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A RE-EMERGING CORONAVIRUS (2019-nCov): A REVIEW

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ABSTRACT

SARS-CoV-2 or 2019-nCov is the Coronavirus first named in 2019 that originated in the city of Wuhan in Hubei province China in December 2019. It causes severe acute respiratory syndrome (SARS). The clinical disease is called COVID-19 by the World Health Organization. SARS-CoV-2 enters the cell via the ACE-2 receptor. COVID-19 rapidly evolved into a pandemic by late February 2020. This review article focuses on the epidemiology, biology, pathogenesis, management and prevention of this virus that has high morbidity and mortality globally. The epicenter of the pandemic rapidly moved from China to Europe, with Italy being the most severely affected; it has since moved to USA, with New York State as the most severely affected. It is transmitted via aerosols and fomites. It causes severe upper and lower respiratory infections. The symptoms include fever, dry cough and malaise. These often rapidly progress to respiratory failure needing aggressive respiratory support. Confirmation of the diagnosis is usually by using Reverse Transcriptase Polymerase Chain Reaction (RTPCR). Some of the WHO recommended preventive measures include, among others, using alcohol based sanitizers, N95 face mask and strict quarantine of patients and contacts.

Keywords: SARS-nCoV-2, COVID-19, morbidity, mortality, pandemic, quarantine, respiratory tract infection, Vaccine.

INTRODUCTION

As the world was welcoming the new year of 2020, little did we know that this will be accompanied by a new infectious agent that would decimate the sanctity of the world in so short a time. In December 2019, Wuhan, Hubei Province of China became the center of an outbreak of pneumonia of unknown cause. This raised an intense attention within China and globally [1]. By early January of 2020, Chinese scientists had isolated a novel coronavirus from patients. The genetic sequence of the virus named 2019-nCoV, enabled the rapid development of RT-PCR diagnostic test specific for 2019-nCoV [1]. The rapid expansion of this outbreak is indication of efficient human to human transmission. The virus has been detected in lower respiratory

tract samples from patients with high viral load in upper respiratory tract samples [2, 3]. Jasper Fuk-Woo and colleagues reported infections in health-care workers caring for patients with 2019-nCov which confirms that there is person to person transmission, indicating that there is risk of much wider spread of the disease [2].

EPIDEMIOLOGY

Chaolin Huang and colleagues reported clinical features of the first 41 patients admitted to designated hospital in Wuhan who were confirmed to be infected with 2019-nCoV by January 2020. Their findings provided first-hand data about the severity of the emerging infection whose symptoms include fever, dry cough and malaise [4, 5]. Unlike other human coronavirus infections, upper respiratory symptoms were notably infrequent; and intestinal presentations observed with Severe Acute Respiratory Syndrome (SARS) also appeared uncommon, although 2 of the 6 cases reported by Chan and colleagues had diarrhoea [2]. The case-fatality proportion appears to be closer to 3% based on wider studies [4]. In 1918 the Influenza pandemic that claimed about 30 million lives had case-fatality ratio to be less than 5% [5]. As an RNA virus, 2019-nCoV still has the inherent potential of high mutation rate thus making this zoonotic pathogen to adapt to become more efficiently transmitted from person to person and possibly more virulent [1]. The Current 2019-nCov outbreak has undoubtedly caused memories of SARS and Middle East Respiratory Syndrome (MERS) to resurface in many people. Considering that substantial numbers of patients with SARS and MERS were infected in health care settings, precautions need to be taken, as suggested by several authors, to prevent nosocomial spread of the virus [6 – 9]. The same should be applicable to 2019-nCoV.

As at April 03 2020, the global cases stood as 1,041,126 with mortality at 55,132. So far, a total of 187 countries have been affected and one international conveyance (Diamond Princess). The World Health Organization (WHO) has since declared COVID-19 a pandemic. A new study on 2019-nCoV in China, involving 200 patients, found that blood group type A patients were more susceptible to infection and tended to develop more severe symptoms, while patients with blood type O seemed more resistant to the disease. Blood types of 206 patients who died from the disease in Wuhan, the epicenter of the virus, were studied. Eighty-five had type A blood group, while 52 had type O [10].

VIROLOGY

SARS-CoV2 (2019-nCoV) belongs to the genus *Betacoronavirus* of the Family *Coronaviridae* along with other Coronaviruses (SARS coronavirus, MERS-CoV coronavirus, human coronavirus HKU 1 and human coronavirus HCoV-OC43) [11, 12]. Coronaviruses have an enveloped helical nucleocapsid, a diameter of 80-160 nm, and

widely spaced club- or petal-shaped projections, 20 nm in diameter, covering the envelope figure 1 [11 – 14]. They have a linear, non-segmented, single-stranded RNA with positive sense.

