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MLS 406

Virology assignment

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QUESTION: Discuss the etiology,origin,structure,pathophysiology of COVID-19

Coronaviruses are a family of eneveloped single-stranded, positive-strand RNA viruses classified within the nidovirales order. This coronavirus family consists of pathogens of many animal species and of humans, including the respiratory syndrome coronavirus (SARS-CoV).

**ETIOLOGY OF CORONAVIRUS-19(COVID-19)**

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome corona virus 2(SARS-CoV-2). Coronavirus is a family of viruses associated with a wide variety of infections, from the common cold to serious infections including SARS and MERS. SARS-COV-2, the virus that causes the COVID-19 infection, emerged in China in late 2019 as a novel form of the Coronavirus. It is unclear exactly where the virus originated, but it is quite likely that there was viral mutation in animal hosts that allowed the virus to infect humans, and those who had contact with these animals developed the first cases. Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, SARS, MERS), and others that circulate among mammals (e.g., bats, camels) and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.

The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019-20 coronavirus pandemic. Common symptoms include fever,cough , and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhea, sore throat, loss of smell, and abdominal pain. While the majority of cases result in mild symptoms, some progress to viral pneumonia and multiple organ failure, As of 28 March 2020, the overall rates of death per number of diagnosed cases is 4.7 percent; ranging from 0.2 percent to 15 percent according to age group and other health problems.In comparison, the mortality rate of the 1918 flu pandemic was approximately 3% to 5%.

The virus is spread mainly through close contact and via respiratory droplets produced when people cough or sneeze. Respiratory droplets may be produced during breathing but the virus is not generally airborne. People may also contract COVID-19 by touching a contaminated surface and then their face. It is most contagious when people are symptomatic, although spread may be possible before symptoms appear. The virus can survive on surfaces up to 72 hours. Time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.

SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to severe acute respiratory syndrome (SARS)-like coronaviruses from bats, but it is distinct from SARS-CoV and Middle East respiratory syndrome (MERS)-CoV.

A preliminary study suggests that there are two major types (or strains) of the SARS-CoV-2 virus in China, designated L and S. The L type was found to be more prevalent during the early stages of the outbreak in Wuhan City and may be more aggressive (although this is speculative), but its frequency decreased after early January.

The disease is caused by the severe acute respiratory syndrome (SARS-CoV-2). It is primarily spread between people during close contact and via respiratory droplets from coughs and sneezes. A study investigating the rate of decay of the virus found no viable viruses after four hours on copper, 24 hours on cardboard, 72 hours on stainless steel, and 72 hours on plastic. However, detection rates did not reach 100% and varied between surface type (limit of detection was 3.33×100.5 per liter of air for aerosols, 100.5 TCID50 per milliliter of medium for plastic, steel, and cardboard, and 101.5 TCID50 per milliliter of medium for copper). Estimation of the rate of decay with a Bayesian regression model suggests that viruses may remain viable up to 18 hours on copper, 55 hours on cardboard, 90 hours on stainless steel, and over 100 hours on plastic. The virus remained viable in aerosols throughout the time of the experiment (three hours). The virus has also been found in faeces, and transmission through faeces is being researched.

The disease spreads faster where people are close together or travel between areas. Travel restrictions can reduce the basic reproduction number from 2.35 to 1.05, allowing the epidemic to be more manageable.

An observational study of nine people found no vertical transmission from mother to the newborn.

The virus has been found in the faeces of as many as 53% of hospitalised people and more anal swab positives have been found than oral swab positives in the later stages of infection. The virus was found in faeces from one to twelve days, and seventeen percent of patients continued to present the virus in faeces after no longer presenting them in respiratory samples, indicating that the viral gastrointestinal infection and the potential fecal-oral transmission can last even after viral clearance in the respiratory tract. Reoccurrence of the virus has also been detected through anal swabs suggesting a shift from more oral positive during the early stages of the disease to more anal positive during later periods.

**ORIGIN**

A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or "wet" market, suggesting a zoonotic origin of the virus.While the potential animal reservoir and intermediary host(s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed.

The analysis of public genome sequence data from SARS-CoV-2 and related viruses found no evidence that the virus was made in a laboratory or otherwise engineered.

By comparing the available genome sequence data for known coronavirus strains, we can firmly determine that SARS-CoV-2 originated through natural processes," said Kristian Andersen, PhD, an associate professor of immunology and microbiology at Scripps Research and corresponding author on the paper.

