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Review Article

A Review of 2019 Coronavirus Disease (COVID-19) Outbreak

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Abstract

COVID-19 coronavirus caused an unusual pneumonia outbreak in Wuhan, Hubei Province, China in mid-December 2019. The spread of the novel coronavirus (COVID-19) has aroused the memories of SARS-COV and MERS-COV that occurred in the last two decades. COVID-19, an enveloped positive-sense RNA virus of 2C beta-CoV lineage, is recognized by club-like spikes attached to their surface and by their affinity to bind to ACE2 receptor. Originally COVID-19 is zoonotic, yet human to human transmission occurred globally reaching 180 countries with 4.92% fatality rate. With no treatment available to suppress such epidemic, several vaccines concepts and approaches are currently investigated. Until an effective vaccine is developed, increased hand hygiene, social distancing and fast detection are the major measures to decrease COVID-19 spread.

Keywords: *COVID-19; SARS-CoV; MERS-CoV; Virology; Epidemiology; Prevention*

Introduction

In the last three decades, China has been the epicenter for most of the emerging viral diseases that has been threatening the world. Towards the end of the 19th century, an outbreak of avian influenza occurred [1]. This was followed by Severe acute respiratory syndrome in 2003 that spread to 26 countries and infected more than 8000 people [2]. In December 12, Wuhan Municipal Health Commission published a warning to WHO about several cases of unusual pneumonia with symptoms similar to SARs and MERs [3]. A month later, the Chinese Control Center was able to identify the causative agent for the unusual pneumonia in patients that were present at Seafood market in Wuhan [4]. On January 30, 2020 the World Health Organization declared Wuhan's COVID-19 an outbreak of a public health emergency of international concern (PHEIC). Nearly a million cases of CoV-19 have been reported in 180 countries, with more than 40,598 deaths which forced the World health Organization to declare CoV-19 a pandemic in March 11, 2020 [5].

This paper discusses the origin, virology, and epidemiology of COVID-19, emphasizing on major sources, modes of transmission, future treatments and preventions.

Origin

On December 31, 2019 Dr. Li Wenliang, a Chinese ophthalmologist at Wuhan Central hospital alerted his colleagues on a possible return of a SARS-like coronavirus. In his online messages, Dr. Li reported that seven patients tested positive for coronavirus and were quarantined at the Wuhan central hospital. Soon after Dr. Li's warning messages went viral on the internet, the Wuhan police accused Dr. Li for spreading rumors. Chinese authorities delayed reporting the presence of unusual pneumonia in Wuhan city and silenced many medics in an attempt to cover the outbreak. However, with the vast spread and increased death cases, China was forced to report to the World Health Organization about the presence of an outbreak as the virus claimed the lives of many infected people including Doctor Li Wenliang [6].

The origin of COVID-19 is still unknown. The outbreak occurred in Wuhan Seafood market in December were different wild animals were sold, but no bats were detected. A phylogenomic analysis of the COVID-19 showed less than 90% similarity with previously isolated bat-like-CoV (bat-SL-CoVZC45 and bat-SL-CoVZXC21), which was expressed by the long chain shared between these viruses [7]. All coronaviruses that are closely linked to the newly identified virus originated from bats, suggesting the COVID-19 originated from bats as well. However, as bats were absent at Wuhan's Seafood market, an intermediary host that served as a transmission vehicle is yet to be identified [8].

Virology

Before the last 3 decades, coronaviruses did not cause more than a common cold in humans. These viruses are categorized into 4 main groups: alpha, beta, Gama, and delta, with only alpha and beta causing infections in humans. Seven types of human coronaviruses are identified: HCoV-229E, HCoV-oC43, HCoVNL663, HCov-HKU1, SARS-COV and MEARS and the newly identified virus 2019-Cov [9].

COVID-19 is a single positive-stranded RNA virus that belongs to the family Coronaviridae and it consists of 29,811 nucleotides [10]. COVID-19 belongs to beta-coronavirus, distant from SARS-Cov and MERS-CoV, yet related to previously isolated bat-like-CoV in Zhoushan, China in 2018 [11]. COVID-19 forms spherical enveloped particles that ranges from 100 - 160 nm. Open reading frames a and b from the 5 terminal side encodes for the viral replicase transcriptase complex. Whereas the other open reading frames encodes the main structural proteins: Spike (S), nucleocapsid (N), envelope (E) and the membrane (M) protein and different secondary proteins [12].

