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REVIEW ON STRUCTURE, PATHOGENECITY, TRANSMISSIBILITY AND EPIDEMIOLOGY OF HUMAN PATHOGENIC CORONAVIRUSES

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ABSTRACT

Coronaviruses cause animal and human respiratory and bowel infections. They have not been deemed highly pathogenic to humans until the outbreak of severe acute respiratory syndrome (SARS) in 2002 and 2003 in Guangdong province, China. Coronaviruses (CoVs) are large, enveloped, positive-sense, single-stranded RNA viruses that can infect both animals and humans. Coronaviruses didn't just appear recently. They are large family of viruses that have been around for a long time. Formerly, coronaviruses (CoVs) were seen as relatively harmless respiratory pathogens to humans. However, two outbreaks of severe respiratory tract infection, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) caused high pathogenicity and mortality rates among human populations as a result of zoonotic CoVs crossing the species barrier. Now the recent detection of the 2019 novel coronavirus (COVID-19), added a new member in corona virus family.The novel coronavirus (COVID 19) is one of the member of coronavirus family which infect human. Scientists have divided coronaviruses into four sub-groupings, called alpha, beta, gamma and delta. Seven of these viruses can infect people. The four common coronaviruses are-229E(alpha),NL63(alpha),OC43(beta),HKU1(beta). The three less-common coronaviruses are-MERS-CoV(beta), SARS-CoV(beta),SARS-CoV-2. Our main target is to describe the the structure, Pathogenecity, Transmissibility and Epidemiology of above mentioned subgroups of corona viruses in our review.

KEYWORDS: Replication-transcription complex, Hemagglutinin esterase, Severe acute respiratory syndrome-related coronavirus, Middle East respiratory syndrome-related coronavirus, Novel coronavirus.

INTRODUCTION

In 1965 the first human coronavirus (HCoV), strain B814, was isolated from a common cold patient's nasal discharge. Since then, they have described more than 30 additional strains. Among them, standard tissue culture was used to isolate prototypic strain HCoV-229E. Using tracheal organ culture, HCoV-OC43 was later recovered and found to be serologically distinct from HCoV-229E. These viruses have been the subject of HCoV work in the following years, until the advent in 2002–2003 of the extremely pathogenic severe acute respiratory coronavirus syndrome (SARS-CoV). Two HCoVs were found in the post-SARS period. HCoV-NL63 (NetherLand 63) was isolated from the aspirate of a 7-month-old infant with bronchiolitis in 2004, whereas HCoV-HKU1 (Hong Kong University 1) was isolated from a Hong Kong patient with pneumonia in 2005. Two more zoonotic HCoVs have since appeared, namely as Middle East coronavirus respiratory syndrome (MERS-CoV) and the 2019 novel coronavirus (SARS-CoV-2). Unlike SARS-CoV, MERS-CoV and SARS-CoV-2 that are associated with severe respiratory disease, the four common HCoVs (229E, OC43, NL63, and HKU1) usually cause mild to moderate upper-respiratory tract illness, probably leading to to 15%–30% of cases of common colds in human (1).

Coronaviruses belong to the family *Coronaviridae* (2). The *Coronaviridae* family is the largest of the four families (3). *Coronaviridae* virus family subdivided into two subfamilies, *coronavirinae* and *torovirinae* (4). The Coronaviruses (CoVs) are species of virus belong to the subfamily *Coronavirinae* and the order *Nidovirales*. Based on their phylogenetic relationships and genomic structures, this subfamily consists of four genera— *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus*. The alphacoronaviruses and betacoronaviruses can only affect mammals. Gammacoronaviruses and deltacoronaviruses infect birds, but some may infect

mammals as well (5). *Alphacoronaviruses* and *betacoronaviruses* typically cause human respiratory disease, and animal gastroenteritis. The two highly pathogenic viruses, SARS-CoV and MERS-CoV, cause severe respiratory syndrome in humans, and the other four human coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1) trigger only moderate upper respiratory diseases in immunocompetent hosts(6).

