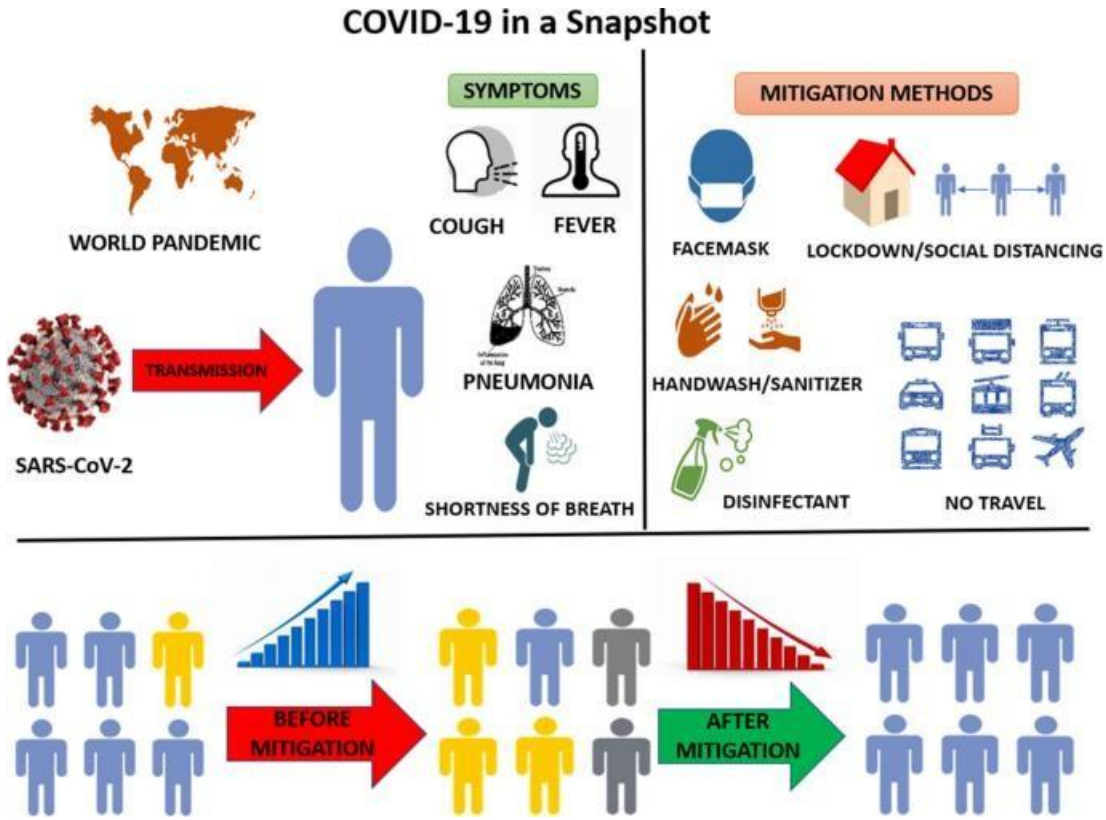

Fig 5: Mode of spreading of COVID-19.

Effect of COVID-19 on Other Organs

COVID-19. According to several studies, 2019-nCoV infection, similar to some viral infections, may be accompanied by cardiac injury. A study of 400 patients hospitalized in Wuhan, China, found that about one-fifth of patients with COVID-19 developed heart disease, which increased the mortality rate in patients. Severe and sudden inflammation of the heart muscle causes arrhythmias and impairs the heart's ability to efficiently pump blood. Therefore, patients with a history of cardiovascular disease and with high blood pressure are at higher risk of death than normal individuals. Oxygen deficiency due to trauma in the lungs damages the lining of the heart and blood vessels. Besides, fatty plaques in the arteries of the heart of people with or without symptoms of cardiovascular disease may become unstable due to fever and inflammation, leadingto vascular obstruction and cardiovascular problems. Other possible disorders seen in hospitalized patients with COVID-19 are abnormal blood clotting and venous thromboembolism, which necessitate the administration of anticoagulants or thromboprophylaxis for these patients. The secretion of various types of inflammatory cytokines in these conditions can exacerbate these complications. Thus, cytokine inhibitors may be effective in reducing the severity of the disease. Some studies have reported that COVID-19 may damage CNS. Some observed symptoms includelosing the

senses of smell, taste or vision, and decreasing alertness. Also, seizures, stroke, and acute necrotizing haemorrhagic encephalopathy have been reported in patients with severe COVID-19 infection.

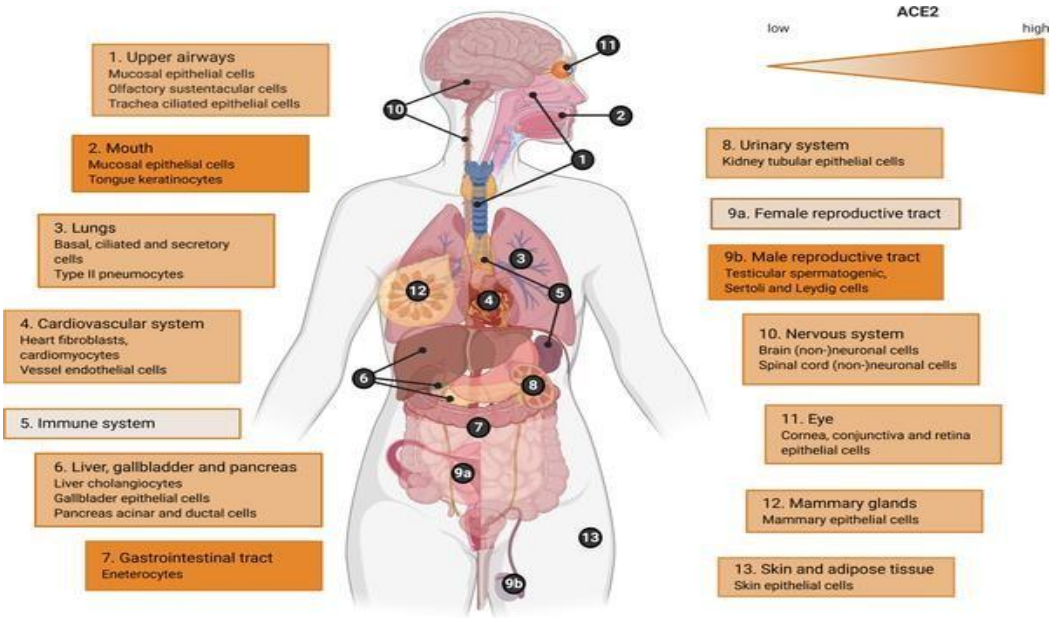

Fig 6: Effect of COVID-19 on Other Organs.