The ability of these viruses to bind to human cell receptors and fuse through its membrane are dictated by the enveloped spike protein which also vital for detecting host tropism and transmission capacity. In coronaviruses, the spike protein is functionally separated into two domains S1 that is mediates binding and S2 that facilitates cell membrane fusion. Through genomic analysis, COVID-19 also known as COVID-19 showed a 68% similarity in S1 domain with bat-isolated viruses, whereas S2 domain showed a 93% sequence identity with bat-SL-CovZC45 and bat-CoVZXC21 viruses. In domain S1, both N-terminal and C-terminal can bind to host receptor. Fifty amino acids were conserved in S1 domain in COVID-19 and SARS-CoV, whereas mutational differences occurred within different bat-derived viruses [13].

The genomic analysis indicated that COVID-19 was related to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level. However, at the level of receptor binding domain, COVID-19 fell under the lineage B which is closely related to SARS-CoV. Similarities were also detected in the external subdomains between SARS-COV and COVID-19. These findings suggest that COVID-19 is able to use an angiotensin-converting enzyme 2 (ACE2) as a cell receptor. Nevertheless, different vital residues accountable for the binding of SARS-CoV receptor binding domain to ACE2 were different in the COVID-19 receptor binding domain [14].

These detected similarities between SARS-CoV and COVID-19 indicates a possible clinical manifestation associated with both diseases, yet variable results might occur with COVID-19.

Epidemiology

The Chinese lunar year (January 25) is considered the world's largest human migration in which 415 million people travel within China to see their families. During the 2020 Chinese lunar year, an unusual pneumonia was circulating in China. The increased movement of Chinese travelers during these festivals exacerbated the spread of the disease across different Chinese cities. COVID-19 outbreak occurred in December 12, were 41 cases of unusual pneumonia were reported associated with Wuhan's Seafood Market. Following the identification of the causative agents and the confirmation of human to human transmission, the Chinese government took stricter health emergency measures to decrease the disease endemic. On January 26, 2020 the Chinese government implemented lockdown on major Chinese cities including Wuhan the origin of the disease. Before implementing the cities lockdown, 5 million people were able to escape Wuhan to other major Chinese cities. The Chinese governmental health emergency response shaped the COVID-19 epidemic and was able to contain its spread throughout China [15].

Around 84% of the COVID-19 cases were located in Hubei the epicenter of the outbreak, whereas the other major cities combined recorded 16% (13,221 case) of the infections. This indicates the effectiveness of the Chinese governmental health emergency methods in containing the outbreak and in shaping the disease endemic pattern (Figure 1).

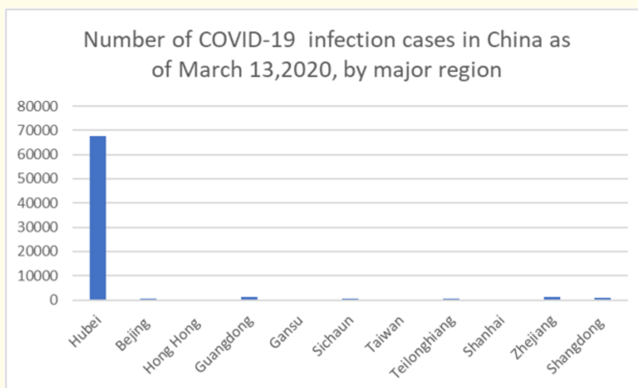

Figure 1: *Number of COVID-19 infection cases up to March 13,2020 [16].*

The modern global travel network connects the world serving as an efficient mechanism by which emerging pathogens can spread rapidly. COVID-19 long incubation period that ranges between 2 - 14 days and asymptomatic carrier increase the difficulty in controlling the spread of COVID-19 through travelers among different nations. The high reproductive number of COVID-19 that ranges between 2.6 - 3.5 suggests the high tendency towards producing an epidemic and the need to block more than 60% of the transmission to effectively contain the outbreak [17].