Most recently the novel coronavirus COVID-19, believed to have arisen in Wuhan, Hubei Province, China. SARS-CoV and MERSCoV are particularly pathogenic in humans and are linked to high mortality rates (7). Novel corona virus (2019) infected 177,418,269 individuals in at least 222 countries and territories and more than 3,838,600 induviduals have died worldwide and only in India 29,633,105 cases and 379,601 deaths have been reported till date of this writing.

REVIEW OF LITERATURE

The name of Coronaviruses derive from the typical crown-like viral particles (virions) that cover their surface. Wide variety of vertebrates, most notably mammals and birds can be infected by this family of viruses and are considered to be a major cause of viral respiratory deseases worldwide(8), With the recent detection of the 2019 novel coronavirus (COVID-19), there are now a total of 7 coronaviruses known to infect humans: 1. Human coronavirus 229E (HCoV-229E) 2. Human coronavirus OC43 (HCoV-OC43) 3. Human coronavirus NL63 (HCoV-NL63) 4. Human coronavirus HKU1 5. Severe acute respiratory syndrome-related coronavirus (SARS-CoV) 6. Middle East respiratory syndrome-related coronavirus (MERS-CoV) 7. Novel coronavirus (COVID-19) (9).

Genomic organization, similarities in genomic sequence, antigenic properties of viral proteins, replication strategies, and structural characteristics of virions, pathogenic, and physicochemical properties has been used for the classification of Coronaviruses (10).

STRUCTURE OF CORONAVIRUSES

Coronaviruses are enveloped positive single stranded RNA viruses. These are round and approximately 80 to 120 nm in diameter. Coronaviruses are enveloped viruses, with the largest RNA genome (approximately 30 kb) reported to date (11). The genome sizes are approximately 27.5 kb for HCoV-229E and HCoV-NL63, and more than 30 kb for HCoV-OC43 and HCoV-HKU1 . Since the genomic RNA possesses a 5'-cap structure and a 3' -polyadenylate tail, it can serve as a messenger RNA(mRNA) that encodes the viral replicase. In fact, the genome also acts as a template for replication of RNA, and the genome is bundled into virions of the progeny. The coding region is flanked by two untranslated regions (UTRs). The 5'-UTR is 292, 210, 286 and 205 nucleotides long respectively in HCoV-229E, -OC43, -NL63, and -HKU1, and contains around 70 nucleotides long leader series at its 5' -terminus. At the other end of the genome, the 3'-UTR in HCoV-229E, -OC43, -NL63, and -HKU1 are 462, 288, 287, and 281 nucleotides, respectively, and it comprises a highly conserved octameric sequence of approx. 70 nucleotides (12). 58% identity on the nsp(non structural protein)-coding region and 43% identity on the structural protein-coding region are found among different CoVs, by using genome sequence alignment with 54% identity throughout the whole genome level . Since the mutation rates in RNA virus replication are much higher than those in DNA viruses, the RNA virus genomes are typically less than 10 kb in length (13).

The 3′-5′ exoribonuclease is unique to CoVs among all RNA viruses and possibly offers an RTC (replication-transcription complex) proofreading function. Sequence analysis reveals that the 2019-nCoV has a typical CoV genome structure and belongs to the SARS-CoV and MERS-CoV coronavirus family. On the basis of the phylogenetic tree of CoVs, 2019-nCoV is closer to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to SARS-CoV (14).

The CoVs have “club-like” projections due to the spike (S) protein under the electron microscope (15,16). During the viral life cycle, this genomic RNA acts in three capacities: (1) as the initial RNA of the infectious cycle; (2) as a template for replication and transcription; and (3) as a substratum for packaging into the virus progeny. Replicase-transcriptase is the only protein translated from the genome, while subgenomic mRNAs derive the viral products of all downstream open reading frames. The replicase gene makes up about 5 'two-thirds of the genome in all CoVs and consists of two overlapping open reading frames (ORFs), ORF1a, and ORF1b, which encodes 16 non-structural proteins. spike (S), envelope (E), membrane (M) and nucleocapsid (N) are four structural protein genes which are encoded by the final one-third of the CoV genomic RNA . Many accessory ORFs are also interspersed along the structural protein genes among CoV species but the number and location varies (17,18).

