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An Overview on Coronavirus (COVID – 19) Outbreak and Its Biochemistry Parameters: A Review

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ABSTRACT

Coronaviruses are a large family of viruses that may cause illness in humans as well as animals. According to the data of the World Health Organization (WHO), there are about more than (13,378,853) confirmed cases have been identified in 28 countries/regions, detected all over the world till 16th July 2020. The World Health Organization (WHO) declared nCoV-19 is the sixth international worry of public health emergency on 30th January 2020. The two categories of bat-SL-CoVZXC21 and bat-SL-CoVZC45 are the main source of SARS-CoV-2 and are responsible for severe acute respiratory syndrome. It is spread by human to human transmission via droplets or direct contact, and infection had been estimated to have a mean incubation period of 14 days and a basic reproduction number of 2.25 – 3.68. Throughout the world COVID-19 has affected more than 13,378,853persons and 5, 80,045 confirmed death around the world till 16th July 2020. It has been observed that this is the first time this kind of virus, COVID-19, coronavirus has been labeled a pandemic, "but at the same time, it is being believed that it will be able to be contained or controlled if adopted proper measures. Patients with pneumonia caused by SARS-CoV-2, fever was the most common symptom, followed by a cough. Bilateral lung involvement with ground-glass opacity was the most common finding from computed tomography images of the chest. Information about this virus is rapidly rising; it is the need of the time to remain updated. In this article, we present an overview of the present important information on the etiology, pathophysiology, epidemiology, clinical manifestations and diagnosis, therapeutic strategies, and management of this novel COVID-19 coronavirus. This review article also aimed to present the concept of epidemic and pandemic phases according to WHO in a defined manner.

1. INTRODUCTION:

Coronavirus is one of the major pathogens that primarily target the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to the seafood and wet animal wholesale market in Wuhan, Hubei Province, China [1, 2]. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, named by WHO on February 11th, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58) [3]. The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019 [4]. From December 18, 2019, through December 29th, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died [5]. In 2003, Hong Kong was ferociously attacked by a then-unknown "pathogen" which overwhelmed the entire medical system within days and caused high casualties in healthcare workers (HCWs) and the general population [6, 7].After the outbreak, all medical disciplines gathered together to draw up an emergency infection control plan with a single objective – protection of patients and staff by preventing cross-infection. These emergency measures were merely based on prevailing medical knowledge and consensus of expert opinions rather than scientifically proven facts. Seventeen years later, a novel coronavirus SARS-CoV-2, returned with a vengeance [8] and the virus has spread across the world within a few months. Unlike SARS, infected subjects of COVID-19 could transmit the virus while being asymptomatic or having minimal symptoms, thus rendering the disease far more infectious and dangerous. Despite the critical situation in Italy, Trevisanuto et al. [9] have done a magnificent job by summarizing key infection control measures against COVID-19 in this issue of Neonatology. In 2009 H_1N_1 influenza was reported. Followed by Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 was first detected in Saudi Arabia and caused about 2,500 disease cases and 800 deaths. The mortality rate of severe acute respiratory syndrome coronavirus (SARS-CoV) was reported by up to 13%.Deaths caused by Middle East respiratory syndrome coronavirus (MERS-CoV) was reported by about 38.3%. The novel coronavirus SARS-CoV-2 spreads faster than its former two preceding relatives, the severe acute respiratory syndrome coronavirus (SARS-CoV), which originated in China, and Middle East respiratory syndrome

coronavirus (MERS-CoV) which originated in Saudi Arabia, but has lower percent mortality. Because of it spreading speed the global impact declared it to epidemic to pandemic is yet to be understood. People can catch COVID-19 from others who have the virus. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 metre (3 feet) away from others. Serum biochemical parameters and hemogram analysis are commonly used, easy to measure, routine and cheaper techniques helping diagnosis and progression of diseases [10]. Lymphopenia (lymphocyte count <1000), increased lactate dehydrogenase (LDH) levels, the ALT/AST ratio, prothrombin time, creatinine, D-dimer, CPK, peripheral absolute monocyte count (AMC), absolute neutrophil count (ANC) levels are tightly associated with COVID-19 progression. [11-12]. Moreover, leukocyte and granulocyte levels are associated with disease progression as well [13]. Artificial intelligence had been used to find biomarkers for the prognosis and evaluation of progression of diseases. Besides, laboratory test ordering, data mining, interpretations of test results, early diagnosis, disease monitoring, personalized treatments and clinical trials can be achieved by artificial learning. Therefore, we should use machine learning techniques for collecting all biochemistry and hemogram data of people infected by COVID-19 worldwide to find biomarkers which can be used in the combination with PCR and CT results. Moreover, infected people even not shown severe symptoms can be tested for hemogram and serum biochemistry parameters daily basis to evaluate progression of COVID-19 [14-16]. With reference to COVID-19, the WHO raised the threat to the CoV epidemic to the "very high" level, on 28th February 2020. However 8th March 2020, Tedros Adhamon Ghebreyesus, director-general of WHO, declared that the intimidation of a pandemic is becoming a reality, and WHO decided to call the outbreak a pandemic, believed that it would be “the first pandemic that could be actually controlled” [17]. At the same time, scientists around the world work tirelessly and gathering information and scientific evidence about the etiology, Pathophysiology, epidemiology, clinical manifestations and diagnosis, therapeutic strategies, and management of this novel coronavirus disease. Information regarding to both the virus-host interaction and the evolution of the epidemic, with specific reference to the times when the epidemic will reach its peak, is still to be collected. At the same time, the major therapeutic strategies to face the problem of infection are only

supportive, and prevention aimed at reducing transmission in the community is the best measure.