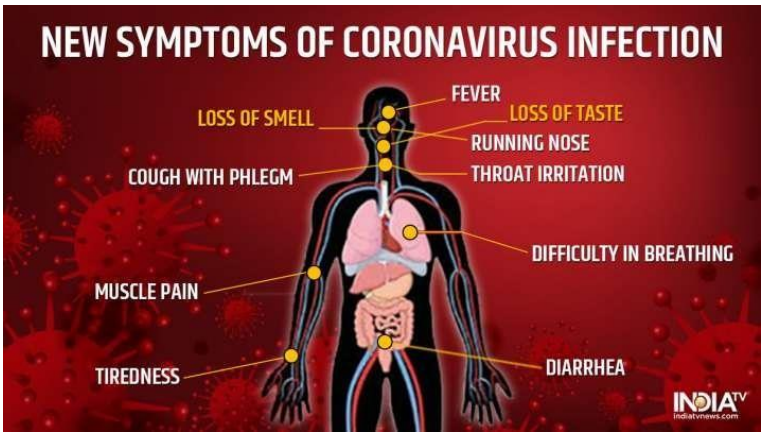

Fig 7: New symptoms of COVID-19.

Therapeutic results have shown that neurological symptoms gradually decrease in patients receiving viral encephalitis treatment. About half of patients with COVID-19 show evidence of protein or blood in the urine, which indicates early renal damage. It has been reported that 15 to 30% of hospitalized patients with COVID-19 in China and New York need to receive renal treatments or dialysis. However, the direct attack of the virus on the kidneys is still being debated. The presence of the virus in the fecal samples of some patients with COVID-19 indicates that the virus can reach the human gastrointestinal tract. About half of all patients

sufferfrom vomiting, diarrhoea, and other gastrointestinal disorders. Acute viral hepatitis has also been found in some of these patients. After developing symptoms of fever and cough, physicians connect gastrointestinal disorders with COVID-19.

Treatment of the COVID-19

- **Outpatient Management of Acute COVID-19**

Outpatient management of acute COVID-19 should include providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation. Specific Therapy for Outpatients.

1. With Mild to Moderate COVID-19

The COVID-19 Treatment studies recommends using one of the following combination anti-SARSCoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization criteria.

- Bamlanivimab 700 mg plus etesevimab 1,400 mg.
- Casirivimab 1,200 mg plus.
- Imdevimab 1,200 mg.

The studies recommend against the use of chloroquine or hydroxychloroquine with or without azithromycin. The use of dexamethasone or other systemic glucocorticoids in outpatients in the absence of another indication. There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19, and systemic glucocorticoids may cause harm in these patients. the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of anotherindication.

- **Outpatient Management of Patients With COVID-19 in an Ambulatory Care Setting:**

Approximately 80% of patients with COVID-19 have mild illness that does not warrant medical intervention or hospitalization. Most patients with mild COVID-19 (defined as the absence of viral pneumonia and hypoxemia) can be managed in an ambulatory care setting or at home.

Patients with moderate COVID-19 (those with viral pneumonia but without hypoxemia) and severe COVID-19 (those with dyspnea, hypoxemia, or lung infiltrates >50%) need in-person

evaluation and close monitoring, as pulmonary disease can progress rapidly and require hospitalization. Older patients and those with chronic medical conditions have a higher risk for hospitalization and death; however, SARS-CoV-2 infection may cause severe disease and deathin patients of any age, even in the absence of any risk factors. The decision to monitor a patientin the outpatient setting should be made on a case-by-case basis.

2. Therapeutic Management

Anti-SARS-CoV-2 Monoclonal Antibodies The studies recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the Emergency UseAuthorization (EUA) criteria.

- Bamlanivimab 700 mg + etesevimab 1,400 mg; or.
- Casirivimab 1,200 mg + imdevimab 1,200 mg.

Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test and within 10 days of symptom onset.. Two combination anti-SARS-CoV-2 monoclonal antibody products.

- Bamlanivimab plus Etesevimab.
- Casirivimab plus Imdevimab.

have received EUAs from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in outpatients who are at high risk of clinical progression. In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab.

1. Remdesivir

Remdesivir is currently the only drug approved by the FDA for the treatment of COVID-19. It isrecommended for use in hospitalized patients who require supplemental oxygen. In some cases, ahospital bed may not be available for patients who require supplemental oxygen; for these patients,remdesivir should only be administered in health care settings that can provide a similar level of care to an inpatient hospital.

2. Dexamethasone

The Studies recommends against the use of dexamethasone or other systemic glucocorticoids

to treat outpatients with mild to moderate COVID-19 (AIII). There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19, and systemic glucocorticoids may cause harm in these patients. In hospitalized patients with COVID-19, dexamethasone was shown to reduce mortality in patients who required supplemental oxygen.