Hemagglutinin esterase(HE) is an additional membrane protein pouseses by some coronaviruses (19). It is not an essential protein, and it has been speculated to aid in viral entry and pathogenesis . HE is not encoded in the SARS-CoV genome. In addition, each group of coronaviruses encodes a group of special small proteins; although these proteins are non-essential and have been speculated as accessory proteins and as integral proteins (20).

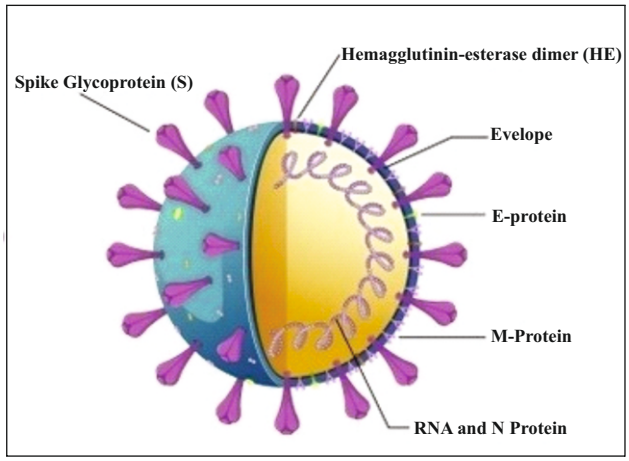

Fig. 1: The Coronavirus Virion Consists of Structural Proteins, Namely Spike (S), Envelope (E), Membrane (M), Nucleocapsid (N) and, for some Betacoronaviruses, Haemagglutinin-Esterase

Human coronavirus-229E, -OC43,-NL63, and -HKU1 releases progeny virions from non-permissive host cells, thus enhancing the spread of virions in the extracellular environment. Iinitial comparisons revealed that at the nucleotide level, SARSCoV-2 was about 79 per cent similar to SARS-CoV. Similarity patterns vary greatly between genes, and SARS-CoV and SARS-CoV-2 show only 72 per cent similarity of nucleotide sequence. S protein, the key surface glycoprotein of CoVs interacts with host cell receptors. The SARSCoV-2 spike protein has a functional polybasic (furin) cleavage site at the S1–S2 boundary by inserting 12 nucleotides8, which led to the predicted acquisition of 3 O-linked glycans around the site(21).

The SARS-CoV genome has a total of 29,727 nucleotides including 11 open reading frames (ORFs). The SARS-CoV rep gene, which contains about two-thirds of the genome, encodes at least two polyproteins (encrypted by ORF1a and ORF1b) undergoing cotranslational proteolysis process (22). For many reasons such as the short anchor of the S protein, the specific number and location of small ORFs, this virus is significantly different from the previously reported coronaviruses. The MERS-CoV genome is larger than the SARS-CoV genome with a length of 30,119 nucleotides and consists of a 50 terminal cap structure and a poly(A) tail at the end of the 3' .the MERS-CoV genome does not encode a HE protein comparing to other beta-coronaviruses. (23). The genetic code consists of 61 different codons that match standard 20 amino acids. (24). The MERS CoV genome consists of 10 open read frames. There is one wide open reading frame (ORF), ORF1ab, at the 5′ end of the genome, which is translated into polyprotein 1ab. The polyprotein 1ab encodes the viral replicase and sites of ribosome interactions. The other 8 ORFs translate to form structural and nonstructural proteins (25).

PATHOGENESIS

Different types of CoVs show diverse host range and tissue tropism. Many patients have direct or indirect connection with the Wuhan seafood market .Species, including bats and wild animals sold on the market might be the cause of the transmission from animal to human (26).

Human coronavirus 229E was discovered during 1966(27). Symptoms of infection with 229E include general pain , headache, nasal discharge, sneezing and sore throat (28). A small percentage of patients(10-20%) will also show fever and cough. The incubation period is roughly 2–5 days, followed by 2-18 days of illness(29) . Human coronavirus OC43 was identified in 1967 and OC43-infected patients have the same clinical symptoms as 229E (30).OC43 is also distributed globally. Patients diagnosed with SARS-CoV initially suffering from fever, myalgia, headache, malaise and chills, followed by unproductive cough, dyspnea and respiratory failure usually 5 to 7 days later, which can lead to death (31). HCoV-229E and HCoV-OC43 replicate primarily in the epithelial cells of the upper respiratory tract where they produce virus and cause local respiratory disease (32).