All the preventive measures implemented outside China unfortunately weren't able to stop the vast spread of the COVID-19. As of January 21, 2020, the World health organization reported the spread of COVID-19 in 3 new countries: Japan, Thailand and Republic of Korea. All the confirmed cases are associated with people exported from Wuhan, China (Figure 2).

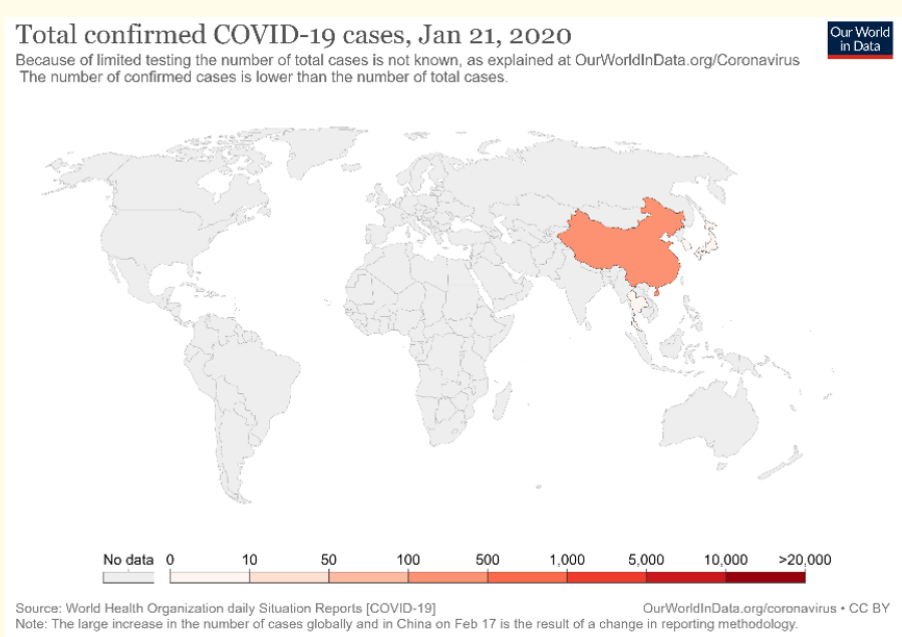

Figure 2: *Total confirmed COVID-19 cases in Jan 21-2020 [18].*

As of February 20,2020 COVID-19 was able to spread 26 countries across the globe, with a total 75,748 cases with a mortality rate 2.84% (Figure 3).

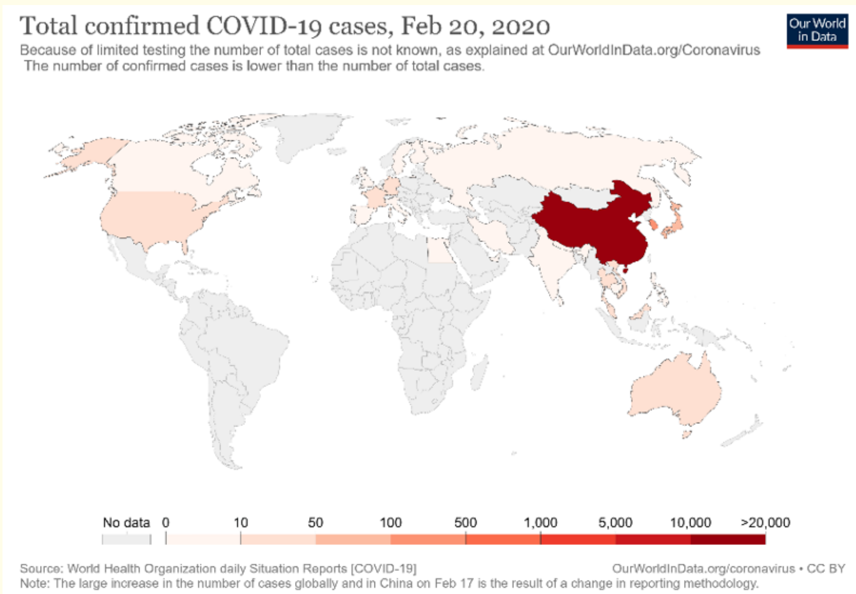

Figure 3: *Total confirmed COVID-19 cases in Feb 20-2020 [19].*

As of March 11, 2020, the World Health Organization declared COVID-19 a pandemic due to its shocking levels of spread and severity [20]. In April 1, 2020, a total of 823,626 cases were confirmed in 180 countries with 40,598 deaths confirmed (Figure 4).

