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A REVIEW ON PANDEMIC DISEASE COVID-19: STRUCTURE, PATHOPHYSIOLOGY, EPIDEMIOLOGY AND TREATMENT

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ABSTRACT

A beginning of life threatening novel beta-coronavirus (2019-nCoV) was from December, 2019 in Wuhan, China, which was caused by severe acute respiratory syndrome-2 (SARS-CoV-2). Initially virus was named as 2019-nCoV, WHO announced the name COVID-19 on 11, February 2020. The COVID-19 was different from SARS-CoV but it has the same host receptor, human angiotensin converting enzyme-2 (ACE-2). On 11, March 2020, WHO declared COVID-19 outbreak as a pandemic. COVID-19 is a zoonotic which means it transfer from animals to human. It is a respiratory disease and symptoms reported by WHO includes fever, tiredness, dry cough, and shortness of breath, aches and pains, sore throat. To date no specific antiviral treatment and vaccines was proven effective against COVID-19. On 25, March 2020 the reported confirmed cases were 414179 with 18440 deaths all over the world. Day by day number of confirmed cases increases drastically. According to situation report-67 by WHO, on 27, March 2020 showed that number of confirmed cases with 94985 and deaths 4895 all over the world, it showed the severity of COVID 19. The major role of health related to public is prevention of disease and to reduce the impact, by taking necessary action, for wellbeing of all human beings. So, in this review an attempt has been made to focuses on structure, pathophysiology, epidemiology, preventive measures of COVID-19 and WHO reference laboratories to provide confirmatory testing for COVID-19, from the studies, reports and surveys.

Keywords: Coronavirus; Wuhan-China; COVID-19; Pandemic; Epidemiology

1. INTRODUCTION

An emergence of novel beta coronavirus has been marked from December, 2020 originated in Wuhan, China [1]. The outbreak of COVID-19 was spread in all over the world within two months. COVID-19 was declared pandemic on 30, January 2020. The general definition of a pandemic is as an infection that spreads globally, COVID-19 [2]. So, it is important to know the types, structure, pathophysiology, and epidemiology and preventive measures of COVID-19. A bunch or group of viruses, belonging to family Coronaviridae, with sub family Orthocoronavirinae and order of Nidovirales are the corona virus. The name "coronavirus" is derived from the Latin word Corona which means crown [3]. Coronaviruses are zoonotic, meaning they are transmitted between animals and human being. Human coronaviruses were first identified in the late 1960s. Prior to the April 16, 2003 SARS outbreak in Asia, only 19 coronaviruses were identified, which includes 2 humans, 4 avian and 13 mammalian coronaviruses [4].

Following the 2003 SARS pandemic, more than 20 additional novel coronaviruses with full genome sequences have been identified after the SARS epidemic. Subgroups of coronaviruses are of four types such as alpha, beta, gamma, and delta coronaviruses. Till date seven coronaviruses have been found to infect humans and cause respiratory diseases. They are 1) 229E (alphacoronavirus) 2) NL63 (alpha-coronavirus) 3) OC43 (beta-coronavirus) 4) HKU1 (beta-coronavirus) 5) MERS-CoV (the beta-coronavirus that causes Middle East Respiratory Syndrome or MERS) 6) SARS-CoV (the beta-coronavirus that causes Severe Acute Respiratory Syndrome or SARS) 7) SARS-CoV-2 (2019 Novel Coronavirus or COVID-19) [5].

2. HUMAN CORONAVIRUS TYPES 2.1.HCoV-229E

Coronavirus 229E (HCoV-229E) is one of the first reported corona virus in humans. Such viruses account for 4 to 15% of acute respiratory disease in adults every

year and up to 35% at peak periods. Children's average infection rates reach 8%, with peak rates of up to 20%. [6].

2.2.HCo-NL63

In 2004, human coronavirus NL63 (HCo-NL63) was identified in a seven- month old child in the Netherlands. The child was suffered from bronchiolitis. The virus is found primarily in children's, the elderly and immunocompromised patients with acute respiratory illness [7]. As per the reports of Amsterdam, HCo-NL63 was found to be present in \approx 4.7% in familiar respiratory disease [8].