A model for SARS disease was proposed, consisting of three phases: viral replication, immune hyperactivity, and pulmonary destruction (33). Lung SARS pathology was associated with diffuse alveolar damage, proliferation of epithelial cells and an increase in macrophages (34). Latest results based on autopsies of SARS patients indicated that SARS is a systemic disease with widespread extrapulmonary spread, resulting in viral shedding of respiratory secretions, stools, urine and even sweat (35). Proinflammatory cytokines released into the alveoli by stimulated macrophages may play a role in SARS pathogenesis. SARS-CoV infection of macrophages in vitro leads to viral replication and synthesis of viral proteins, but replication is abortive and no virus particles are produced. According to one report SARS-CoV replicates in peripheral blood mononuclear cells (PBMCs) of SARS patients (36-37).

Another pathogenic human coronavirus MERS-CoV cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality (38). In the past SRAS-CoV (2003) infected 8098 peoples with mortality rate of 9%, across 26 contries worldwide , on the other hand, novel corona virus (2019) infected more than 50 million people till date shows that the transmission rate of SARS-CoV-2 is higher than SRAS-CoV. genetic recombination might be the reason for higher transmition event .It has been

reported that S protein in the RBD region of SARS-CoV-2 may have enhanced its transmission ability. The World health organization reported that MERS coronavirus infected more than 2428 individuals and 838 deaths (39). It is essential to establish the source of origination and transmission in order to develop preventive strategies to control the infection. The researchers found that civet palm might be secondary hosts for the SARS-CoV(40). MERS-coronavirus also have camels as a zoonotic source or primary host (41).

MERS-CoV shows its pathogenicity grade depending on the host. This is because MERS-CoV demonstrates a strong tropism for the non-conciliated bronchial epithelia. It is proven during this time that the virus also arrests the host bronchial IFN synthesis. It should be noted at this juncture that most other viruses which cause respiratory diseases attack and damage epithelial cilia, including influenza type A. Studies revealed that cellular receptors for MERS-CoV is exopeptidase (angiotensin converting enzyme 2) (42).In an experiment after neutralization of angiotensin converting enzyme 2 by specific antibodies did not show any affect on infection into bronchus and lung alveolus, may be there is an alternative mechanism for the infection. Extensive studies have shown that other functional cellular receptors called dipeptidyl peptidase-4 have also been involved in disease severity spread in the lungs due to MERS-CoV (43).

Coronaviruses have errorprone RNA-dependent polymerases (RdRP), mutations and recombination events often occur(44), resulting in a variety of quasispecies closely associated with adaptive evolution and disease-causing ability. Recent studies have shown that, during the 2002-2004 outbreak, SARS-CoV evolved to better bind its cell receptor and replication in human cells, thus improving virulence. Therefore, it is important to analyze whether 2019-nCoV behaves like SARS-CoV in order to adapt to the human host, and whether this will increase the R0 value and change its virulence. In comparison, since it was discovered, MERS-CoV has not significantly mutated, which may be due to the fact that the functional cellular receptor (CD26) used by MERS-CoV is very specific, so that the virus has very small capacity for mutation without losing fitness. Notably, ACE2, receptor protein for both the SARS-CoV and 2019-nCoV is abundantly present in humans in the lung and small intestine epithelia (45).

TRANSMISSION

The 2019-nCoV outbreak began in winter close to climate as SARS (46). Like SARS-CoV, 2019-nCoV can be transferred by respiratory droplets directly from person to person and emerging research indicates it can also be transmitted by touch and fomites. Additionally, the asymptomatic incubation period for persons infected with 2019-nCov ranged from 1 to 14 days. A very important threshold quantity associated with the viral transmissibility is the basic reproduction number, which is usually denoted by R0. The epidemiological definition of R0 is the average number of people who will catch a disease from one contagious person. It applies specifically to a population of people who were previously free of infection and had not been vaccinated. Each existing infection causes less than 1 new infection if R0 is less than 1. The disease will worsen in this situation, and ultimately vanish. 2. If R0 equals 1, the disease will remain alive but an epidemic will not occur.3 If R0 exceeded 1 cases may increase exponentially and cause an outbreak or even a pandemic. The calculated R0 value for 2019-nCoV is considerably higher than 1 about what we currently know (47).

