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OPEN TEST

ORIGIN OF COVID 19

COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. Corona virus comprises of a large family of viruses that are common in human beings as animals. Coronaviruses belong to the family Coronaviridae in the order Nidovirales. They can be classified into four genera; Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. They are further divided into seven;

229E (ALPHA CORONAVIRUS)
NL63 (ALPHA CORONAVIRUS)
NL63 (BETA CORONAVIRUS)
0C43 (BETA CORONAVIRUS)
HKU1 (BETA CORONAVIRUS)
MERS-COV (BETA CORONAVIRUS THAT CAUSES MIDDLE EAST RESPIRATORY SYNDROME)
SARS-COV (BETA CORONAVIRUS THAT CAUSES SEVERE ACUTE RESPIRATORY SYNDROME) OR SARS-COV-2 (THE NOVEL CORONAVIRUS THAT CAUSE SEVERE ACUTE RESPIRATORY SYNDROME).

The SARS-C0V-2 is the one that causes the COVID 19. Towards December 2019, this novel corona virus was identified as a cause of lower. Respiratory tract infections in Wuhan, a city in the Hubei Province of China. It, rapidly spread resulting to an epidemic throughout China and then gradually spreading to other parts of the world in pandemic proportions. It has affected almost every continent in the world, except Antartica. 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.

ETIOLOGY OF CORONAVIRUS

CAUSES

It's unclear exactly how contagious the new coronavirus is. It appears to spread from person to person among those in close contact. It may be spread by respiratory droplets released when someone with the virus coughs or sneezes.
It may also be spread if a person touches a surface with the virus on it and then touches his or her mouth, nose or eyes.

RISK FACTORS

Risk factors for COVID-19 appear to include:

- Recent travel from or residence in an area with ongoing community spread of COVID-19 as determined by CDC or WHO.
- Close contact with someone who has COVID-19 — such as when a family member or health care worker takes care of an infected person.

SYMPTOMS

Signs and symptoms of COVID-19 may appear two to 14 days after exposure and can include:

- Fever
- Cough
- Shortness of breath or difficulty breathing

Other symptoms can include:

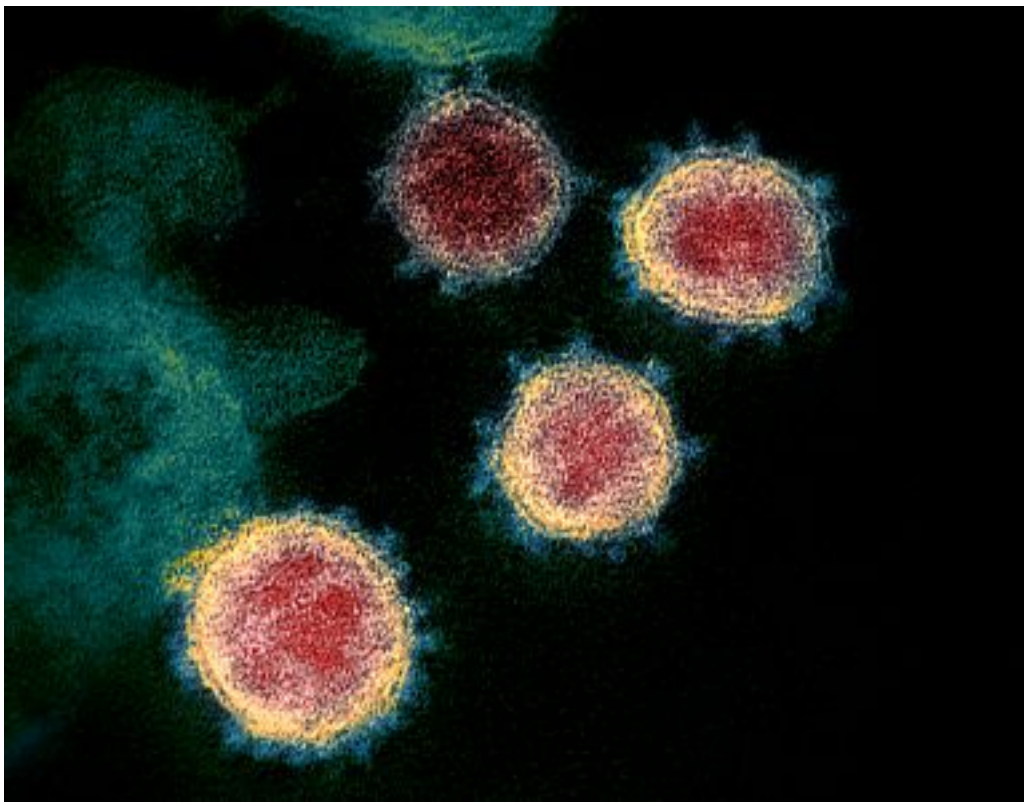
- Tiredness
- Aches
- Runny nose
- Sore throat