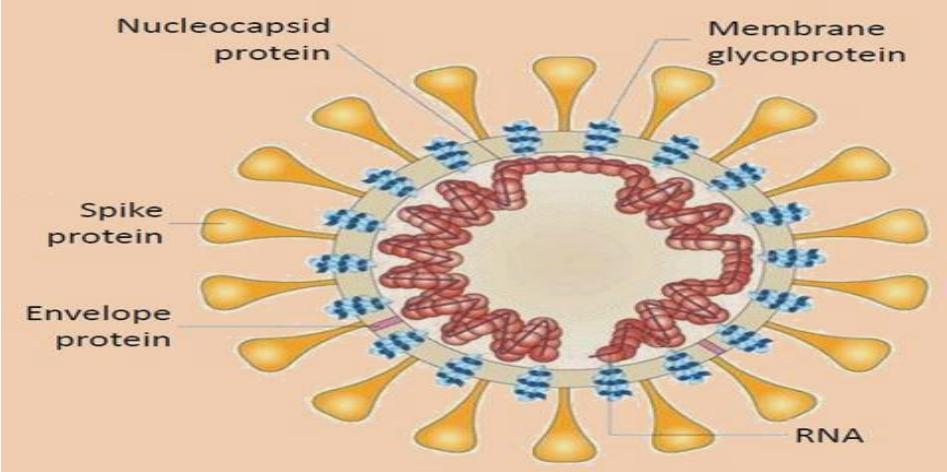


Figure No. 1: Structure of SARS coronavirus structure.

2. ETIOLOGY:

Corona Virus is a positive- single stranded RNA viruses which have a crown-like appearance under an electron microscope (*corona*, Latin term means crown) due to the presence of spike glycoproteins on the envelope. In 1966 by Tyrell and Bynoe presented a detail explanation of coronaviruses after cultivating viruses from patients suffering from common colds [18]. There are different families and subfamily of *Coronaviridae* family (order *Nidovirales*) classifies into four genera of coronavirus, Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into three sub-genera like SARS-CoV, MHV and MERS-CoV [19]. AlphaCoV sub-genera are TGEV, PEDV and FCoV. GammaCoV sub-genera are IBV. AlphaCoVs and betaCoVs genomic characterization had shown that it belong to bats and rodents gene. DeltaCoVs and gammaCoVs genomic characterization its gene belong to avian species. This is the large family of viruses would cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. Till the date, seven HumanCoVs (HCoVs) - able to infect humans, had been identified. Some of HumanCoVs was identified in the mid-1960s, while others were only detected in the new millennium. It was suggest that about 2% of the healthy population carriers of a Corona Virus and that these viruses are responsible for about 5% to 10% of acute respiratory infections [20]. Human CoVs- HCoV-OC43, and HCoV-HKU1, HCoV-229E, and HCoV-NL63, can cause common colds and upper respiratory infections in those individuals who have weak immunity and immunocompromised subjects and the elderly,

suffer lower respiratory tract infections. The other human CoVs- SARS-CoV, SARS-CoV-2, and MERS-CoV, can cause epidemics with variable clinical severity featuring respiratory and extra-respiratory problems. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 15% and 40%, respectively.SARS-CoV-2 belongs to the betaCoVs category. Like other coronavirus, it is sensitive to ultraviolet rays and heat. Further, these viruses could be effectively inactivated by lipid solvents including ether (70%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for Chlorhexidine. In the genetic term, Chan et al. have proven that the genome of the new HumanCoVs, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 90% nucleotide identity with bat SARS-like-CoVZXC21 and 85% with that of human SARS-CoV[21]. Due to this reason, the new virus was called SARS-CoV-2. It is single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids, its origins are not entirely understood, and these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, not studied.