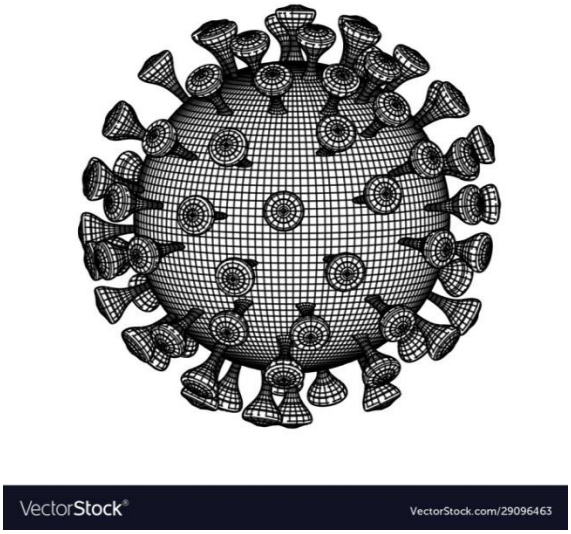

Fig 1: 3D Illustration of Coronavirus. Downloaded (29th March 2020) https://www.vectorstock.com/royalty-free-vector/coronavirus-2019-ncov-virus-3d-vector-29096463 [13]

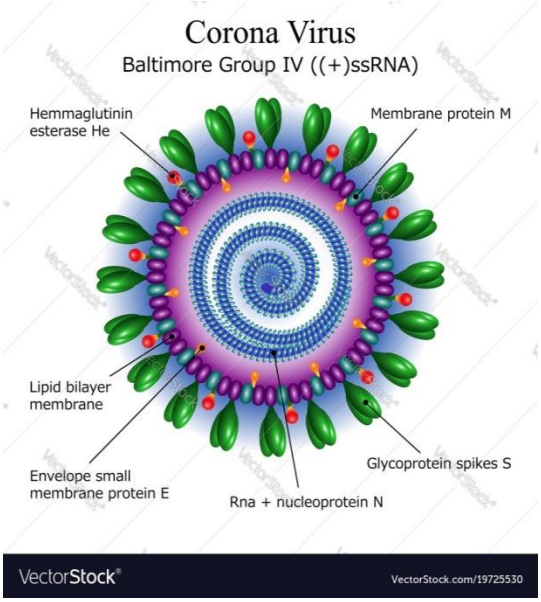

Fig 2: Artists representation of Coronavirus Downloaded (29th March 2020) https://www.vectorstock.com/royalty-free-vector/diagram-of-corona-virus-particle-structure-vector-19725530 [14]

The structural proteins in the virus of SARS-CoV2 (2019-Cov) include a 50-60 kDa Phosphorylated Nucleocapsid (N) protein, a 20-35 kDa Membrane (M) glycoprotein – a Matrix protein embedded in the lipoprotein bilayer, a 180-220 kDa Spike glycoprotein (S) – the petal-shaped peplomers, and a 65 kDa glycoprotein, (Haemagglutinin Esterase dimer HE), which causes haemagglutination, and has Acetylesterase activity figure 2 [14].

VIRAL ATTACHMENT AND REPLICATION

The virus uses defined receptor-binding domain (RBD) on the glycoprotein spikes (S or HE) that specifically recognizes the host receptor Angiotensin-Converting Enzyme-2 (ACE-2) on the epithelial cells of the nasopharynx and oropharynx. They get into these cells by means of endocytosis. Mast cells contribute to SARS-CoV2 (2019-nCoV)-induced inflammation of the submucosa of the respiratory tract and the nasal cavity.

Histamine, protease, IL-1 and IL-33 are released, thus leading to inflammation and oedema [17]. On getting inside the cells viral uncoating takes place and viral RNA is released. Viral specific RNA-dependent polymerase is produced by translation of the relevant open reading frame (ORF) on viral RNA. This enables the host cells to translate minus-sense strands of viral RNA from positive sense viral RNA. Minus-sense strands of viral RNA serve as template for the production of several copies of positive-sense viral RNA, which then leads to the production of both constitutive and non-constitutive viral proteins, viral components are produced.

Helical nucleocapsids are assembled in the cytoplasm. The Spike protein (S) is heavily glycosylated, and it utilizes an N-terminal signal sequence to gain access to the endoplasmic reticulum (ER). Upon budding through host rough endoplasmic reticulum (ER) and Golgi apparatus (GA), the nucleocapsids acquire their membranes (from ER or GA), thus forming mature viral particles [18]. Upon the death of the endothelial cells, mature viral particles get released. It is also possible that SARS-CoV2 (2019-nCoV) can establish persistent infection, and are therefore not always cytocidal [18]. All coronaviruses exhibit a high frequency of mutation and recombination during viral replication. This might have contributed to the evolution of this new coronavirus SARS-CoV2 (2019-nCoV).