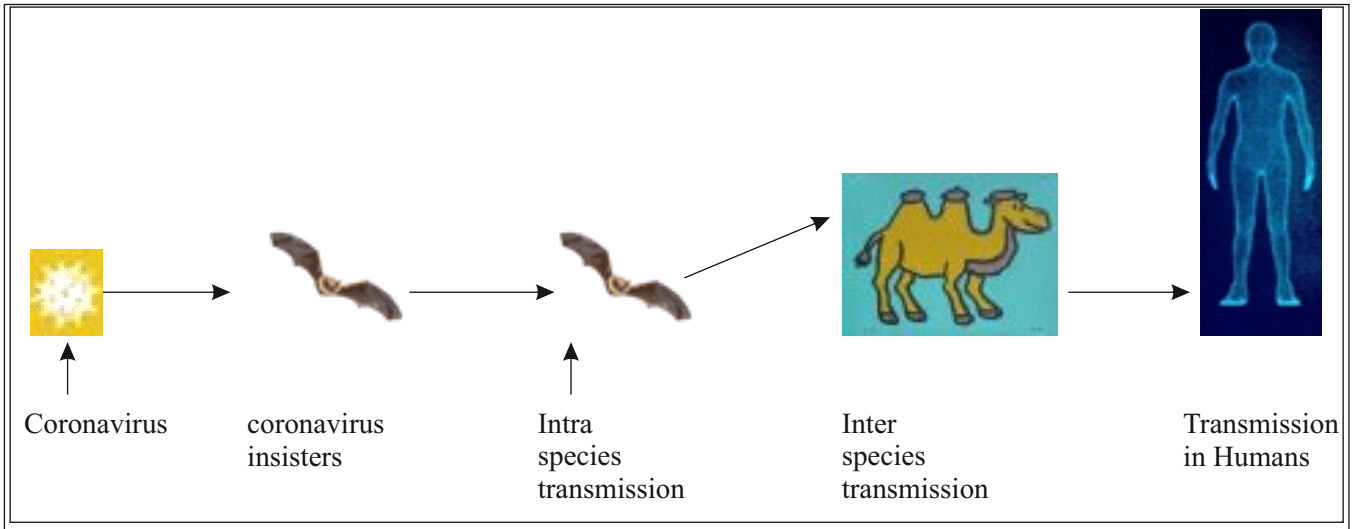

Fig. 2: Mode of Transmission of Coronaviruses from Animal to Humans

One route for the transmission of SARS-CoV and MERS-CoV from animals to humans might be direct contact with the intermediary host. Some studies have shown that camel workers in Saudi Arabia with a high prevalence of MERS-CoV infection may contribute to MERS transmission (48). Some customs and habits, such as consuming milk, urine, or uncooked meat, may also be conducive to transmission (49).Delays in diagnosis in hospitals may lead to secondary cases among healthcare staff, family members, or other patients sharing rooms. Nosocomial transmission for MERS has been detected in the Middle East (50) and in the Republic of Korea (51). Outbreaks in other countries all resulted from the reported cases in the Middle East or North Africa, and transmission is due to international traveling.

SARS-CoV transmission was relatively inefficient, since it only spread after the onset of disease through direct contact with infected individuals. Thus, the outbreak was largely contained within households and healthcare settings (52). The outbreak was controllable by quarantining as a result of the relatively ineffective transmission of SARS-CoV. (53).

A pandemic of respiratory infection was documented when HCoV-OC43 crossed species to infect humans from domestic animals around 1890 (54). It has been reported that bats might transmit HCoV-229E to humans directly. MERS-CoV's evolutionary origin from bats is recognized and has also been confirmed by subsequent findings (55). Besides the different types of animal hosts, three major viral factors are also critical in facilitating CoVs to cross barriers to species (56). First, their relatively high rates of mutation in RNA replication. CoVs have a proof-reading exoribonuclease, deletion of which results in exceedingly high mutability and attenuation or even inviability. CoV mutation rates are approximately one million times higher than their hosts' (57).