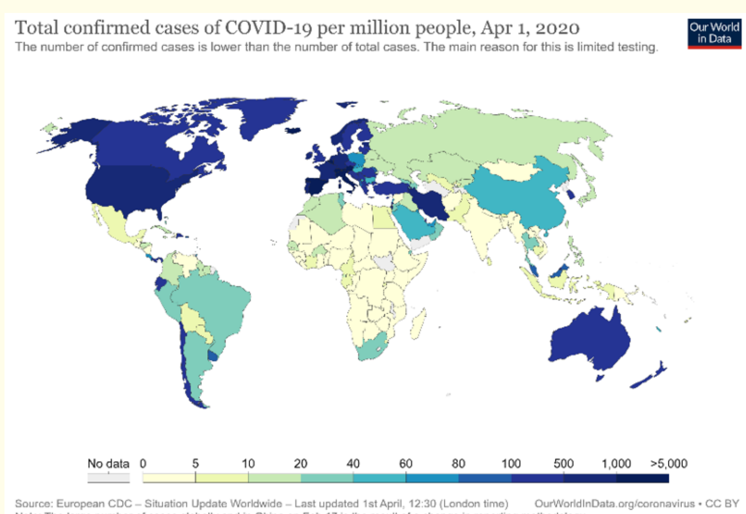

Figure 4: *Total confirmed COVID-19 cases in April 1-2020 [21].*

Iran, Italy, Spain and the United States are exhibiting an alarming pattern in confirmed COVID-19 as they near combined a total of 500,000 confirmed cases. The slow testing and lack of early detection in these countries will further exuberate the situation.

Transmission and sources

Mode of transmission

COVID-19 is commonly transmitted through direct transmission routes such as coughing, sneezing and inhalation of contaminated droplets [22]. In addition to contact transmission which occur when the newly emerged virus is in direct contact with oral, nasal and eye mucous. COVID-19 symptoms doesn't include eye manifestation, yet the investigation of different conjunctival samples obtained from confirmed cases suggested the eye exposure provides a suitable route of entry to COVID-19 [23]. Furthermore, a study highlighted the ability of COVID-19 to transmit through saliva [24]. COVID-19 was detected in stool of infected patients at day 7, yet the amount of virus shed from each patient, infectivity of the shed virus and the period of which the virus is continuously shed is still unknown. Until now, no fecal-oral route of COVID-19 is detected [25].

Cross-species transmission

Until now, scientists have not identified the original source of how humans acquired the disease. The outbreak occurred in a Seafood market where different live animals including snakes, hedgehog, marmots, birds and frogs were sold suggesting a possible zoonotic origin for the disease. In an attempt to locate the possible virus reservoir, a comparative sequence analysis was performed to find similarities in codon usage between COVID-19 and different animal species. Results obtained imply that the COVID-19 is a recombinant virus that originated from bat-Coronavirus and origin-unknown coronavirus. Snakes had the highest codon usage similar to that of COVID-19, which indicate the presence of homologous recombination which confirms the cross-species transmission [26].

Human to human transmission

Genomic and protein modelling analysis indicate the ability of COVID-19 to use S protein to bind to ACE2 receptor on human cell, while indicating a lower affinity to ACE receptor in comparison with SARS-CoV. These results suggest that theoretically the newly identified coronavirus may be not able to cause a fatal human infection in comparison with SARs-CoV. The lower pathogenicity of COVID-19 extends the virus incubation period which ranges from 2- to 14 days and allows a better adaptation to human cells and increased efficient transmission [27].