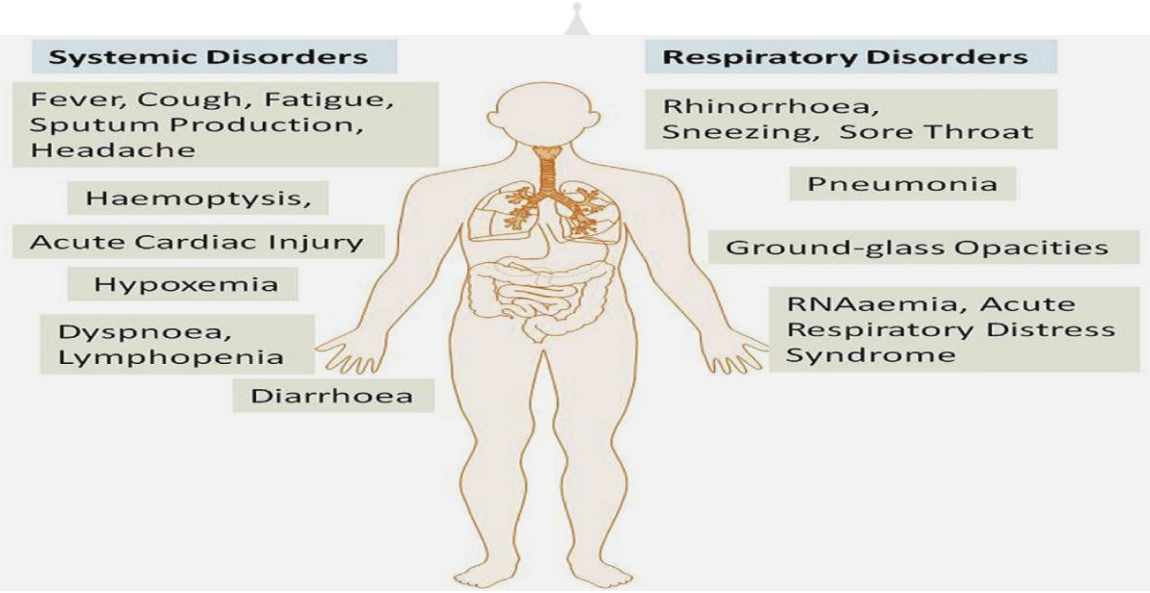
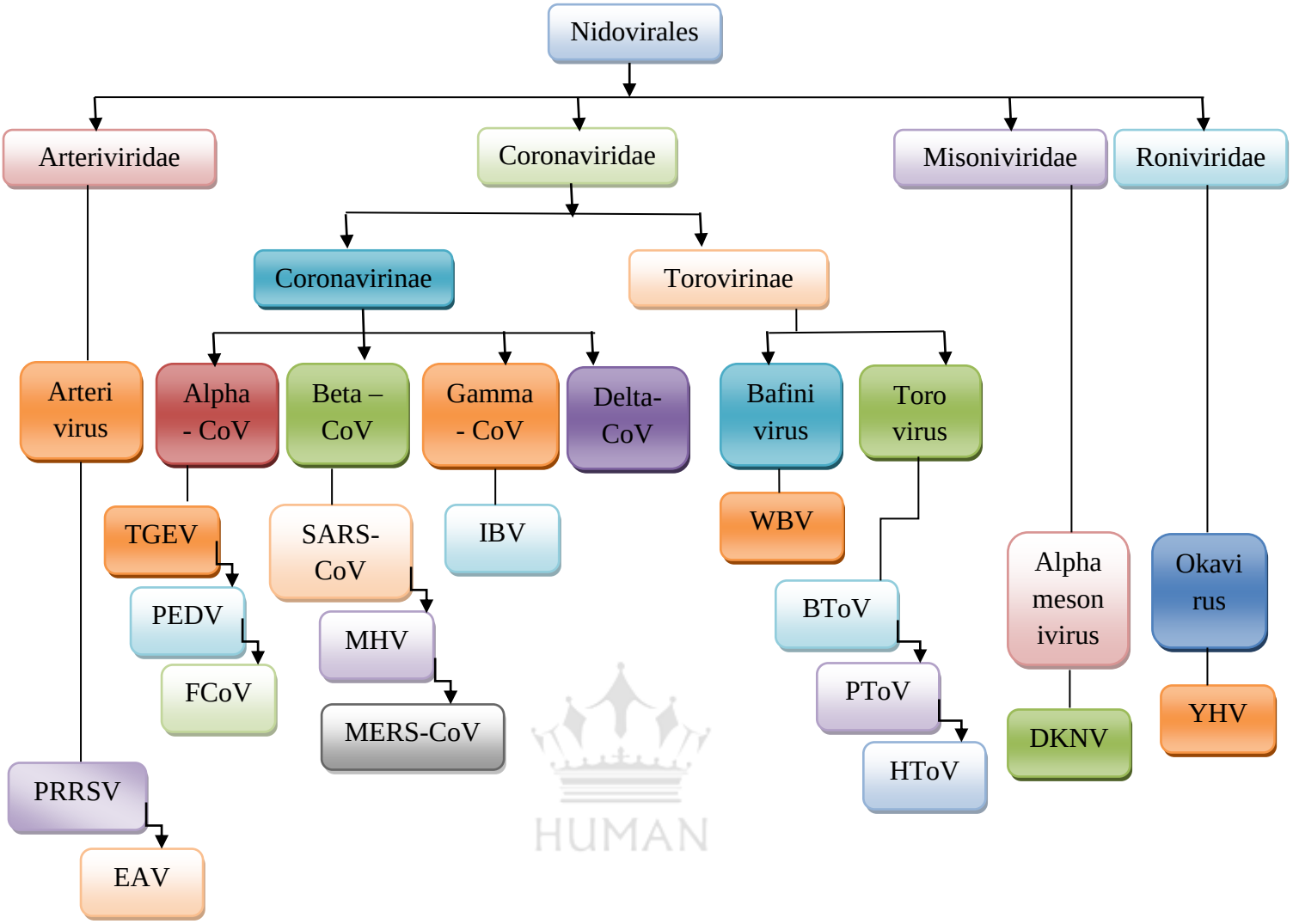