There was no observed benefit of dexamethasone in hospitalized patients who did not receive oxygen support.26 Outpatients with mild to moderate COVID-19 were not included in this trial; thus, the safety and efficacy of corticosteroids in this population have not been established. The Studies recommends against the use of corticosteroids in this population as there are no clinical trial data to support their use. Moreover, the use of corticosteroids can lead to adverse effects, such as hyperglycemia, neuropsychiatric symptoms, and secondary infections, all of which may be difficult to detect and monitor in an outpatient setting. In some cases, a hospital bed may not be available for patients who require supplemental oxygen; for these patients, clinicians can consider administering dexamethasone only if the patient is placed in a health care setting that can providea similar level of care to an inpatient hospital.

3. Antithrombotic Therapy

Anticoagulants and antiplatelet therapy should not be initiated in the outpatient setting for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIII). For more information, see Antithrombotic Therapy in Patients With COVID-19. Patients should be encouraged to ambulate,and activity should be increased according to the patient's tolerance.

4. Antibacterial Therapy

The use of antibacterial therapy (e.g., azithromycin, doxycycline) for outpatient treatment of covid-19 in the absence of another indication.

- **Managing pregnant outpatients with COVID-19**

Is similar to managing nonpregnant patients. Clinicians should offer supportive care, take steps toreduce the risk of SARS-CoV-2 transmission, and provide guidance for when to seek an in-personevaluation. In pregnant patients, SpO2 should be maintained at 95% or above at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients. In general, there are no changes to fetal monitoring

recommendations in the outpatient setting, and fetal management should be similar to that provided to other pregnant patients with medical illness.31 However, these monitoring strategies can be discussed on a case-by-case basis with an obstetrician.

- **Considerations in Children**

Children and adolescents with acute COVID-19 are less likely than adults to require medical intervention or hospitalization, and most can be managed in an ambulatory care setting or at home. In general, the need for ED evaluation or hospitalization should be based on the patient's vital signs, physical exam findings (e.g., dyspnea), and risk factors for progression to severe illness. Certain groups, including young infants, children with risk factors, or those with presentations thatoverlap with multisystem inflammatory syndrome in children (MIS-C), may require hospitalization for more intensive monitoring. However, this should be determined on a case-by- case basis. Most children with mild or moderate COVID-19, even those with risk factors, will not progress to more severe illness and will recover without specific therapy. There are insufficient pediatric data to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products in children with COVID-19 who are not hospitalized but who have risk factorsfor severe disease. Based on adult studies.

- bamlanivimab plus etesevimab.
- casirivimab plus imdevimab.

May be considered on a case-by-case basis for non-hospitalized children who meet the EUA criteria, especially those who meet more than one criterion or are aged ≥16 years. The Studies recommends consulting a pediatric infectious disease specialist in such cases. In general, pediatric patients should not continue receiving remdesivir, dexamethasone, or other COVID19-directed therapies following discharge from an ED or an inpatient setting.

5. Oxygenation and Ventilation

For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Studies recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BIIa). In the absence of an indication for endotracheal intubation, the Studies recommends a closely monitored trial of NIPPV for adults with COVID- 19 and acute hypoxemic respiratory failure and for whom HFNC is not available (BIIa). For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whomendotracheal intubation is not otherwise indicated, the Studies

recommends considering a trial of awake prone positioning to improve oxygenation (CIIa). The Studies recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII). If intubation becomes necessary, the procedure should be performed by an experienced practitionerin a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 exposure to health care practitioners during intubation (AIII).

6. Acute Kidney Injury and Renal Replacement Therapy

For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, the Studies recommends continuous renal replacement therapy (CRRT), if available (BIII). If CRRT is not available or not possible due to limited resources, the Studies recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis.

- **List of Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19**

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. the COVID-19 Treatment Guidelines provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.

1. Remdesivir.
2. Chloroquine or Hydroxychloroquine With or Without Azithromycin.
3. Lopinavir/Ritonavir and Other HIV Protease Inhibitors.
4. Ivermectin.
5. Fluvoxamine.
6. Interferons (Alfa, Beta).
7. Interleukin-1 Inhibitors.
8. Interleukin-6 Inhibitors.
9. Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton’s Tyrosine Kinase Inhibitors.
10. Supplements.
11. Vitamin C • There are insufficient data for the COVID-19 Treatment studies to recommend either for or against the use of vitamin C for the treatment of COVID-19.

12. Vitamin D • There are insufficient data for the experts to recommend either for or against the use of vitamin D for the treatment of COVID-19.
13. Zinc • There are insufficient data for the Studies to recommend either for or against the use of zinc for the treatment of COVID-19. • The Studies recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.

AYUSH treatment for covid-19

Ayurveda, Siddha, Unani, and Homeopathy (referred to as AYUSH) are Indian medicinal systems that use natural drugs of plant, animal, and mineral origin for treatment. At present pandemic, AYUSH has recommended that the Homeopathy and Ayurveda as immune-boosters have sufficient potential to prevent and treat COVID-19. Considering the success of AYUSH systems in managing several epidemics and restoring health, AYUSH system recommends some herbs including Chyavanprash, Herbal tea, and Turmeric milk as immune boosters and has suggested some herbal formulations for treating COVID-19. In Iran, an herbal formula called Imam Kazem has been reported by Islamic medicine, which is said to be effective in treating colds and influenza. This herbal formula was used for COVID-19 patients and they claimed that it could prevent the disease from getting worse and reduce the symptoms of the disease. The composition of this herbal formula in summer is Terminalia chebula, Foeniculum vulgare, and red sugar, and in winter it consists of Terminalia chebula, Pistacia lentiscus and red sugar (Red sugar means sugarcane sugar that has not been processed industrially). Despite the positive reports of this herbal formula in the treatment of lung diseases in our country, no experimental or clinical reports were found to refer. Rosewater as other herbal products is flavored water made by steeping rose petals in water. In addition to oral consumption, it has antimicrobial properties and can be sprayed on surfaces and space as a disinfectant solution. Other examples of herbal medicine used in COVID-19 treatment include: Ginseng (Panax ginseng) regulates the activity of immune cells including T cells, and B cells, macrophages, dendritic cells, natural killer cells - Ginger (Zingiber officinale) has anti- apoptotic, anti-inflammatory, anti-tumor activities, anti-tumorigenic, anti-hyperglycaemic, antioxidant, and analgesic properties, garlic (Allium sativum) product is a strong immune stimulator, Echinacea extract (Echinacea purpurea (L.) Moench) with antimicrobial and antioxidant activities is used to improve the immune system and to treat pulmonary symptoms caused by bacterial infections. Despite such treatments, there are few reports of improved patients with negative COVID-19 test, that after a while, their COVID-19

test has been positive again. Thehospital reports have confirmed, it is possible that improved patients with negative COVID-19 tests become positive again for 2019-nCoV RNA, although a small portion of discharged COVID-19 has shown recurrent recurrences. There are reports of improved people that showed second recurrences with positive PCR tests after discharge from the hospital or during quarantine, and were hospitalized again.