2.3.HCoV-OC43

HCoV-OC43, known as Human coronavirus OC43, intended for 5 to 30 % of human being respiratory disorders. Both HCoV-229E and HCoV-OC43 cause lower respiratory tract infections including pneumonia in infants [9].

2.4.HCoV-HKU1

HCoV-HKU1 was first spot in 2004, in a 71 year old man who was suffering acute respiratory distress and diolographically confirmed bilateral pneumonia. The man had history of travelling Shenzhen, China to Hong Kong. The patients with URTI showed symptoms like fever, cold and cough with nose running and patients with LRTI similar symptoms as URTI including dyspnea [10].

2.5.SARS-CoV

This SARS-CoV, called as Severe acute respiratory syndrome coronavirus was first recognized 2002, November, and in Province of Guangdong. The source for it was from civet cats to human beings. When the people got infected due to it, symptoms of pneumonia were seen that further showed the way to acute respiratory distress syndromes. According to common finding in SARS patients is the number of lymphocytes was decreased in the circulating blood. SARS initially emerged in Guangdong, China and then spread rapidly around the globe with more than 8000 infected persons and 776 deaths [11].

2.6. MERS-CoV

Later on in the year 2012, couple of Saudi Arabia was identified with infection of coronavirus. The detected virus was confirmed as a member of coronaviruses and named as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [12, 13]. In the same year, on 22nd September United Kingdom clued-up WHO, with keen respiratory condition due to travelling to Qatar from Saudi Arabia. The examination revealed this condition was transmitted to humans from camels. As per WHO, this infection was for 2428 people and around death of 838. This infection starts with mild respiratory disorder that cause severed condition later. These people further suffer from pneumonia, with acute respiratory distress syndromes and kidney malfunction. At the end of November 2019, WHO reported that a total 2494 laboratory-confirmed cases of MERS-CoV, including 858 associated deaths (case fatality rate: 34.4%) were reported globally. Most of the reports (2102) were from Saudi Arabia (death cases - 780 and 37.1% case related fatality [14-16].

2.7.COVID-19 (SARS-CoV-2)

Coronavirus disease 2019 is a pandemic infectious disease. It is caused by severe acute respiratory syndrome-2 (SARS-CoV-2). The first patient (Male, 61 year old) was reported with fever and cough on 20, December 2019 in Wuhan. It was due to regular who use to visit the seafood market, that deteoriated his condition, and was on ventilation. China was first reported to the WHO Country office in China on 31, December 2019 [17]. The first patient died on 9, January and biopsy specimen was obtained. The World Health Organization declared on 9, January 2020 that Chinese authorities have identified a novel coronavirus. The virus is related to a pneumonia outbreak in Wuhan City, Hubei Province, China and 2019-nCoV is the 7 th member of the coronavirus family and like MERS-CoV and SARS-CoV, it also infects humans. On 11, February 2020, WHO announced a name for the new coronavirus disease as COVID-19 [18].

3. STRUCTURE OF CORONA VIRUS (CoV)

Coronaviruses are enveloped, positive sense stranded RNA viruses with nucleocapsid. In CoV, the genomic structure is organized in a +ssRNA of approximately 26-32 Kb in length (the largest known viruses) and with 5'cap structure and 3'-poly (A) tail [19]. CoV are spherical with diameter of 125 nm. The most marked component of coronaviruses is the club-shape spike projections. The name corona is derived due to the specific structure of virion that gave manifestation of a solar carona. The structure of the COVID-19 was different from SARS coronavirus but receptor-binding gene region is very similar and the virus has been shown to use the same receptor, the angiotensin-converting enzyme-2 (ACE-2). Transcription terminates occurs at transcription regulatory sequences, located between the so called open reading frames (ORFs) that work as templates for the production of sub genomic mRNAs. The genome of SARS-CoV-2 contains at least ten ORFs. The first ORFs (ORFs a/ ORFs b) are translated into the pp1a and pp1ab polypeptides that are processed for two papain like proteases for producing 16 non-structural proteins (nsp1nsp16) which form the viral replicase transcriptase complex [20,21]. The replication and transcription, the nsps reorganize membranes that originate through rough endoplasmic reticulum in twofold vesicles. Other one of genome encode for structural proteins, third including spike (S), membrane (M), envelope (E), nucleocapsid (N) proteins [22].