Figure No. 2: The incubation period of COVID-19 infection is approximately 5.2 days. Mainly there are general similarities in the symptoms between COVID-19 and previous Betacoronavirus. Therefore COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. Additionally, patients infected with COVID-19 developed intestinal symptoms like diarrhoea only allow percentage of MERS-CoV or SARS-CoV patients exhibited diarrhoea.



Classification of the Coronaviridae family with reference to subfamily.

3. PATHOGENESIS:

On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths. The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years [22].CoVs and SARS-CoV-2 has links to the function of the nsps and structural proteins. Research underlined that nsp is able to block the host innate immune response [23]. The functions of structural proteins and envelope play crucial role in virus pathogenicity as it promotes viral assembly and release. Although, many of these features (e.g., those of nsp 2, and 11) have not yet been described.

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs and a body temperature of 39.0°C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection [24]. The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Significantly high blood levels of cytokines and chemokine were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity [25]. Research will be needed for determining the structural characteristics of SARS-COV-2 that underlie pathogenic mechanism. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. According to available data it indicates that viral infection able to produce immune reaction in the host. In some cases, reaction takes place which as a labeled ‘cytokine storm', the effect is extensive tissue damage. Protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocyte which acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes growth of some variety of cells, and inhibits the growth of others. It accelerates production of protein and play crucial role in thermoregulation, function of CNS and maintenance of bone. The most important role of interleukin 6 (IL-6) is pro-inflammatory and it also show anti-inflammatory activity.

3.1 CORONAVIRUS CONTROL MECHANISM OF OVER THE CELL:

From the development of genetic multiplicity between coronaviruses and their consequential ability to cause disease in human beings is mainly obtained through infecting peridomestic animals. These animals exist to live near human habitation can act as intermediate hosts encouraging recombination and mutation [26, 27]. SARS-CoV, SARS-CoV-2, and MERS-CoV are human CoVs (HCoVs) that belongs to betaCoVs of B and C lineage and are able to causing epidemics with unpredictable medical severity producing respiratory and extra respiratory symptoms. In the starting, the respiratory and enteric epithelial cells serve as the site of replication for coronaviruses, which then further produce cytopathic changes because

of which the host cell is not capable to reproduce [28]. SARS-CoV reported to conquer in upper respiratory tract ciliated epithelial cells of bronchi and type 2 Pneumocystis through angiotensin-converting enzyme 2 (ACE 2) receptor. MERS-CoV infects unciliated bronchial epithelial cells and types 2 Pneumocystis. MERS-CoV attacks through dipeptidyl peptidase (DPP4) receptor, which is a transmembrane glycoprotein [29-32]. SARS-CoV-2 comes under B lineage of betaCoVs genera. Diameter of SARS-CoV-2 is about 60–140 nm and is identify by round, elliptical, and with pleomorphic shape. Genetically, it had been proved that the genome of the SARS-CoV-2, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide phylogenetically indistinguishable with bat SARS-like CoVZXC21 and 82% with that of human SARS-CoV [33-35]. It is positive single-stranded RNA genome is composed of 29891 nucleotides, encoding for 9860 amino acids, its genesis is not completely understood, but these genomic studies proposed that SARS-CoV-2 possibly originated from a strain recognize in bats. It was also been assumed that the novel virus might use angiotensin-converting enzyme 2 (ACE 2) as a receptor-like SARS-CoV. In contrast to SARS-CoV or MERS-CoV, 2019-nCoV proliferates primarily in human respiratory epithelial cells in a better way than standard tissue culture cells [36]. Sensitivity to ultraviolet rays and heat among the members of the Coronaviridae family has been reported.

3.2 CORONAVIRUS CONTROL MECHANISM OF OVER CELL:

The SARS-CoV-2 Coronavirus: The virus that causes COVID-19. At least six other types of coronavirus are known to infect humans, with some causing the common cold and two causing outbreaks: SARS and MERS.

Covered With Spikes: The coronavirus is named after the crown-like spikes that protrude from its surface. The virus is enveloped in a bubble of oily lipid molecules, which falls apart on contact with soap.

Entering a Vulnerable Cell: The virus enters the body through the nose, mouth or eyes, and then attaches to cells in the airway that produce a protein called ACE2. The virus is believed to have originated in bats, where it may have attached to a similar protein.