Worldwide covid-19 candidate vaccines

In order to respond quickly and effectively to the COVID-19 pandemic, a broad range of candidate COVID-19 vaccines are being investigated globally using various technologies and platforms. These include viral-vectored, protein subunit, nucleic acid (DNA, RNA), live attenuated and inactivated vaccines. Some of these candidates have entered clinical trials.

1. COVAXIN

COVAXIN, India's indigenous COVID-19 vaccine Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV).

This indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3(Bio-Safety Level 3) high containment facility.

Fig 8: Covaxin Vaccine.

The vaccine received approval from Drug Controller General of India (DCGI) for Phase I & II Human Clinical Trials and an Adaptive, Seamless Phase I, Followed by Phase II Randomized, Double blind, Multicentre Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152).

2. Covishield

The Serum Institute of India (SII) and Indian Council of Medical Research are jointly conducting a Phase II/III, Observer-Blind, Randomized, Controlled Study to Determine the Safety and Immunogenicity of Covishield (COVID-19 Vaccine).

Fig 9: covishield vaccine.

3. ZyCoV-D

Zydus Cadila, focused on discovering and developing NCEs, Novel Biologicals, Biosimilars and Vaccines, announced that its plasmid DNA vaccine to prevent COVID-19, ZyCoV-D. Safety in Phase I clinical trial of ZyCoV-D in healthy subjects established as endorsed by the independent Data Safety Monitoring Board (DSMB). Zydus commenced Phase II trial.

Fig 10: ZyCov-D vaccine.

4. Sputinik

Dr Reddys Laboratories Limited and Sputnik LLC are jointly conducting Multi-centre, phase

II/III adaptive clinical trial to assess safety and immunogenicity of Gam-COVID-Vac combined vectorvaccine.

Fig 11: Sputinik vaccine.

5. BBV154 - Intranasal vaccine

Bharat Biotech is conducting Multicenter Study to Evaluate the Reactogenicity, Safety, and Immunogenicity of an Intranasal Adenoviral vector COVID-19 vaccine (BBV154) in Healthy Volunteers. BBV154 is an intranasal vaccine stimulates a broad immune response – neutralizing IgG, mucosal IgA, and T cell responses. Immune responses at the site of infection (in the nasal mucosa) – essential for blocking both infection and transmission of COVID-19.

6. COVOVAX

Indian Council of Medical Research and Serum Institute of India jointly performing a phase 2/3, observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVOVAX [SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M1™ adjuvant] in Indian adults.

Fig 12: covovax.

7. mRNA based vaccine (HGCO19)

Randomized, Phase I/II, Placebo-controlled, Dose-Ranging, study to evaluate the Safety, Tolerability and Immunogenicity of the candidate HGCO19 (COVID-19 vaccine) in healthy adultsubjects. The trial is being conducted by Gennova Biopharmaceuticals Limited.

8. Pfizer-BioNTech

Based on **evidence from clinical trials**, the Pfizer-BioNTech vaccine was 95% effective at preventing laboratory-confirmed COVID-19 illness in people without evidence of previous infection. CDC will continue to provide updates as we learn more about how well the Pfizer-BioNTech vaccine works in real-world conditions.

Fig 13: Pfizer.

9. Moderna

Based on **evidence from clinical trials**, the Moderna vaccine was 94.1% effective at preventing laboratory-confirmed COVID-19 illness in people who received two doses who had no evidence of being previously infected. The vaccine appeared to have high effectiveness in clinical trials (efficacy) among people of diverse age, sex, race, and ethnicity categories and among persons with underlying medical conditions. Although few people in the clinical trials were admitted to the hospital, this happened less often in the people who got the Moderna vaccine compared to people who got the saline placebo. CDC will continue to provide updates as we learn more abouthow well the Moderna vaccine works in real-world conditions.

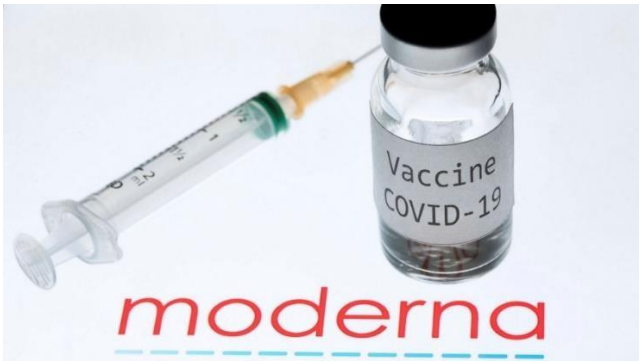

Fig 14: Moderna.

10. Johnson & Johnson's janssen

The J&J/Janssen vaccine was 66.3% effective in clinical trials (efficacy) at preventing laboratory-confirmed COVID-19 illness in people who had no evidence of prior infection 2 weeks after receiving the vaccine. People had the most protection 2 weeks after getting vaccinated. The vaccine had high efficacy at preventing hospitalization and death in people who did get sick. No one who got COVID-19 at least 4 weeks after receiving the J&J/Janssen vaccine had to be hospitalized. Early evidence suggests that the J&J/Janssen vaccine might provide protection against asymptomatic infection, which is when a person is infected by the virus that causes COVID-19 but does not get sick. CDC will continue to provide updates as we learn moreabout how well the J&J/Janssen vaccine works in real-world conditions.