Fig 1: Structure of Human Coronavirus (SARS-CoV-2)

4. PATHOGENESIS OF CORONAVIRUS

Generally, interface between receptor and S protein, initiates connection of virion to host cell. The envelope spike glycoprotein binds to its cellular receptor, such as ACE-2 for SARS-CoV and for SARS-CoV-2, CD209 (a C-type lectin also called L-SIGN) for SARS-CoV, DPP4 for MERS-CoV. Following receptor binding, the virus must next access to the host cell cytosol. After the fusion of the viral and cellular membranes, S protein cleavage occurs at two sites within S2 portion of the protein. [23] The second footstep is replication of gene from through RNA. The replicase gene encodes two large ORFs which express two co-terminal polyproteins (pp1a, pp2ab). In order to express both polyproteins, the virus utilizes a sequence (5'UUUAAAC-3') slippery and RNA

pseudoknot, after which the viral genome begins to replicate [24]. After replication process and synthesis of, the viral structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum (ER). These proteins move along the secretory pathway into the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC) There, viral genomes encapsidated by N protein bud into membranes of the ERGIC containing viral structural proteins, forming mature virions [25]. At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus by exocytosis process.

5. TRANSMISSION OF COVID-19

The hosts for coronaviruses are many domestic and wild animals, including camels, cats, and bats. With regard to COVID-19, early patients were reported to have some link to the Human Seafood Market in Wuhan, China, suggesting that these early infections were due to animal to human transmission. After that more cases were infected with COVID -19 with no history of exposure to that market or visiting Wuhan, which was taken as indication for human to human transmission [26].

The latest guidelines from Chinese health authorities described three main transmission routes for the COVID-19: 1) Direct transmission 2) Aerosol transmission 3) Contact transmission. Direct transmission occurs when the virus is released in the respiratory secretions when an infected person coughs, sneezes or talks [27]. Aerosol transmission occurs when respiratory droplets mix in to the air, forming aerosols and causing infection when inhaled into the lungs. Contact transmission may occur when a person touches a surface or object contaminate with virus. COVID-19 can be caused by coming in contact with the surface that is already with virus and later having contact with one's face. With this, one report also indicates that digestive system, is also probable way in causing this infection. [28].

6. SYMPTOMS OF COVID-19

After an incubation period of ≈ 5.2 days, start showing the symptoms. The incubation period is approximately 14 days [29]. Patients with confirmed COVID-19 infection mostly had respiratory signs and symptoms [30]. As information given by WHO, common symptoms are fever, tiredness, dry cough and other symptoms include shortness of breath, aches and pains, sore throat. Most of the patients reported GIT symptoms. Very few people reported the symptom of runny nose [31, 32].

7. EPIDEMIOLOGY OF COVID-19

On 27th December, 2019 three patients were admitted in Wuhan hospital, China. The WHO China Country Office was informed on 31, December 2019 cases of pneumonia with unknown etiology (causes) identified in Wuhan City, Hubei Province of China. China government was closed the market on New Year and one week later, on 7, January 2020. The first case of COVID-19 was reported outside the China on 13, January 2020 in the Thailand followed by Japan on 15, January 2020 and South Corea on 20, January 2020.