Releasing Viral RNA: The virus infects the cell by fusing its oily membrane with the membrane of the cell. Once inside, the coronavirus releases a snippet of genetic material called RNA.

Hijacking the Cell: The virus's genome is less than 30,000 genetic "letters" long. (Ours is over 3 billion.) The infected cell reads the RNA and begins making proteins that will keep the immune system at bay and help assemble new copies of the virus.

Making Viral Proteins: As the infection progresses, the machinery of the cell begins to churn out new spikes and other proteins that will form more copies of the coronavirus.

Assembling New Copies: New copies of the virus are assembled and carried to the outer edges of the cell.

Spreading Infection: Each infected cell can release millions of copies of the virus before the cell finally breaks down and dies. The viruses may infect nearby cells, or end up in droplets that escape the lungs.

Immune Response: Most COVID-19 infections cause a fever as the immune system fights to clear the virus. In severe cases, the immune system can overreact and start attacking lung cells. The lungs become obstructed with fluid and dying cells, making it difficult to breathe. A small percentage of infections can lead to acute respiratory distress syndrome, and possibly death.

Leaving the Body: Coughing and sneezing can expel virus-laden droplets onto nearby people and surfaces, where the virus can remain infectious for several hours to several days.

A Possible Vaccine: A future vaccine could help the body produce antibodies that target the SARS-CoV-2 virus and prevent it from infecting human cells. The flu vaccine works in a similar way, but antibodies generated from a flu vaccine do not protect against coronavirus.

Sources: Dr. Matthew B. Frieman and Dr. Stuart Weston, Univ. of Maryland School of Medicine; Fields Virology; Fenner and White"s Medical Virology; Nature; Science; The Lancet; New England Journal of Medicine; Centers for Disease Control and Prevention.https://www.nytimes.com/interactive/2020/03/11/science/how-coronavirus-hijacks-your-cells.html

The spike glycoprotein, which is also called S glycoprotein attaches the virion to the host cell membrane, is assumed to impart host range restriction feature coronaviruses [37]. In addition, these viruses can be efficiently inactivated when putting in contact with chlorine-containing disinfectant, lipid solvents including ether (75%), ethanol, peroxyacetic acid, and chloroform.

4. EPIDEMIOLOGY:

Based on observations of data from the early outbreak in mainland China from 10–24 January 2020, the trend of an increasing incidence largely follows exponential growth, and the mean basic reproduction number (R0) was estimated to range from 2.24 [95% confidence interval (CI) 1.96–2.55] to 3.58 (95% CI 2.89–4.39), associated with two- to eight-fold increases in the reporting rate [38]. Another estimation based on data from 31 December 2019 to 28 January 2020 suggested similar findings, with the *R* 0 for COVID-19 being 2.68 [95% credible interval (CrI) 2.47–2.86] and the epidemic doubling time being 6.4 days (95% CrI 5.8–7.1 days) [39]. The current estimate of the mean incubation period for COVID-19 is 6.4 days, ranging from 2.1 days to 11.1 days (2.5th to 97.5th percentile) [40], with potential asymptomatic transmission. Although the situation is evolving and further updated data are required to confirm these estimations, there is great potential for a large outbreak of COVID-19 soon. On 11th February 2020, data from the WHO showed that there were a total of 43 103 cases of COVID-19. There has been a steady rise in the daily total number of COVID-19 cases globally, both within and outside China. Several reports of clusters of cases among families and infection of 16 health care workers pointed to the human-to-human transmission of the virus [41-42]. Being major transportation hubs of China, the city of Wuhan was proved an ideal breeding ground for the outbreak [43]. The global spread of the infection started in China, maybe because of frequent traveling occurred due to the Chinese New Year. It mainly in international conveyance (Japan) on 11th February 2020. Twenty-eight countries/regions have reported confirmed cases, including mainland China, Japan, Singapore, Hong Kong Special Administrative Region (SAR), Thailand, South Korea, Taiwan, Australia, Malaysia, Germany, Vietnam, the USA, Macao SAR, the United Arab Emirates, Canada, France, the Philippines, the UK, Italy, India, Russia, Finland, Sweden, Sri Lanka, Cambodia, Nepal, Spain and Belgium. As on March 30, 2020, 723,328, total confirmed cases with 33, 997 total deaths globally were recorded Figure 3. In India, 1024 confirmed cases with 27 deaths have been recorded on March 30, 2020. Of note, the first COVID 19 positive case observed in India on January 29, 2020. However, based on these data, 21% recovery rates globally, and 9.3 % in India were observed [44]. As per the data obtained from the foremost cases in

Wuhan and studies conducted by the Centers for Disease Control and Prevention China, the incubation time could usually be within 3 to 7 days and up to 14 days as the longest time from infection to symptoms was 12.5 days [45]. This data also revealed that this new epidemic doubled about every week, while the basic reproduction denoted as BCR or R0 ranges from 2 to 6.47 in various modeling studies [46]. More clearly, on average, every single patient can transmit the infection to further 2 to 6.47 individuals. Distinctively, assessment of the BCR of the SARS-CoV epidemic in 2002-2003 was approximately 3 and that of the H1N1 outbreak in 2009 in the United States in which over 60 million people were affected, 274, 304 hospitalizations and 12,469 deaths were recorded [47-49].