Fig 15: Johnson & Johnson's janssen.

11. mRNA COVID-19 Vaccines

mRNA vaccines are a new type of vaccine to protect against infectious diseases. To trigger an immune response, many vaccines put a weakened or inactivated germ into our bodies. Not mRNA vaccines. Instead, they teach our cells how to make a protein—or even just a piece of a protein—that triggers an immune response inside our bodies. That immune response, which produces antibodies, is what protects us from getting infected if the real virus enters our

bodies. Researchers have been studying and working with mRNA vaccines for decades. Interest has grown in these vaccines because they can be developed in a laboratory using readily available materials. This means the process can be standardized and scaled up, making vaccine development faster than traditional methods of making vaccines. mRNA vaccines have been studied before for flu, Zika, rabies, and cytomegalovirus (CMV). As soon as the necessary information about the virus that causes COVID-19 was available, scientists began designing the mRNA instructions for cells to build the unique spike protein into an mRNA vaccine. Future mRNA vaccine technology may allow for one vaccine to provide protection for multiple diseases, thus decreasing the number of shots needed for protection against common vaccine- preventable diseases. Beyond vaccines, cancer research has used mRNA to trigger the immunesystem to target specific cancer cells.

12. Viral vector vaccines

Scientists began creating viral vectors in the 1970s. Besides being used in vaccines, viral vectors have also been studied for gene therapy, to treat cancer, and for molecular biology research. For decades, hundreds of scientific studies of viral vector vaccines have been done and published around the world. Some vaccines recently used for Ebola outbreaks have used viral vector technology, and a number of studies have focused on viral vector vaccines against other infectiousdiseases such as Zika, flu, and HIV.

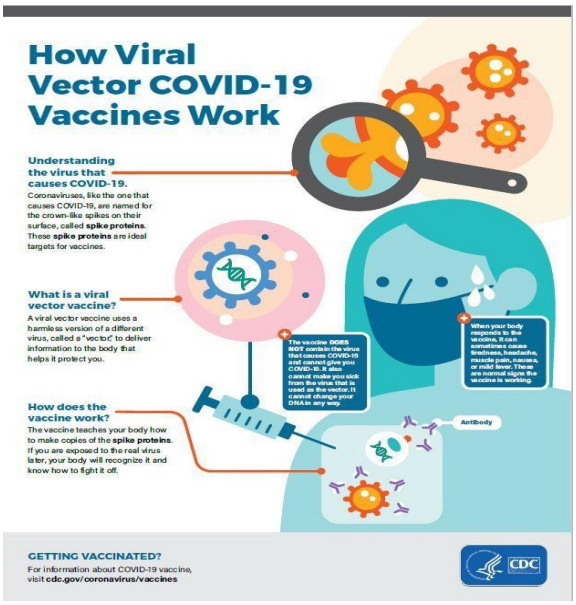

Fig 8: The phylogenetic illustration of the receptor-binding domain (RBD) in various betacoronaviruses a. The structure of RBD in SARS-CoV b, 2019-nCoV c, and MERS-CoVd.

CONCLUSION

There are hundreds of coronaviruses, most of which circulate in animals. Only seven of these viruses infect humans and four of them cause symptoms of the common cold. But, three times in the last 20 years, a coronavirus has jumped from animals to humans to cause severe disease. SARS,a beta coronavirus emerged in 2002 and was controlled mainly by aggressive public health measures. There have been no new cases since 2004. MERS emerged in 2012, still exists in camels,and can infect people who have close contact with them. COVID-19, a new and sometimes deadly respiratory illness that is believed to have originated in a live animal market in China, has spread rapidly throughout that country and the world. The new coronavirus was first detected in Wuhan, China in December 2019. Tens of thousands of people were infected in China, with the virus spreading easily from person-to-person in many parts of that country. The novel coronavirus infections were at first associated with travel from Wuhan, but the virus has now established itselfin 177 countries and territories around the world in a rapidly expanding pandemic. Health officials in the United States and around the world are working to contain the spread of the virus through public health measures such as social distancing, contact tracing, testing, quarantines and travel restrictions. Scientists are working to find medications to treat the disease and to develop a vaccine. The World Health Organization declared the novel coronavirus outbreak “a public health emergency of international concern” on January 30. On March 11, 2020 after sustained spread ofthe disease outside of China, the World Health Organization declared the COVID-19 epidemic a pandemic. Public health measures like ones implemented in China and now around the world, will hopefully blunt the spread of the virus while treatments and a vaccine are developed to stop it.

REFERENCES

1. Sutton D, Fuchs K, D'Alton M, Goffman D (April 2020). "Universal Screening for SARS-CoV-2 in Women Admitted for Delivery". The New England Journal of Medicine, 382(22): 2163–2164. doi:10. 1056/NEJMc2009316.PMC 7175422. PMID 32283004.
2. "Dutch study suggests 3% of population may have coronavirus antibodies". Reuters. 16 April 2020. Retrieved 20 April 2020.
3. "Interactive Serology Dashboard for Commercial Laboratory Surveys". cdc. gov. 21 July 2020. Retrieved 24 July 2020.
4. Vogel G (21 April 2020). "Antibody surveys suggesting vast undercount of coronavirus infections may be unreliable". Science. doi:10.1126/science.abc3831.S2CID218794298.