PATHOGENESIS

SARS-CoV2 (2019-nCovV), like other coronaviruses, may have Chinese horseshoe bats, chickens and pigs as their reservoir. The index case was probably zoonotic. They have tropism for the epithelial cells of the respiratory tract. And so, human-to-human transmission of infection easily occurs through aerosols, kissing and fomites [11,12,17,18].

Respiratory tract infections:

Critical damage to the epithelial cells of the respiratory tract, and subsequent descending infection into the lungs lead to upper respiratory tract infection, pneumonia and severe oedema of the lung tissue. Patients may present with acute respiratory distress syndrome (ARDS) and are featured by refractory hypoxemia, and dyspnea [8]. Chest CT would reveal pure ground-glass opacities (GGOs) in 77% of patients, GGOs with interstitial and/or interlobular septal thickening in 75% of patients, and GGOs with consolidation in 59% of patients [19].

Septic shock**:**

SARS-CoV2 (2019-nCoV) can cause damage and dysfunction of other organs. When dysfunction of extrapulmonary system such as blood and digestive system occurs, development of sepsis and septic shock should be considered; and mortality rate increases significantly [19, 20]. Coagulation disorders (prolonged prothrombin time and elevated level of d-dimer); myocardial damage (increased level of myocardial enzyme, electrocardiogram

ST-T changes, cardiomegaly and cardiac insufficiency in severe cases); gastrointestinal dysfunctions with raised level of liver enzymes are frequently observed.

DIAGNOSIS:

Early clinical diagnosis of infection needs a high degree of suspicion. People who recently travelled to countries and regions where SARS-CoV2 (2019-nCoV) infection cases have occurred, people with fever, myalgia, pneumonia, cough, rhinorrhea, sore throat and close contacts of test-positive cases need to be quarantined and screened for possible infection.

Specimens to be taken for laboratory diagnosis include nasal, naso-pharyngeal and pharyngeal swabs; stool and blood samples [10]. Laboratory tests include viral RNA antigen detection by reverse transcriptase polymerase chain reaction (RT-PCR), viral load in upper respiratory tract specimens, targeting the constitutive N and non-constitutive Open Reading Frame (ORF) 1b genes [15, 16]. CT scan can demonstrate ground glass appearance of the lung fields, with or without septal thickening and consolidation [11, 12]. Vero monkey kidney cells are useful for viral isolation [17]. Serological markers of COVID-19 agent are shown in Table 1.

TABLE 1: Laboratory markers in SARS-CoV2 (2019-nCOV) infected patients [21]

MOST FREQUENTLY:	
↓	Lymphocytes
↓	Albumin
↓	Hemoglobin
↑	C-Reactive Protein (CRP)
↑	Erythrocyte Sedimentation Rate (ESR)
↑	Lactate Dehydrogenase
↑	D – Dimer
IN SEVERE COVID–19	
↑	Neutrophils
↑	Alanine Amino Transferase
↑	Aspartate Amino Transferase
↑	Cardiac Biomarkers
↑	Procalcitonin

RECOMMENDED MANAGEMENT:

Currently, there are no WHO, National Institute of Health (NIH USA) and USA Food and Drug Administration (FDA) therapies recommended for the treatment of COVID-19. Recently the CDC updated the "Information for Clinicians on Therapeutic Options for COVID-19 Patients" [22]. They listed Remdesivir, Hydroxychloroquine and Chloroquine as investigational treatments. Other drugs such as Lopinavir-Ritonavir were also mentioned. However, they concluded that the current research findings are still preliminary [22]. Currently, both WHO and FDA considered most of the COVID-19 therapies as investigational. This is because their efficacy and safety are not yet fully tested. In addition, most of the medications have some potential adverse effects on patients [22]. The current recommendation is that all suggested therapies should be evaluated on a case-by-case basis by the researchers. The recommendation by WHO is that "use of investigational anti- SARS-CoV2 (COVID-19) treatments must be carried out under proper ethical clearance, randomized controlled trials" [21, 22]. However management should focus mainly on case detection and isolation. Some authors have recommended that the use of broad-spectrum antibiotics and corticosteroids should be avoided for cases with mild symptoms [17, 18].

For the severe and critical cases, antiviral agents, antibiotics to prevent bacterial super infection, corticosteroids, broncho-alveolar lavage, mechanical ventilation, and other more invasive intervention, such as blood purification and extracorporeal membrane oxygenation (EMCO) should be applied cautiously [18].

Multidisciplinary cooperation includes monitoring patient's conditions closely and adjusting the therapeutic protocols timely through multidisciplinary cooperation is of great significance [18-24]. Currently there are no effective antivirals for children. However, appropriate doses of Interferon-α2b nebulization can be administered [18]. Chloroquine phosphate, an old drug for treatment of malaria, has shown apparent efficacy and acceptable safety against SARS-CoV2 (COVID-19) associated pneumonia in multicenter clinical trials conducted in China [19]. With occurrence of acute respiratory distress syndrome (ARDS), encephalitis, encephalopathy, or septic shock, the use of corticosteroids should be considered [18].