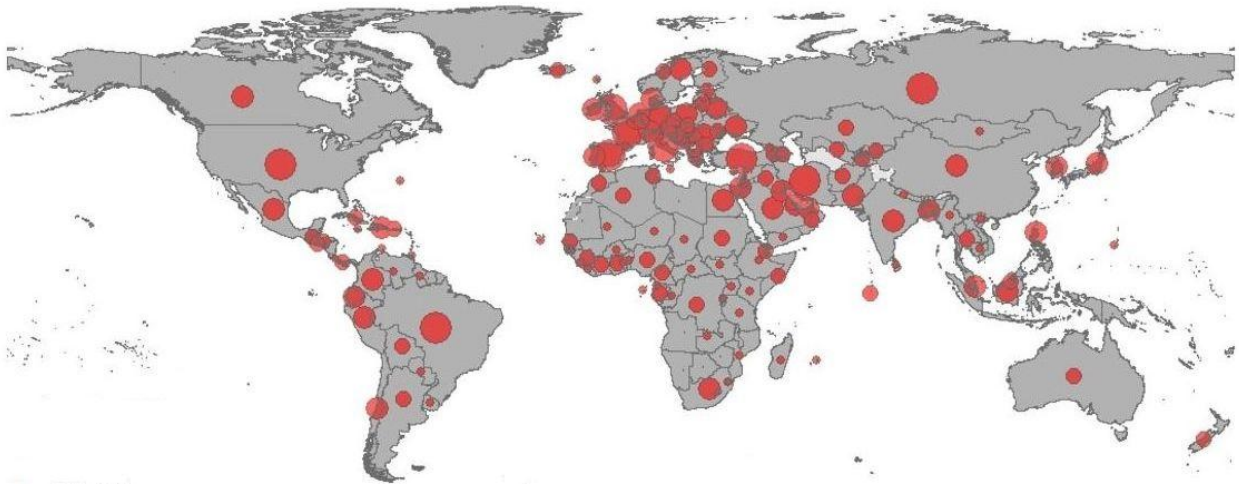


Figure No. 3: Global Distribution of Coronavirus Covid-19 Cases:

5. OUTBREAK MANAGEMENT:

Coronaviruses are a group of viruses belonging to the family of Coronaviridae, which infect both animals and humans. Human coronaviruses can cause mild disease similar to a common cold, while others cause more severe disease (such as MERS - Middle East Respiratory Syndrome and SARS – Severe Acute Respiratory Syndrome). A new coronavirus that previously has not been identified in humans emerged in Wuhan, China in December 2019. Its transmission from human to human of COVID-19 is reported in society [50]. Due to this reason, it is immensely significant to prevent some additional spread in the public and healthcare surroundings. The spread of coronaviruses from contaminated dry inanimate surfaces had also been reported. Even self-inoculation of mucous membranes of nose, eyes, or mouth is also contagious [51, 52]. According to number of review analysis, it was found that the human coronaviruses such as Severe Acute Respiratory Syndrome (SARS)

coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus and Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) can stay on non-living surfaces like plastic, glass or metal for as long as 9 days. Although these substances can render inactivate surface disinfection measures with 62 to 71% ethanol, 0.5% hydrogen peroxide or 0.05 to 0.1% sodium hypochlorite, 0.2% benzalkonium chloride, or 0.02% Chlorhexidine digluconate within 1 min. World Health Organization (WHO) recommends " To ensuring that environmental neatness cleanliness and disinfection procedures are followed constantly in a correct way. Carefully cleaning of environmental surfaces with the help of water and detergent and applying commonly used disinfectants such as sodium hypochlorite are effective and sufficient procedures"[53]. By the use of bleach, which is 5% sodium hypochlorite at a dilution of 1:100 of resulting in a last concentration of 0.05% sodium hypochlorite, is suggested [54]. Now there is no exact therapies are available for SARS-CoV-2, early containment and prevention of further spread will be critical to limit the spread and to control COVID-19 [55].

5.1 PANDEMIC PHASES:

Differentiation in the stage of an epidemic is based on the pathogenesis of disease and several other epidemiological factors. World Health Organization (WHO) released first influenza pandemic awareness plan in which it summarized suitable response based on six clearly defined phases in 1999 [56]. The main objective of plan is to manage global response by providing nations asan outline from which they might illustrate their own national strategies based on available resource [57]. Main fundamental model could be applied with few or more deviations to other epidemics, such as malaria and tuberculosis. First, three phases are deliberated to helped public health officials to understand that it is the time to make up the speed and action plans to respond to an approaching commination. According to World Health Organization (WHO) phase 4, 5, and 6 designate the time were action plans executed. Changing of phases was done by the (WHO) in 2009 for better form of a distinction between attentiveness and action execution phase. Plan was exclusively offer to deal with influenza pandemics designated their high mutation rate and ability of the virus to genesis zoonotic diseases that pass from animal to human being [58].