5. "China: age distribution of novel coronavirus patients 2020". Statista. Retrieved 11 April 2020.
6. Scott D (23 March 2020). "The Covid-19 risks for different age groups, explained". Vox. Retrieved 12 April 2020.
7. Bi, Qifang; Wu, Yongsheng; Mei, Shujiang; Ye, Chenfei; Zou, Xuan; Zhang, Zhen; Liu, Xiaojian; Wei, Lan; Truelove, Shaun A; Zhang, Tong; Gao, Wei; Cheng, Cong; Tang, Xiujuan; Wu, Xiaoliang; Wu, Yu; Sun, Binbin; Huang, Suli; Sun, Yu; Zhang, Juncen; Ma, Ting; Lessler, Justin; Feng, Tiejian (August 2020). "Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study". The Lancet Infectious Diseases, 20(8): 911–919. doi:10. 1016/S1473-3099(20)302875. PMC 7185944. PMID 32353347.
8. "Statement on the meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus 2019 (n-CoV) on 23 January 2020". World Health Organization (WHO). Retrieved 9 April 2020.
9. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R (April 2020). "High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2". Emerging Infectious Diseases, 26(7): 1470–1477. doi:10.3201/eid2607.200282.PMC 73 23562. PMID 32255761. S2CID 215410037.
10. Roberts L (8 May 2020). "The importance of the coronavirus R rate in other countries across the globe". The Daily Telegraph. Retrieved 14 May 2020. Jump up to: a b c "European Centre for Disease Prevention and Control". Retrieved 31 December 2020.
11. "Italy's coronavirus deaths could be underestimated in data: Official". Reuters. 31 March 2020.
12. "Coronavirus: Is Covid-19 really the cause of all the fatalities in Italy?". Stuff. Retrieved 16 April 2020.
13. Wu J, McCann A, Katz J, Peltier E. "28, 000 Missing Deaths: Tracking the True Toll of the Coronavirus Crisis". The New York Times. ISSN 0362-4331. Retrieved 22 April 2020.
14. "Tracking covid-19 excess deaths across countries". The Economist. ISSN 0013- 0613. Retrieved 22 April 2020.
15. "What 'Excess Deaths' Do and Don't Tell Us About COVID-19". Reason. 29 April 2020. Retrieved 4 May 2020.
16. Meyerowitz-Katz G, Merone L (December 2020). "A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates". International

Journal of Infectious Diseases, 101: 138–148. doi:10. 1016/j. ijid. 2020. 09. 1464. PMC7524446. PMID 33007452.

17. Yang W, Kandula S, Huynh M, Greene S, Van Wye G, Li W, Chan H, McGibbon E, Yeung A, Olson D, Fine A, Shaman J (19 October 2020). "Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis". Lancet Infectious Diseases, 21(2): "Tracking covid-19 excess 203–212. doi:10. 1016/S1473-3099(20)30769-6. PMC 7572090. PMID 33091374.
18. Pastor-Barriuso R, Pérez-Gómez B, Hernán M, Pérez-Olmeda M, Yotti R, Oteo-Iglesias J, Sanmartín J, León-Gómez I, Fernández- García A, Fernández-Navarro P, Cruz I, Martín M, Delgado-Sanz C, Fernández N, León J, Muñoz-Montalvo J, Blanco F, Larrauri A, Pollán M (27 November 2020).
19. "Infection fatality risk for SARS- CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study". British Medical Journal. 371: m4509. doi:10. 1136/bmj. m4509. PMC 7690 290. PMID 33246972. Fox, Justin (24 April 2020).
20. "The Coronavirus Isn't Just the Flu". Bloomberg. Verity, Robert; Okell, Lucy C; Dorigatti, Ilaria; Winskill, Peter; Whittaker, Charles; Imai, Natsuko; Cuomo-Dannenburg, Gina; Thompson, Hayley; Walker, Patrick G T; Fu, Han; Dighe, Amy; Griffin, Jamie T; Baguelin, Marc; Bhatia, Sangeeta; Boonyasiri, Adhiratha; Cori, Anne; Cucunubá, Zulma; FitzJohn, Rich; Gaythorpe, Katy; Green, Will; Hamlet, Arran; Hinsley, Wes; Laydon, Daniel; Nedjati-Gilani, Gemma; Riley, Steven; van Elsland, Sabine; Volz, Erik; Wang, Haowei; Wang, Yuanrong; Xi, Xiaoyue; Donnelly, Christl A; Ghani, Azra C; Ferguson, Neil M (June 2020).
21. "Estimates of the severity of coronavirus disease 2019: a model-based analysis". The Lancet Infectious Diseases, 20(6): 669–677. doi:10.1016/S1473-3099(20)30243-7.PMC 7158570.PMID 32240634.
22. "COVID-19 Pandemic Planning Scenarios" (PDF). CDC. 10 July 2020. Retrieved 29 September 2020. Meyerowitz-Katz, Gideon; Merone, Lea (7 July 2020).
23. "A systematic review and meta- analysis of published research data on COVID-19 infection-fatality rates". MedRxiv, 101: 138–148. doi:10.1101/2020.05.03.20089854. PMC 7524446. PMID 33007452.
24. Lisboa Bastos, Mayara; Tavaziva, Gamuchirai; Abidi, Syed Kunal; Campbell, Jonathon R; Haraoui, Louis-Patrick; Johnston, James C; Lan, Zhiyi; Law, Stephanie; MacLean, Emily; Trajman, Anete; Menzies, Dick; Benedetti, Andrea; Ahmad Khan, Faiz (1 July 2020). "Diagnostic accuracy of serological tests for covid-19: systematic review and

meta-analysis". BMJ. 370: m2516. doi:10.1136/bmj.m2516.PMC7327913. PMID 32611558.