In addition to Andersen, authors on the paper, "The proximal origin of SARS-CoV-2," include Robert F. Garry, of Tulane University; Edward Holmes, of the University of Sydney; Andrew Rambaut, of University of Edinburgh; W. Ian Lipkin, of Columbia University.

Coronaviruses are a large family of viruses that can cause illnesses ranging widely in severity. The first known severe illness caused by a coronavirus emerged with the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic in China. A second outbreak of severe illness began in 2012 in Saudi Arabia with the Middle East Respiratory Syndrome (MERS).

On December 31 of last year, Chinese authorities alerted the World Health Organization of an outbreak of a novel strain of coronavirus causing severe illness, which was subsequently named SARS-CoV-2. As of February 20, 2020, nearly 167,500 COVID-19 cases have been documented, although many more mild cases have likely gone undiagnosed. The virus has killed over 6,600 people.

Shortly after the epidemic began, Chinese scientists sequenced the genome of SARS-CoV-2 and made the data available to researchers worldwide. The resulting genomic sequence data has shown that Chinese authorities rapidly detected the epidemic and that the number of COVID-19 cases have been increasing because of human to human transmission after a single introduction into the human population. Andersen and collaborators at several other research institutions used this sequencing data to explore the origins and evolution of SARS-CoV-2 by focusing in on several tell-tale features of the virus.

The scientists analyzed the genetic template for spike proteins, armatures on the outside of the virus that it uses to grab and penetrate the outer walls of human and animal cells. More specifically, they focused on two important features of the spike protein: the receptor-binding domain (RBD), a kind of grappling hook that grips onto host cells, and the cleavage site, a molecular can opener that allows the virus to crack open and enter host cells.

**Evidence for natural evolution**

The scientists found that the RBD portion of the SARS-CoV-2 spike proteins had evolved to effectively target a molecular feature on the outside of human cells called ACE2, a receptor involved in regulating blood pressure. The SARS-CoV-2 spike protein was so effective at binding the human cells, in fact, that the scientists concluded it was the result of natural selection and not the product of genetic engineering.

This evidence for natural evolution was supported by data on SARS-CoV-2's backbone -- its overall molecular structure. If someone were seeking to engineer a new coronavirus as a pathogen, they would have constructed it from the backbone of a virus known to cause illness. But the scientists found that the SARS-CoV-2 backbone differed substantially from those of already known coronaviruses and mostly resembled related viruses found in bats and pangolins.

"These two features of the virus, the mutations in the RBD portion of the spike protein and its distinct backbone, rules out laboratory manipulation as a potential origin for SARS-CoV-2" said Andersen.

Josie Golding, PhD, epidemics lead at UK-based Wellcome Trust, said the findings by Andersen and his colleagues are "crucially important to bring an evidence-based view to the rumors that have been circulating about the origins of the virus (SARS-CoV-2) causing COVID-19."

"They conclude that the virus is the product of natural evolution," Goulding adds, "ending any speculation about deliberate genetic engineering."

**Possible origins of the virus**

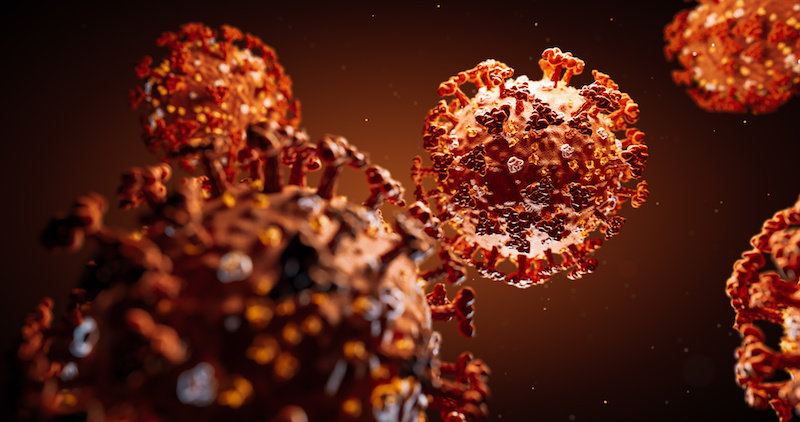
The most likely origins for SARS-CoV-2 followed one of two possible scenarios.