Clinical manifestation and diagnosis

The incubation period of COVID-19 ranges between 2 - 14 days post exposure. The main symptoms associated with COVID-19 include fever, dry cough, dyspnea, fatigue, sputum production and headache. Furthermore, gastrointestinal symptoms are shown in significant number of patients [28]. CT-Scan imaging of the lungs indicates ground glass opacity or consolidation which indicates the presence of a substance replacing air at the level of the lungs [29]. COVID-19 infection is able to progress into acute respiratory distress syndrome ARDS, acute cardiac and kidney injuries and finally shock which leads to death.

As the clinical symptoms of COVID-19 are atypical, epidemiological history and supplementary examination techniques such as nucleic acid detection, CT-Scan, ELISA and blood culture are crucial for COVID-19 diagnosis [30]. Real time quantitative PCR method represent the most useful and straightforward method in detecting COVID-19 in respiratory section, blood and fecal material [31]. CT scan image was proposed as another necessary auxiliary diagnostic method to avoid the negative consequences of a missed diagnosis due to RT-qPCR false negative results. High resolution CT scan imaging provides an essential mean for early disease detection and assessment of disease severity [32]. To avoid the false-negative results produced by RT-qPCR and CT-scan images, ELISA kits against COVID-19 are needed. Currently, some of the COVID-19 ELISA kits are produced and tested, yet no commercial product is provided [33].

Treatment and prevention

No antiviral drug is recommended against COVID-19. Supportive treatment can be done to relief the symptoms. Supportive treatment includes oxygen therapy, fluid management and application of antibiotics to fight secondary bacterial infections [34]. Several therapeutic approaches are currently tested to produce an effective method against COVID-19. Remdesivir which an adenosine analogue capable of blocking the viral RNA synthesis through RNA-dependent RNA polymerase inhibition showed promising result against broad range of RNA viruses [35]. Furthermore, flavonoids [36] and cinanserin [37] provide an interesting option to target nonstructural proteins located on COVID-19 surface that are vital for its replication. Antibody and plasma therapy which includes the COVID-19 human monoclonal antibody could provide an important alternative option in neutralizing the virus [38].

Recently, Chloroquine and hydroxychloroquine are gaining interest in the medical community as potential cure for COVID-19. These anti-malaria drugs have a long history of use (since 1940s) and relatively of low cost which make them suitable for mass production. *In-vitro* trials in China indicated that hydroxychloroquine can effectively neutralize COVID-19 [39]. Based on these promising results, a group of French scientists conducted an open-label non-randomized clinical trial to test Chloroquine and hydroxychloroquine efficacy. Patients participating in this experiment, received 600 mg of hydroxychloroquine daily. Based on their clinical manifestations, some of the patients received azithromycin in their treatment. The results obtained indicated a significant decrease in viral carriage at day six following the application of the treatment in comparison with control patients. The added antibiotic azithromycin increased efficiently the elimination of COVID-19 from patients [40].

In-vivo and *in-vitro* studies concerning the efficacy of Chloroquine and hydroxychloroquine coupled with azithromycin provide a promising treatment for COVID-19. However, these early interpretations should be taken cautiously. Chloroquine has shown diverse promising activity in cell culture against Ebola and chikungunya virus, yet it lacked therapeutic activity in clinical trials [41]. Chloroquine and hydroxychloroquine are known for their ocular toxicity, cardiotoxicity, heart arrythmia and renal damage [42], which questions its efficacy in critical ill or old vulnerable patients. Therefore, it is crucial to understand the mechanism of interaction of chloroquine/hydroxychloroquine and azithromycin with COVID-19 to be able to develop a preventive and therapeutic protocol.

To reduce disease fatality, viral shedding and transmission, a vaccine is required. Several vaccines that were tested in animals for SARS-CoV and MERS-CoV could help in paving the way towards producing COVID-19 vaccine. These promising vaccine methods include attenuated live vaccines, inactivated vaccines, subunit vaccines [43].

Three months following its emergence, COVID-19 became a pandemic threating the world. Without creating a vaccine, the control of such vast spread seems impossible. The main characteristics of the ideal COVID-19 vaccine is its safety in immunocompromised individuals, adults with chronic problems like diabetes and hypertension, and the ease of its production.

Genomic analysis of COVID-19 revealed 89% nucleotide similarities with SARS-COV that caused an outbreak in 2003. Both viruses' affinity to bind to ACE2 receptor on human cells and their similar pathogenicity helped scientists to base COVID-19 vaccine approach on SARS-CoV prior knowledge [44].