Intravenous immunoglobulin can be used in severe cases when indicated, but its efficacy needs further evaluation [18]. Some recommended guidelines to reduce human to human transmission includes travel restrictions, isolation and 14-day quarantine of patients and contacts (the presumed latency period of the virus), social distancing (no handshake, no hugs or kisses), use of gloves, goggles, masks, with brand name as N95 and respirators. Regular hand washing with soap and water and

disinfection with alcohol-based sanitizers before touching face or after touching surfaces like doorknobs, table, chair, gas dispenser, shopping cart and others [18]. All these precautions are very important in containing the spread of COVID-19. SARS-CoV2 is sensitive to ultraviolet radiation and heating. The virus can be inactivated by heating at 56 °C for 30 minutes and by using lipid solvents such as 75% ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform, but not by chlorhexidine [18]

VACCINES:

Vaccines against SARS-CoV2 are under investigation. The viral RNA has been reverse transcribed into DNA, and select pieces of the virus that computer simulations have suggested are immunogenic. Those selected bits of DNA are then inserted into bacteria, which produce large quantities of protein snippets to be used in the vaccine-production process [24]. Some investigators have mapped the molecular structure of the spike glycoprotein, in an attempt to use them to produce vaccines that can act specifically on the S glycoprotein. Figure 3 shows an illustration of the 3D atomic scale map or molecular structure, of the SARS-nCoV2 spike protein. The FDA has given an emergency approval to Moderna- a Cambridge, Massachusetts-based biotechnology company- to begin vaccine trial in Seattle, Washington State. The vaccine is called mRNA1273 [24].

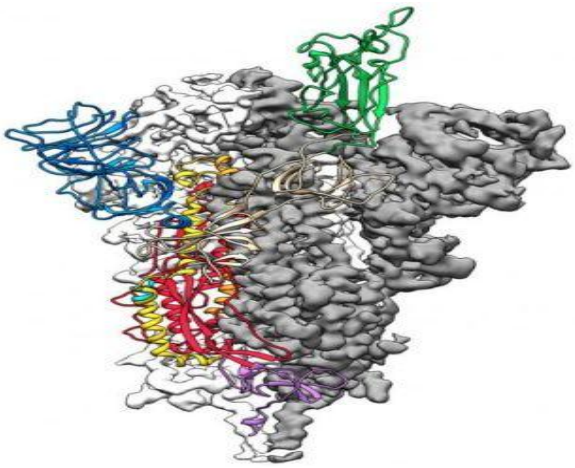

Fig 3: This is a 3D atomic scale map, or molecular structure, of the SARS-CoV2 (2019-nCoV) spike protein. The protein takes on two different shapes, called conformations – one before it infects a host cell and another during infection. This structure represents the protein before it infects a cell, called the prefusion conformation. (credit: Jason McLellan/UT at Austin). This was done in an attempt to develop vaccines against some viral epitope that is perceived to be immunogenic [25]. https://www.livescience.com/coronavirus-spike-protein-structure.html

Antibodies against SARS-CoV2 are also being developed, but mainly aimed at developing ELISA and other sero-diagnostic reagents [26].

SUMMARY:

SARS-CoV2 (COVID-19) is a new mutant of the Coronavirus that first appeared in Wuhan in December 2019 and became an epidemic in China within one month [1, 2]. As at April 03 2020, the global cases stood as 1,041,126 with mortality at 55,132 according to reports from Johns Hopkins University. The virus was quickly sequenced which makes it possible to prepare diagnostic reagents for quick identification. The virus is transmitted through aerosols and fomites [11]. It multiplies in the epithelium of the upper respiratory tract, with an incubation period of 4-10 days before producing the first symptoms [12]. During this period, the virus can be transmitted from humans to humans through aerosols. The first symptoms are nasopharyngeal irritation and dry cough. Viral replication leads to descending infection into the lower respiratory tract and the intestinal tract [11, 12]. The virus produces ground glass opacities in the lungs as a result of inflammatory changes and consolidation [15, 18]. These may lead to dyspnea, and severe respiratory distress. Viraemia follows rapidly and may lead to cardiomyopathies and renal dysfunction [17, 18].

Several investigational therapies are under considerations [27 – 29]. Specimens for viral antigen identification are those of naso-pharyngeal swabs, sputum (if any), stool, urine, and blood samples. Currently RT-PCR is one of the best methods for viral identification [15-16]. Vaccines are under production. They focus on targeting the glycoprotein spikes (S) and the haemagglutinin esterase (HE) on the viral surface (24, 25]. Antibodies are also being developed for quick identification procedures, such as ELISA [26].

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