In one scenario, the virus evolved to its current pathogenic state through natural selection in a non-human host and then jumped to humans. This is how previous coronavirus outbreaks have emerged, with humans contracting the virus after direct exposure to civets (SARS) and camels (MERS). The researchers proposed bats as the most likely reservoir for SARS-CoV-2 as it is very similar to a bat coronavirus. There are no documented cases of direct bat-human transmission, however, suggesting that an intermediate host was likely involved between bats and humans.

In this scenario, both of the distinctive features of SARS-CoV-2's spike protein -- the RBD portion that binds to cells and the cleavage site that opens the virus up -- would have evolved to their current state prior to entering humans. In this case, the current epidemic would probably have emerged rapidly as soon as humans were infected, as the virus would have already evolved the features that make it pathogenic and able to spread between people.

In the other proposed scenario, a non-pathogenic version of the virus jumped from an animal host into humans and then evolved to its current pathogenic state within the human population. For instance, some coronaviruses from pangolins, armadillo-like mammals found in Asia and Africa, have an RBD structure very similar to that of SARS-CoV-2. A coronavirus from a pangolin could possibly have been transmitted to a human, either directly or through an intermediary host such as civets or ferrets.

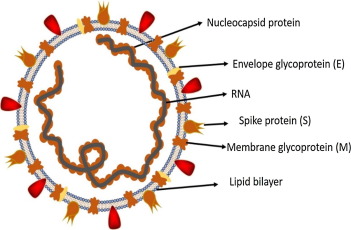
Then the other distinct spike protein characteristic of SARS-CoV-2, the cleavage site, could have evolved within a human host, possibly via limited undetected circulation in the human population prior to the beginning of the epidemic. The researchers found that the SARS-CoV-2 cleavage site, appears similar to the cleavage sites of strains of bird flu that has been shown to transmit easily between people. SARS-CoV-2 could have evolved such a virulent cleavage site in human cells and soon kicked off the current epidemic, as the coronavirus would possibly have become far more capable of spreading between people.



**Structure**

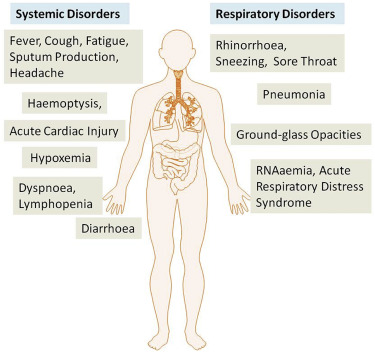
All coronaviruses contain specific genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation. The glycoprotein spikes on the outer surface of coronaviruses are responsible for the attachment and entry of the virus to host cells . The receptor-binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts. Other coronaviruses mostly recognize aminopeptidases or carbohydrates as a key receptor for entry to human cells while SARS-CoV and MERS-CoV recognize exopeptidases. The entry mechanism of a coronavirus depends upon cellular proteases which include, human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes MERS-coronavirus employs dipeptidyl peptidase 4 (DPP4), while HCoV-NL63 and SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a key receptor.

SARS-CoV-2 possesses the typical coronavirus structure with spike protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins. The spike protein of SARS-CoV-2 contains a 3-D structure in the RBD region to maintain the van der Waals forces. The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor.



**Symptoms**

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days . The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days . This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia . Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death .In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities .



**Transmission dynamics**

Transmission dynamics of the virus are currently unknown and the situation is rapidly evolving. Person-to-person spread has been confirmed in community and healthcare settings, with local transmission reported in many countries around the world.It is uncertain how easily the virus spreads between people, but transmission in chains involving several links is increasingly recognized. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs, or via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care.

The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours). This study also found that the virus was viable in aerosol particles for up to 3 hours; however, aerosols were generated using high-powered apparatus that do not reflect normal human cough conditions or a clinical setting where aerosol-generating procedures are performed. The World Health Organization has confirmed that there have been no reports of airborne transmission.

The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, saliva, tears, cerebrospinal fluid, and conjunctival secretions.

An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before the 1st January 2020 were linked to the Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market. This confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers.