25. Spencer, Elizabeth; Henighan, Carl (1 September 2020). "Overview of BMJ: Diagnostic accuracy of serological tests for covid-19: systematic review and meta- analysis". CEBM. Retrieved 24 September 2020. Spencer, Elizabeth; Jefferson, Tom; Brassey, Jon; Heneghan, Carl (11 September 2020). "When is Covid, Covid?". CEBM. Retrieved 19 September 2020. 2020).
26. "Prevalence and Characteristics of Taste Disorders in Cases of COVID-19: A Meta-analysis of 29, 349 Patients". Otolaryngology–Head and Neck Surgery: 1–10. doi:10. 1177/0194599820981018. PMID33320033.
27. Islam MA (April 2021). "Prevalence and characteristics of fever in adult and paediatric patients with coronavirus disease 2019 (COVID-: A systematic review and meta- analysis of 17515 patients". PLOS ONE. 16 (4): e0249788. doi:10. 1371/journal. pone. 024978 8. PMC 8023501. PMID 33822812.
28. "Clinical characteristics of COVID- 19". European Centre for Disease Prevention and Control. Retrieved 29 December 2020. Niazkar HR, Zibaee B, Nasimi A, Bahri N (July 2020). "The neurological manifestations of COVID-19: a review article". Neurological Sciences, 41(7): 1667–1671. doi:10. 1007/s10072-020-04486- 3. PMC 7262683. PMID 32483687.
29. "Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)". U. S. Centers for Disease Control and Prevention (CDC). 6 April 2020. Archivedfrom the original on 2 March 2020. Retrieved 19 April 2020. Oran DP, Topol EJ (January 2021).
30. "The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review". Annals of Internal Medicine. doi:10. 7326/M20- 6976. PMC 7839426. PMID 33481642.
31. "Transmission of COVID-19". European Centre for Disease Prevention and Control. Retrieved 6 December 2020. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (August 2020). "Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review". JAMA, 324(8): 782–793. doi:10.1001/jama.2020.12839.PMID32648899. S2CID220465311.CDC(11 February 2020).
32. "COVID-19 and Your Health". Centers for Disease Control and Prevention. Retrieved 23 January 2021.

33. "Transmission of COVID- 19". www. ecdc. europa. eu. 7 September 2020. Retrieved 14 October 2020. Fox D (January 2020). "What you need to know about the novel coronavirus". Nature. doi:10.1038/d41586-020-00209-y.PMID33483684.
34. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. (February 2020). "A Novel Coronavirus from Patients with Pneumonia in China, 2019". The New England Journal of Medicine, 382(8): 727–733. doi:10.1056/NEJMoa2001017. PMC 70 92803. PMID 31978945.
35. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. (March 2020). "The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS- CoV-2". Nature Microbiology, 5(4): 536–544. doi:10.1038/s41564-020-0695- z. PMC 7095448. PMID 32123347.
36. Li C, Zhao C, Bao J, Tang B, Wang Y, Gu B (November 2020). "Laboratory diagnosis of coronavirus disease-2019 (COVID- 19)". Clinica Chimica Acta; International Journal of Clinical Chemistry. 510: 35 46. doi:10.1016/j.cca.2020.06.045.PMC7329657.PMID 32621814.
37. "2019 Novel Coronavirus (2019-nCoV) Situation Summary". U. S. Centers for Disease Control and Prevention (CDC). 30 January 2020. Archived from the original on 26 January 2020. Retrieved 30 January 2020.
38. "Coronavirus disease (COVID-19) technical guidance: Laboratory testing for 2019-nCoV in humans". World Health Organization(WHO). Archived from the original on 15 March 2020. Retrieved 14 March 2020. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. (December 2020).
39. "Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Qin, Amy (7 March 2020). "China May Be Beating the Coronavirus, at a Painful Cost". The New York Times. McCurry J, Ratcliffe R, Davidson H (11 March 2020).
40. "Mass testing, alerts and big fines: the strategies used in Asia to slow coronavirus". The Guardian. Diagnostic Samples". Clinical Infectious Diseases, 71(10): 2663–2666. doi:10. 1093/cid/ciaa638.PMC 73141 98.PMID 32442256.
41. Palmieri L, Andrianou X, Barbariol P, Bella A, Bellino S, Benelli E, et al. (22 July 2020). Characteristics of SARS-CoV-2 patients dying in Italy Report based on available data on July 22nd, 2020 (PDF)(Report). Istituto Superiore di Sanità. Retrieved 4 October 2020.
42. "Fever Screening | IntelliSEC | Durban, Johannesburg, Cape Town". IntelliSEC. Baird RP (11 March 2020). "What It Means to Contain and Mitigate the Coronavirus". The New Yorker.

43. "Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand" (PDF). Imperial College COVID-19 Response Team. 16 March 2020.
44. "Expert interview: What is contact tracing?". Blog: Public Health Matters. Public Health England, Government of the United Kingdom. Retrieved 28 February 2020.
45. ingram D, Ward J (7 April 2020). "Behind the global efforts to make a privacy-first coronavirus tracking app". NBC News. Retrieved 10 April 2020.
46. "Apple and Google are launching a joint COVID-19 tracing tool for iOS and Android". TechCrunch. Retrieved 10 April 2020.
47. Privacy-Preserving Contact Tracing". Apple. 10 April 2020. "Apple and Google partner on COVID-19 contact tracing technology". 10 April 2020. Retrieved 10 April 2020.
48. "Symptoms of Coronavirus". U. S. Centers for Disease Control and Prevention (CDC). 22 February 2021. Archived from the original on 4 March 2021. Retrieved 4 March 2021.
49. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, Wade RG (23 June 2020). "The prevalence of symptoms in 24, 410 adults infected by the novel coronavirus (SARS-CoV-2; COVID- 19): A systematic review and meta-analysis of 148 studies from 9 countries". PLOS ONE, 15(6): e0234765. Bibcode: 2020PLoSO. 1534765G. doi:10. 1371/journal. pone. 0234765. PMC 73 10678. PMID 32574165. S2CID 220046286.
50. Islam MA (November 2020). "Prevalence of Headache in Patients With Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis of 14, 275 Patients". Frontiers in Neurology, 11: 562634. doi:10.3389/fneur.2020.562634. P MC 7728918. PMID 33329305.
51. Saniasiaya J, Islam MA (April 2021). "Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27, 492 Patients". The Laryngoscope, 131(4): 865–878. doi:10.1002/lary.29286.PMC7753439.PMID33219539.
52. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 24 January 2020. 18.
53. European Centre for Disease Prevention and Control (ECDC). Case definition and European surveillance for human infection with novel coronavirus (2019-nCoV) [14 feb 2020]. Available from: https: //www. ecdc. europa. eu/en/case- definition-and-european-surveillance- human-infection-novelcoronavirus-2019- ncov 19.
54. European Centre for Disease Prevention and Control (ECDC). Health emergency

preparedness for imported cases of high consequence infectious diseases 2019 [14 feb 2020]. Available from: https: //www. ecdc. europa. eu/en/publications- data/ health-emergency-preparedness- imported-cases-highconsequence-infectious- diseases.