On 20, January 2020, the no. of confirmed cases of COVID-19 was 282 with 6 deaths reported from four countries including China (279 cases), Thailand (2 cases), Japan (1 case) and the republic of Corea (1 case). Day by day the number of cases increased drastically. Within the next 5 days, on 25, January 2020 the numbers of confirmed cases were 1320 and 41 deaths globally were reported. Based on the observations data from the early outbreak in China from 10-24 January 2020, the mean basic reproduction number (R_0) was estimated to range of 2.24 [95% confidence interval (CI) 1.96 -2.55] to 3.58 (95% CI 2.89-4.39) [33]. On January month end the number of confirmed cases was 9826 with 213 deaths globally and the 20 countries have reported confirmed cases of COVID -19 including China, Japan, Republic of Korea, Viet Nam, Singapore, Australia, Malaysia, Cambodia, Philippines, Thailand, Nepal, Sri Lanka, India, United States of America, Canada, France, Finland, Germany, Italy, and United Arab Emirates. In the next month, it crossed globally 20630 confirmed cases on the 4, February 2020 with 492 deaths. In the

next 3 days, from 5, February 2020, there were no newer countries with confirmed cases. In the month end of February 85403 cases and 79394 from China were confirmed with 2924 deaths globally. On the 7, March 2020, the number of confirmed cases crossed 101927 and 3486 deaths globally. About 85 countries were infected with COVID-19. On 19 March, 2020 the number of confirmed cases worldwide has exceeded 200000. To reach the count of 100000 established cases, took 3 months, but only 12 days later to reach count of 200000. This showed the brutality of virus. On the 25, March 2020 the number of confirmed cases crossed 414179 globally with 18440 deaths all over the world. Till date according to situation report-67 prepared by WHO showed that number of confirmed cases were 509164 and deaths 23335 globally. The total global number of COVID-19 confirmed cases surpassed 500000. China has had most reported confirmed cases (82078) followed by Italy, United States of America, Spain, Germany, Iran, France, and so on. The Italy has had the most reported deaths (8165) followed by Spain, China, Iran, France and so on. The extreme growth rate of COVID-19 confirmed cases and deaths was graphically shown in Fig 2 and Fig 3. The region wise situation of confirmed cases reported by WHO was as given: European region (286697), Western Pacific region (100018), region of the Americas (81137), Eastern Mediterranean Region (35249), South-East Asia region (2932), and African region (2419). International conveyance has confirmed cases were 712 till date [34]. The region wise report of confirmed cases was showed in Fig 4.



Fig 2: No. of confirmed cases of COVID-19 infection in all over the world (Information reported to WHO Geneva from 20, January 2020 to 25, March 2020)

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Fig 3: No. of deaths due to COVID-19 infection in all over the world (Information reported to WHO Geneva- from 20, January 2020 to 25, March 2020)



Fig 4: No of confirmed cases of COVID-19 infection in region wise (Information reported to WHO Geneva: Situation report-67 on 27, March 2020)

8. DIAGNOSTIC METHODS FOR COVID-19

As information given by Centers for Disease Control and Prevention, CDC has developed a new laboratory test kit for use in testing patient specimens for SARS-CoV-2. The kit used for diagnosis is called Real-Time Reverse Transcriptase (RT)-PCR. It was used to detect viral RNA by targeting a consensus RdRp region of pan β -CoV [35]. The serology test is used to detect the presence of antibodies, which are specific proteins made in response to infections. After testing of infected person, antibodies can be found in the blood and in other tissues The antibodies detected by this test indicate that person had an immune response to SARS-CoV-2. It indicates whether symptoms developed from infection or the infection was asymptomatic. Antibody test results are important in detecting infections in person with few or no symptoms. (Information given by CDC) [36].

9. TREATMENT FOR COVID-19

As per the reports there is no at present drug therapy in terms of antivirals or vaccines against COVID-19. The only option available is using broad spectrum antiviral drugs like Nucleoside analogues and also HIV- protease inhibitors that could attenuate virus infection until the specific antiviral becomes available [37]. According to some published studies, some patients (> 85%) were given drugs orally and parenterally [38]. The dose of Remdesivir for the treatment of COVID-19 is 200 mg intravenously (IV) on 1 day followed by 100 mg IV daily for up to 10 days, infused over 30-60 minutes [39]. The first reported patient with COVID-19 infection in the United State was administered Remdesivir. Based on worsening clinical status, intravenous Remdesivir was given for compassionate use on hospital day 7 [40].