Former World Health Organization (WHO) Stages of a Flu Pandemic: [59]

PHASE-1
The period during which no animal viruses are reported to cause infection in humans.

PHASE-2
The first level of threat wherein a virus is confirmed to have transmitted from an animal to humans.

PHASE-3
When sporadic, intermittent cases or small clusters of the disease are confirmed, but transmission from a human to another human has either not occurred or is not considered to continue to an outbreak.

PHASE-4
It is the point where either human to human transmission or a human to the animal virus has caused an outbreak widely among a community.

PHASE-5
It is when human to human transmission of the virus has caused the spread of disease to at least two countries.

PHASE-6
It is the point at which the disease has declared a pandemic that has spread to at least one other country.

The duration of each phase could change considerably, ranging from months to decades. This is not necessary that all the outbreaks will move to Phase 6, and few of the outbreaks may even return if a virus spontaneously wears out. On 11th March 2020, The World Health Organization announces COVID-19 is a pandemic disease. This is the first pandemic caused by a coronavirus [60]. There are mainly two perspectives to control the COVID-19 pandemic that can be considered [17].

If the virus has slow transmission ability, containment is the preferred approach that allows the implementation of measures that restrict the spread of a pathogen within the well-defined location. For example, steps for identification and isolation of infected patients, contact tracing, and quarantine of small areas where cases have emerged are to be taken as a containment approach.

If the virus begins to spread rapidly and there is a continuous local transmission, rendering it impossible to isolate all cases, mitigation measures should be implemented with the aim of limit down the spread of a pathogen within a country or a region. Mitigation measures include steps like the closure of schools and the prohibition of mass events. The main aim of mitigation measures is to avoid overloading health systems with the rise of cases in need of intensive care. The existing lockdown in various countries to limit the rapid increase of COVID-19 cases has this particular goal.

6. TREATMENT AND CLINICAL MANIFESTATIONS:

The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. At present, there are no specific antiviral drugs or vaccines against COVID-19 infection for potential therapy of humans. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogs and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available [61]. Until now there is no specific antiviral treatment recommended for COVID-19, and there is no vaccine is available right now. Treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be required in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is crucial for managing septic shock. On 28th January 2020, the World Health Organization (WHO) delivered a document summarizing WHO guidelines and scientific evidence procure from the treatment of previous epidemics HCoVs. This is the document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications; treatments; and considerations for pregnant patients. Special precautions are necessary during intubation. The procedure should be executed by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, disposable gown long sleeve raincoat, disposable double socks, and gloves. Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Concerning HFNO or non-invasive ventilation (NIV), the experts' panel, points out that these approaches performed by systems with good interface fitting do not create

widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission [62]. Clinical appearance of the disease was divided according to their severity by the authors of the CDC report released by the Centre for disease control, China:

Mild Stage: About 81% of cases are not suffering from pneumonia or with mild pneumonia

Severe Stage: This stage was observed in 14% of cases. Major symptoms are eupnoea, which is characterized by shortness of breath and dyspnoea that is characterized by breathing difficulties.

Critical Stage: About 5% of cases reached to this stage. Major symptoms are respiratory failure, septic shock, and/or multiple organ dysfunction or failure [62].

Most of the patients, the medical track of disease seems to forecast a praising trend butin some of the patients, the clinical conditions complicated all of a sudden with rapid deterioration in respiratory efficiency, and even multiple organ dysfunction or failure is found after a week. The criteria of the severity of respiratory insufficiency and criteria of sepsis and septic shock can be considered as a reference for presenting a more clinical image [63]. Illness can be classified as:

Uncomplicated or Mild Illness: Which accompanies symptoms like mild fever, dry cough, sore throat, nasal congestion, malaise, headache, muscle pain.

Moderate Pneumonia: This accompanies symptoms like cough and tachypnea.

Severe Pneumonia: This accompanies symptoms like cough, severe dyspnoea, respiratory distress, and tachypnea

Acute Respiratory Distress Syndrome (ARDS): It can be mild, moderate, or severe ARDS on the basis of the degree of hypoxia.

Sepsis: According to the International Consensus Definitions is a life-threatening organ dysfunction that is caused by an unregulated host response to suspected or proven infection [64].

Septic Shock: It is linked with increased mortality, circulatory, and cellular and metabolic abnormalities.