55. Zhao Z, Zhang F, Xu M, Huang K, Zhong W, Cai W, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J Med Microbiol, 2003; 52: 715– 20.
56. Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, et al. Broadspectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Inf Secur, 2013; 67: 606–16.
57. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis, 2014; 20: 42–6.
58. Al-Qahtani AA, Lyroni K, Aznaourova M, Tseliou M, Al-Anazi MR, Al-Ahdal MN, et al. Middle East respiratory syndrome corona virus spike glycoprotein suppresses macrophage responses via DPP4-mediated induction of IRAK-M and PPARγ. Oncotarget, 2017; 8(6): 9053–66. doi:10. 18632/oncotarget. 14754.
59. Bin Saeed AA, Abedi GR, Alzahrani AG, Salameh I, Abdirizak F, Alhakeem R, et al. Surveillance and testing for Middle East respiratory syndrome Coronavirus, Saudi Arabia, April 2015–February 2016. Emerg Infect Dis, 2017; 23(4): 682–5. doi:10. 3201/eid2304. 161793.
60. "Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19)". U. S. Centers for Disease Control and Prevention (CDC). 11 February 2020. Archived from the original on 4 March 2020. Retrieved 26 March 2020.
61. "Real-Time RT-PCR Studies for Detection 2019-nCoV". U. S. Centers for Disease Control and Prevention (CDC). 29 January 2020. Archived from the original on 30 January 2020. Retrieved 1 February 2020.
62. "Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases". World Health Organization (WHO). Archived from the original on 17 March 2020. Retrieved 13 March 2020.
63. "Viral Load Exposure Factors". ReallyCorrect.com.
64. Ding S, Liang TJ. Is SARS-CoV-2 Also an Enteric Pathogen with Potential Fecal-Oral Transmission: A COVID-19 Virological and Clinical Review. Gastroenterology, 2020: S0016-5085(20)30571-0.

65. Fung TS, Liu DX. Human coronavirus: host- pathogen interaction. Ann Rev Microbiol. 2019; 73: 529–57.
66. Wu R, Wang L, Kuo H-CD, Shannar A, Peter R, Chou PJ, et al. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep, 2020; 1: 1- 15
67. Sawalha AH, Zhao M, Coit P, Lu Q. Epigenetic dysregulation of ANG II and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immun, 2020; 108410.
68. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid19 does not lead to a "typical" acute respiratory distress syndrome. Am J Resp Crit Care Med, 2020; 201(10): 1299–300.
69. Perales C, Domingo E. Antiviral strategies based on lethal mutagenesis and error threshold. Quasispecies, 2015; 323–39.
70. Pruijssers AJ, Denison MR. Nucleoside analogues for the treatment of coronavirus infections. Curr Opinion Virol, 2019; 35: 57– 62.
71. Lu H. Drug treatment options for the 2019- new coronavirus (2019-nCoV). Biosci Trends, 2020; 14(1): 69–71.
72. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med, 2020; 26(5): 672–5.
73. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2: 69.
74. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diab Metab Syndr, 2020; 14(3): 241–6.
75. Prajapati S, Kumar N. SARS-CoV-2 pandemic: an opportunity for Indian traditional medicines (AYUSH). Int J Complement Alt Med, 2020; 13(3): 103–5.
76. Khanal P, Duyu T, Dey YN, Patil B, Pasha I, Wanjari M. Network pharmacology of AYUSH recommended immune-boosting medicinal plants against COVID-19. 2020.
77. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of rosa damascena. Iran J Basic Med Sci, 2011; 14(4): 295–307.
78. Kang S, Min H. Ginseng, the 'Immunity Boost': The Effects of Panax ginseng on Immune System. J Ginseng Res, 2012; 36(4): 354–68.
79. Shahrajabian MH, Sun W, Cheng Q. The power of natural Chinese medicine, ginger and

ginseng root in an organic life. Middle- East J Sci Res, 2019; 27(1): 64–71.

80. Daliri EBM, Kim SH, Park BJ, Kim HS, Kim JM, Kim HS, et al. Effects of different processing methods on the antioxidant and immune stimulating abilities of garlic. Food Sci Nutr, 2019; 7(4): 1222–9.
81. Sharifi-Rad M, Mnayer D, Morais-Braga MFB, Carneiro JNP, Bezerra CF, Coutinho HDM, et al. Echinacea plants as antioxidant and antibacterial agents: From traditional medicine to biotechnological applications. Phytother Res, 2018; 32(9): 1653–63.
82. Chen D, Xu W, Lei Z, Huang Z, Liu J, Gao Z, Peng L. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. Int J Infect Dis, 2020; 93: 297–9.
83. Hoang VT, Dao TL, Gautret P. Recurrence of positive SARS-CoV-2 in patients recovered from COVID-19. J Med Virol. 2020. https: //doi. org/10. 1002/jmv. 26056.
84. Hoang VT, Dao TL, Gautret P. Recurrence of positive SARS-CoV-2 in patients recovered from COVID-19. J Med Virol. 2020. Publisher's Note Springer Nature remains neutral with regard to jurisdictional. Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, et al. Zinc and respiratory tract infections: Perspectives for COVID-19. Int J Mol Med, 2020; 46(1): 17– 26.
85. Seftel J. Profile: Irene Pepperberg & Alex. Boston: WGBH; 2011. [cited March 11, 2013].