EPIDEDEMIOLOGY

About 15-30% to the total respiratory tract infections in humans occurs due to HCoV-229E and HCoV-OC43 coronaviruses each year. These viruses target mainly the individuals with weak immunity such as the infants, the people of older age group, and the ones with other chronic diseases. The mortality rate of SARS-CoV outbreak was 9%. Around 8098 cases of SARS were identified during this epidemic, and 774 of those infected cases died from the infection. The mortality rate in the elderly population (over 60 years) was higher (50 per cent) (74).

Coryza, conjunctivitis, fever, and bronchiolitis occur frequently in HCoV-NL63 disease (75). HCoV-HKU1 was confirmed to be associated with acute asthmatic exacerbation, in addition to community-acquired pneumonia and bronchiolitis. HCoV-HKU1 was found worldwide , causing mild respiratory diseases, similar to HCoV-NL63, HCoV-229E and HCoV-OC43 (76).

The major clinical features of SARS infection include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache and dyspnoea but diarrhea occurs in 40-70% of patients after hospital admission. Respiratory failure is the main complication of SARS; at least 50% patients need additional oxygen during the acute period, while about 20 % of patients progress to acute respiratory distress syndrome that requires intrusive mechanical ventilation assistance. severity is generally mild in infected young children (77).

In comparison to SARS, many MERS patients have experienced acute renal failure, which is currently unusual among HCoV-caused diseases for MERS. About 30 per cent of patients with gastrointestinal symptoms such as diarrhea and vomiting (78-80) are present.

The SARS-CoV-2 virus can survive 2 hours in the air. SARS-CoV-2 incubation period is about 3-6 days post-

Virus	Genus	Incubation Period	Natural host	Clinical Symptoms
HCoV-229E	alpha-CoV	2-5 days	bats	Malaise, Headache, Nasal discharge, sore throat, fever, cough (58-61).
HCoV-OC43	Beta-CoV	2-5 days	rodents	Malaise, Headache, Nasal discharge, sore throat, fever, cough (62).
SARS-CoV	Beta-CoV	2-11 days	bats	Fever, myalgia, headache, malaise, dry cough, dyspnea, respiratory distress, diarrhea (63-65).
HCoV-NL63	Alpha-CoV	2-4 days	bats	Cough, rhinorrhea, tachypnea, fever, hypoxiaCroup (66-67).
HCoV-HKU1	Beta-CoV	2-4 days	rodents	Fever, running nose, cough, dyspnea (68-69).
MERS-CoV	Beta-CoV	2-13 days	bats	Sorethroat, fever, cough, myalgia, arthralgia, dyspnea, pneumonia, diarrhea and vomiting, acute renal impairment (70-72).
SARS-CoV-2	Beta-CoV	3-6 days	Bats	fever, dry cough, myalgia, dyspnea, headache, diarrhea (73).

Table 1: Comparison of Clinical Features of Human Pathogenic HCoVs

infection. Though people of all ages are vulnerable to SARSCoV-2 infection, older adults with comorbidity are at higher risk(81-83). The respiratory droplets are considered the primary route of transmission of SARS-CoV-2 up to now. Nevertheless, the faecal-oral transmission route is also thought to serve as another form of SARS-CoV-2 transmission, but recent studies show no evidence of viral nucleic acid in the faecal samples of patients with pneumonia (84).

CONCLUSION

Over the last 50 years , many different coronaviruses have emerged which cause a wide variety of human and veterinary diseases. A lot of aspects of viral replication and pathogenesis will continue to be explored in future work on coronaviruses. The virus and host involved a variety of factors in viral infection and subsequent pathogenesis. In this review, we first showed human pathogenic corona viruses their genome structure and how viral factors could manipulate the pathogenesis. We also highlighted how multiple cellular and viral factors responsible for their pathogenesis and how coronaviruses can be transmit. Phylogenetic research in the history of HCoVs has provided evidence for interspecies transmission events. These types of studies should help us refine and focus on controlling and treating Covid-19. The SARS-CoV-2 has a significant economic and social effect on the population. Several aspects of the covid-19 outbreak, including propagation mechanisms and the broad range of clinical disease, are not yet completely understood.

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