Asymptomatic transmission

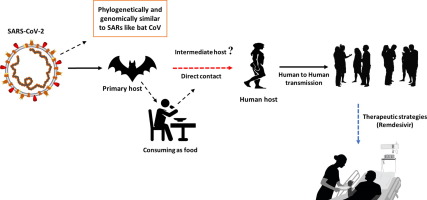
Estimating the prevalence of asymptomatic cases in the population is difficult. The best evidence so far comes from the Diamond Princess cruise ship, which was quarantined with all passengers and crew members repeatedly tested and closely monitored. A modeling study found that approximately 700 people with confirmed infection (18%) were asymptomatic.

Superspreading events

Multiple superspreading events have been reported with COVID-19. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages.

Perinatal transmission

It is unknown whether perinatal transmission (including transmission via breastfeeding) is possible. Retrospective reviews of pregnant women with COVID-19 found that there is no evidence for intrauterine infection in women with COVID-19. There have been case reports of infection in neonates born to mothers with COVID-19, and virus-specific antibodies have also been detected in neonatal serum samples.

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**Pathophysiology**

Incubation period

Current estimates of the incubation period range from 1 to 14 days, according to the World Health Organization and the Centers for Disease Control and Prevention. The median incubation period has been estimated to be approximately 5 days. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. However, a preprint study (not peer reviewed) suggests that the median incubation period may be longer (7 days in adults and 9 days in children with a range of 0 to 33 days). Transmission may be possible during the incubation period.

Reproductive number

Preliminary reports suggest that the reproductive number (R₀), the number of people who acquire the infection from an infected person, is approximately 2.2. om However, as the situation is still evolving, the R₀ may actually be higher or lower.

Angiotensin-converting enzyme-2 receptor

While the pathophysiology of this condition is currently unknown, it is thought that the virus binds to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests that it may have a similar pathogenesis to SARS.However, a unique structural feature of the spike glycoprotein receptor binding domain of SARS-CoV-2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE2 on host cells compared with SARS-CoV

A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses. Coutard B, Valle C, de Lamballerie X, et al. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade.

Antiviral Based on an analysis of single-cell RNA sequencing datasets derived from major human physiologic systems, the organs considered more vulnerable to SARS-CoV-2 infection due to their ACE2 expression levels include the lungs, heart, esophagus, kidneys, bladder, and ileum. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection.

Mechanistic evidence from other coronaviruses suggests that SARS-CoV-2 may downregulate ACE2, leading to a toxic overaccumulation of angiotensin-II, which may induce acute respiratory distress syndrome and fulminant myocarditis. Viral load and shedding

High viral loads have been detected in nasal and throat swabs soon after symptom onset, and it is thought that the viral shedding pattern may be similar to that of patients with influenza. An asymptomatic patient was found to have a similar viral load compared with symptomatic patients al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort

The duration of viral shedding has been estimated to be between 8 and 20 days after symptoms resolve. Also, the virus has been detected in sputum and feces for up to 39 days after pharyngeal swabs became negative. However, it is unclear whether the virus is capable of transmission later in the course of the disease or after negative pharyngeal swabs.

**Classification**

World Health Organization: clinical classification of COVID-19 based on World Health Organization.

**Mild illness**

Patients with uncomplicated upper respiratory tract viral infection may have nonspecific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting.

Older and/or immunosuppressed patients may present with atypical symptoms.

Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events (e.g., dyspnea, fever, gastrointestinal symptoms, fatigue) may overlap with COVID-19 symptoms.

**Pneumonia**

Adults: pneumonia with no signs of severe pneumonia (see below) and no need for supplemental oxygen.

Children: pneumonia with cough or difficulty breathing plus fast breathing (i.e., <2 months of age: ≥60 breaths/minute; 2-11 months of age: ≥50 breaths/minute; 1-5 years years of age: ≥40 breaths/minute) and no signs of severe pneumonia (see below).

Severe pneumonia in adults and adolescents

Fever or suspected respiratory infection plus one of the following:

Respiratory rate >30 breaths/minute

Severe respiratory distress

SpO₂ ≤93% on room air.

Severe pneumonia in children

Cough or difficulty breathing plus at least one of the following:

Central cyanosis or SpO₂ <90%

Severe respiratory distress (e.g., grunting, very severe chest indrawing)

Signs of pneumonia with a general danger sign (i.e., inability to breastfeed or drink, lethargy or unconsciousness, or convulsions).