Recently, the China National Center for Biotechnology Development indicated that chloroquine is one of the drugs with a promising profile against the new SARS-CoV-2 coronavirus with a recommended dose of 500 mg twice a daily [41, 42]. Various other drug candidates are currently being evaluated against infection such as Nafamostat, Nitazoxanide, Nelfinavir, Ribavirin, Penciclovir, Favipiravir, Baricitinib, AAk1, TZLS-501, Sofosbuvir. [43].

The information given in the landscape document for COVID-19 candidate vaccines prepared by WHO (updated on 26 March, 2020) that 2 candidates are in the clinical evaluation (phase 1 trial). The vaccines are the Adenovirus type 5 vector vaccine developed by CanSino Biological Inc. and Beijing Institute of Biotechnology against COVID-19 and LNP-encapsulated mRNA based vaccine developed by Moderna/NIAID. Other 52 candidate vaccines are in preclinical evaluation [44].

10. LABORATORIES FOR TESTING OF COVID-19

Table 1: Currently, 16 WHO reference laboratories provide confirmatory testing for COVID-19 (updated on 2, March 2020) [45]

WHO Reference Laboratories to Provide Confirmatory Testing for COVID-19			
Sr. No	Country	City	Laboratory
1	China	Beijing	China CDC (TBD)
2	China Hong Kong SAR	Hong Kong	School of Public Health
			The University of Hong Kong
3	Japan	Nagasaki	Institute of Tropical Medicine, Nagasaki University
4	Singapore	Singapore	National Public Health Laboratory
5	Australia	Melbourne	Victorial Infectious Diseases : Reference Laboratory
			National Institute of Health,
6	Thailand	Nonthaburi	Department of Medical Sciences,
			Ministry of Public Health
7	Thailand	Bangkok	Armed Forces Research Institute of Medical Science
8	India	Pune	ICMR-National Institute of Virology,
9	USA	Atlanta	Respiratory Viruses Diagnostic Laboratory, US-CDC
10	South Africa	Johannesburg	Centre for Respiratory Diseases and Meningitis, National
			Institute for Communicable Diseases
11	Senegal	Dakar	Institut Pasteur Dakar
12	Russian Federation	Koltsovo	The State Research Center of Virology and Biotechnology
			VECTOR
13	Germany	Berlin	Institute of Virology, Charité, Robert Koch Institute
14	The Netherlands	Rotterdam	Erasmus MC Department Viroscience
15	United Kingdom	London	Public Health England
16	France	Paris	Institute Pasteur Paris

- 11. PREVENTIVE MEASURES OF COVID-19 [46, 47]
- Wash the hands regularly with soap and water, or clean with alcohol-based hand rub.
- Maintain at least 1 meter distance from people who are coughing or sneezing.
- Avoid contact with patients in order to prevent the spread of viruses by droplets.
- Avoid touching the face.
- Cover the mouth and nose while coughing or sneezing
- Avoid such activities that worsen the condition of lungs and make them weak
- Follow social distancing and be at home to avoid it.

12. CONCLUSION

The recent COVID-19 outbreak has been deemed to be a global health emergency and it became life threating disease to human being. Internationally the number of confirmed cases has continued to increase in number suggested that COVID-19 was more contagious than SARS- CoV and MERS- CoV. According to situation report reported by WHO, currently on date 27, March 2020 number of confirmed cases crossed 509164 with deaths 23335 all over the world. The preventive and cure measures of COVID-19 are under research and development. Many research laboratories are working to understand the COVID-19 completely to discover the treatment and vaccine to prevent the disease. Information reported to WHO Geneva on 27, March 2020 indicates that China has had most reported confirmed cases and the highest deaths were occurred in the Italy due to COVID-19. Containment and prevention is the best option for decline the human to human transmission and spreading of COVID -19.

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