Whole virus vaccines

Live attenuated vaccines and inactivated vaccines production revolutionized the world of infectious diseases that led to the birth of immunology. Johnsen and Johnsen an American multinational company announced that their subsidiary company Janssen Pharmaceutical company is currently working on COVID-19 non-replicating viral vector vaccine. The company is applying a similar approach to the one used in developing their Ebola vaccine [45]. Furthermore, the Serum institute of India announced its collaboration with America's Codagenix to work on a recombinant measles virus vectored vaccine to protect against COVID-19. The recombinant measle vaccine harbors codon-optimized proteins from COVID-19 that will induce solid neutralizing immunity against COVID-19 infection [46]. In addition to that, a modified influenza vaccine that contains surface antigens from COVID-19 was developed at the University of Hong Kong [47]. Their intrinsic immunogenicity and ability to stimulate toll like receptors are the main advantages of these vaccines. However, their ability to cause the infection in immunocompromised hosts will hinder their production especially when looking for a vaccine to protect the most vulnerable people.

Subunit vaccines

The genomic analysis of COVID-19 revealed 80% similarities in the amino acids of the receptor binding domain between COVID-19 and SARS-CoV. These similarities presented an opportunity to use these identified proteins as subunits vaccines. Supported by the Coalition for Epidemic Preparedness (CEPI) fund, The University of Queensland are using a "Molecular Clamp" to create key surface protein easily recognized by the immune system [48]. Likewise, an old subunit vaccine made of RBD (Receptor Binding Domain) of SARS-CoV spike protein S assembled on alum and mixed with a synthetic glucopyranosyl lipid A could serve as possible COVID-19 vaccine candidate. Moreover, the developed and tested vaccine against SARS could provide a cross-protection against COVID-19 [49]. The tested results detected an increased level in neutralizing antibody without causing Th2-type immunopathology; therefore, subunit vaccines provide a safe approach when used in immunocompromised individuals [50].

Prevention

Controlling viral diseases dictates a clear understanding of the virus' features, mode of transmission and degree of illness it may cause, along with available pharmaceutical and non-pharmaceutical measures. To reduce the exposure and transmission of COVID-19, the World Health Organization has established standard recommendations such as: regular hand cleaning and avoiding close contact with sick people or contact with contaminated surface to assure the safety of healthy individuals. The increased hygiene practices can decrease up to 22% of virus' transmission [51]. Furthermore, increased hand hygiene practices at the airport can actually decrease the potential of a pandemic by 24% to 69% [52]. Other recommendations include steps to protect others such as: self-isolation in case of infection until seeking medical health, in addition to wearing a facemask to decrease virus spread by droplets generated through coughing and sneezing [53].

In the absence of an effective pharmaceutical drug coupled with limitation of the medical resources, non-pharmaceutical interventions are vital to contain disease outbreaks. The Chinese non-pharmaceutical interventions taken to mitigate COVID-19 spread include intercity travel bans as major Chinese cities were place under lockdown [54], coupled with improved screening, diagnosis, detection, isolation and recording of suspected ill and confirmed cases [55]. Moreover, the Chinese government encouraged social distancing as it urged people to stay at their homes. Holidays were extended from January 30 to March 10 for people in Hubei and for February 9 for other major cities in an attempt to cover the suspected incubation period of COVID-19 [56].

The Chinese health emergency measures seem to be effective in containing the outbreak of COVID-19 as confirmed cases in China declined rapidly at the end of February and early March. Without the implementation of such intervention a 67-fold increase in cases would have been recorded. However, if such extreme measures were applied one week, two week and three weeks earlier the detected confirmed cases would be less by 66%,86% and 95% respectively. On the other hand, if the Chinese government delayed those NPI methods by one, two and three weeks the cases across the country would have increased by 3-fold,7-fold and 18-fold, respectively [57].

Conclusion

A combination of CDC recommendations and health emergency measures taken by the Chinese authorities could establish a guideline to countries that are currently struggling with COVID-19 outbreak. these measures are vital in battling COVID-19 spread and in giving the medical system a hope in doing so.

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