Other signs of pneumonia may be present in children including chest indrawing or fast breathing (i.e., <2 months of age: ≥60 breaths/minute; 2-11 months of age: ≥50 breaths/minute; 1-5 years years of age: ≥40 breaths/minute).

While the diagnosis is made on clinical grounds, chest imaging may identify or exclude some pulmonary complications

**REFRENCES**

* Lancet. 2020 Feb 15;395(10223):497-506. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext <http://www.ncbi.nlm.nih.gov/pubmed/31986264>
* Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7 <http://www.ncbi.nlm.nih.gov/pubmed/32007143?tool=bestpractice.com>
* Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. 2020 Jan 29 [https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 <http://www.ncbi.nlm.nih.gov/pubmed/31995857>.
* Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019.. 2020 Feb 20 https://www.nejm.org/doi/full/10.1056/NEJMoa2001017 <http://www.ncbi.nlm.nih.gov/pubmed/31978945>
* Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus Lancet. 2020 Feb 22;395(10224):565-74. <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8> <http://www.ncbi.nlm.nih.gov/pubmed/32007145>
* Paraskevis D, Kostaki EG, Magiorkinis G, et al.. Infect Genet Evol. 2020 Jan 29;79:104212. <http://www.ncbi.nlm.nih.gov/pubmed/32004758>
* Emerg Infect Dis. 2020 Mar 18;26. https://wwwnc.cdc.gov/eid/article/26/6/20-0495\_article <http://www.ncbi.nlm.nih.gov/pubmed/32187007>
* Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. March 2020 [internet publication].

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

* Zhu N, Zhang D, Wang W, et al. https://www.nejm.org/doi/full/10.1056/NEJMoa2001017 <http://www.ncbi.nlm.nih.gov/pubmed/31978945.com>
* Lu R, Zhao X, Li J, et al. binding. Lancet. 2020 Feb 22;395(10224):565- <http://www.ncbi.nlm.nih.gov/pubmed/32007145>
* Ren LL, Wang YM, Wu ZQ, et al.. Chin Med J (Engl). 2020 Jan 30 [http://www.ncbi.nlm.nih.gov/pubmed/32004165
* Ji W, Wang W, Zhao X, et al. Cross-species transmission of the newly identified coronavirus 2019-nCoV. J Med Virol. 2020 Apr;92(4):433-40. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25682 <http://www.ncbi.nlm.nih.gov/pubmed/31967321>.
* Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 .Juang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5> <http://www.ncbi.nlm.nih.gov/pubmed/31986264?tool=bestpractice.com>
* Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020 Jan 29 . https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 <http://www.ncbi.nlm.nih.gov/pubmed/31995857>
* Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-23. <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30154-9> http://www.ncbi.nlm.nih.gov/pubmed/31986261.
* Burke RM, Midgley CM, Dratch A, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 - United States, January-February 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 6;69(9):245-6. https://www.cdc.gov/mmwr/volumes/69/wr/mm6909e1.htm http://www.ncbi.nlm.nih.gov/pubmed/32134909 outbreak.
* Curr Biol. 2020 Mar 13 van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. https://www.nejm.org/doi/full/10.1056/NEJMc2004973 <http://www.ncbi.nlm.nih.gov/pubmed/32182409?tool=bestp>.
* World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. March 2020 . https://www.who.int/publications-detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
* Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. January 2020 [internet publication]. <https://www.biorxiv.org/content/10.1101/2020.01.30.927806v1>
* Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020 Dec;9 https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1729071 <http://www.ncbi.nlm.nih.gov/pubmed/32065057>
* To KK, Tsang OT, Chik-Yan Yip C, et al. ConsistentEmerg Infect Dis. 2020 Mar 18;26. https://wwwnc.cdc.gov/eid/article/26/6/20-0495\_article <http://www.ncbi.nlm.nih.gov/pubmed/32187007>
* Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. March 2020 [internet publication].

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

* Zhu N, Zhang D, Wang W, et al. https://www.nejm.org/doi/full/10.1056/NEJMoa2001017 <http://www.ncbi.nlm.nih.gov/pubmed/31978945>
* Lu R, Zhao X, Li J, et al. binding. Lancet. 2020 Feb 22 <http://www.ncbi.nlm.nih.gov/pubmed/32007145>
* Ren LL, Wang YM, Wu ZQ, et al.. Chin Med J (Engl). 2020 Jan 30 http://www.ncbi.nlm.nih.gov/pubmed/32004165
* . Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China