Till the date, there is no recommended and acceptable antiviral treatment are available for COVID-19. There are no vaccines available for COVID-19. Treatment is only supportive, and oxygen therapy is the major treatment involvement for patients with a severe respiratory infection. Mechanical ventilation may be necessary in cases of respiratory failure that are unmanageable to oxygen therapy, while hemodynamic support is essential for controlling septic shock. World Health Organization (WHO) released a documented briefing on 28th January 2020, the World Health Organization guidelines, and scientific evidence obtained from the treatment of coronavirus of earlier epidemics caused due to HCoVs [65]. It predicted through artificial intelligence that drugs-related with associated protein kinase 1 (AAK1) could be used in the therapy as disruption of these proteins can restrain the entry of the virus into the target cells [66]. Baricitinib, a drug used in the treatment of rheumatoid arthritis, is an AAK1 inhibitor and is recommended for controlling viral replication [67]. Remdesivir is an adenosine analog that is previously developed for the treatment of Ebola virus disease acts as a viral protein inhibitor, has improved the condition in one patient as reported in a clinical study. It was also reported that Chloroquine could block viral infection by increasing the endosomal pH[68]. Chloroquine affects the replication of HCoV-229E but affecting the activation of p38 mitogen-activated protein kinase (MAPK), which has a significant role in viral replication [69]. Antiretroviral drugs Ritonavir and Lopinavir, when used in combination, it was noted that ameliorate the clinical condition of SARS-CoV patients [70], it could be further used in novel coronavirus infections. An ongoing randomized controlled trial safety and efficacy of Lopinavir, Ritonavir, and interferon-α 2b in patients with COVID-19 were initiated on 10th January 2020 [71]. Literature also suggests that many other possibilities include leronlimab, a humanized monoclonal antibody (CCR5 antagonist), or galidesivir, which is a nucleoside RNA polymerase inhibitor [72]. Uses of these available drugs for immediate use in treatment in SARS-CoV-2 infections can improve the present available clinical management [73]. About more than 220 studies of status including both recruiting and not yet recruiting had been presently registered at the ClinicalTrials.gov website for the treatment of COVID-19, which is a rising, quickly spreading condition [74]. Even so, isolation and other supportive measures such as oxygen therapy, fluid management, and administration of antimicrobials for the management of secondary bacterial infections are currently recommended by the World Health Organization. These supportive measures can reduce the symptoms and prevent further chances of multiple organ dysfunctions in suspected as well as confirmed cases necessitating hospitalization [75].

6.1 PLAN OF ACTION FOR PREVENTION:

The preventive procedures are the current plan of action to limit the spread of cases. Plan of action for prevention is focused on the quarantine or isolation of patients and infection control, including relevant measures to be taken during the diagnosis/ treatment and provision of clinical care for an infected patient. For instance, droplet, contact, and airborne precautions should be acquired during sample collection, and sputum induction should be avoided. The infection from even or before the onset of manifestation in the brooding period, transmission from asymptomatic people, non-specific characteristic of the disease, long brood period, a long-lasting period of disease and transmission even after clinical improvement, the susceptibility of transmission through mucosal surfaces such as through the nose and the conjunctiva are few characteristics of novel CoV-19, that makes prevention difficult. Separation of confirmed or suspected cases with mild illness at home or the hospital is the major plan of action for prevention. The most important master plan for the population to take-up frequently wash their hands and use mobile hand sanitizer and to keep away contact with their face and mouth after interacting with a possibly infected environment. Healthcare workers used before caring for an infected person should utilize contact and airborne preventive precautions like PPE such as N95 or FFP3 masks, eye protection, and gloves to prevent transmission of the pathogen. The World Health Organization and other government organizations have released the following general recommendations:

- Wash hands frequently in every 15-20 min for at least 30-45 seconds, especially after contact with contaminated people or their environment.
- Keep away from touching with eyes, face and mouth after contact with a probably infected environment.
- Stay away from close contact with patients suffering from acute respiratory infections must be avoided.
- Persons having low immunity should avoid public gatherings.
- To take strict precaution before interacting unguarded contact with farm or wild animals.
- In emergency medicine departments, strict sterility procedure taken for the prevention and control of infection such as washing and sanitizing hands should be practiced.

Person with symptoms of acute airway infection should keep the distance, cover coughs or sneezes with disposable tissues or clothes, and wash their hands.

Scientific research is growing to develop a coronavirus vaccine. Now in current days, China has announced the first animal tests, and researchers from the University of Queensland in Australia have also announced that, after completing the three-week in vitro study, they are moving on to animal testing. Furthermore, in the U.S., the National Institute for Allergy and Infectious Diseases (NIAID) has announced that a phase-1 trial has begun for a novel coronavirus immunization in Washington State.

7. CONCLUSION:

The novel coronavirus, which originated from a viral family Coronaviridae, had led to a public health emergency of international concern, according to the World Health Organization (WHO). The COVID-19 outbreak, which has now been declared as "Pandemic" by WHO, has confronted that the economic, medical, and public health infrastructure of many countries, including China, the United States of America, Italy, France, and many more all over the world. In India, even after applying proper and timely containment and reduction measures, COVID-19 newer cases are being detected daily. India has continuing facing the situation in a well-planned approach so far. India has been quarantined from the rest of the world by the Indian government, upcoming few weeks are very critical for the country.

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