The severity of COVID-19 symptoms can range from very mild to severe. Some people have no symptoms. People who are older or have existing chronic medical conditions, such as heart or lung disease or diabetes, may be at higher risk of serious illness. This is similar to what is seen with other respiratory illnesses, such as influenza.

STRUCTURE OF CORONAVIRUS

Coronavirus virions are spherical to pleomorphic enveloped particles. The envelope is studded with projecting glycoproteins, and surrounds a core consisting of matrix protein enclosed within which is a single strand of positive-sense RNA associated with nucleoprotein. The envelope glycoproteins are responsible for attachment to the host cell and also carry the main antigenic epitopes, particularly the epitopes recognised by neutralising antibodies.

Like other coronaviruses, SARS-CoV-2 particles are spherical and have proteins called spikes protruding from their surface. These spikes latch onto human cells, then undergo a structural change that allows the viral membrane to fuse with the cell membrane. The viral genes can then enter the host cell to be copied, producing more viruses.



Transmission electron microscope image shows SARS-CoV-2, the virus that causes COVID-19, isolated from a patient in the U.S. Virus particles are emerging from the surface of cells cultured in the lab. The spikes on the outer edge of the virus particles give coronaviruses their name.

The coronavirus spike protein is a multifunctional molecular machine that mediates coronavirus entry into host cells. It first binds to a receptor on the host cell surface through its S1 subunit and then fuses viral and host membranes through its S2 subunit. Two domains in S1 from different coronaviruses recognise a variety of host receptors, leading to viral attachment. The spike protein exists in two structurally distinct conformations, perfusion and post-fusion. The transition from perfusion to post-fusion conformation of the spike protein must be triggered, leading to membrane fusion.

The coronavirus spike contains three segments: a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail. The ectodomain consists of a receptor-binding subunit S1 and a membrane-fusion subunit S2. Electron microscopy studies revealed that the spike is a clove-shaped trimer with three S1 heads and a trimeric S2 stalk. During virus entry, S1 binds to a receptor on the host cell surface for viral attachment, and S2 fuses the host and viral membranes, allowing viral genomes to enter host cells. Receptor binding and membrane fusion are the initial and critical steps in the coronavirus infection cycle; they also serve as primary targets for human inventions.

The coronavirus spike is believed to be a member of the class I viral membrane fusion proteins that also include those from influenza virus, human immunodeficiency virus (HIV), and Ebola virus. Among these proteins, the hemagglutinin glycoprotein (HA) of the influenza virus is arguably the best studied. HA is expressed as a single-chain precursor. During molecular maturation, it triremes and is cleaved by host proteases into receptor-binding subunit HA1 and

membrane-fusion subunit HA2, which still associate together through noncovalent interactions. This perfusion state of HA on the newly packaged virions is a proteolytically primed and metastable trimer. During cell entry, HA1 binds to a sugar receptor on the host cell surface for viral attachment, and then HA1 dissociates and HA2 undergoes a dramatic conformational change to transition to the post-fusion state. During this transition, three pairs of heptad repeat regions HR-N and HR-C in trimeric HA2 form a six-helix bundle structure. Three previously buried hydrophobic fusion peptides in trimeric HA2 become exposed and insert into the target host membrane. The fusion peptides and transmembrane anchors are eventually positioned on the same end of the six-helix bundle, bringing the viral and host membranes together to fuse. Because the six-helix bundle structure is energetically stable, a large amount of energy is released during the conformational transition of HA, driving membrane fusion forward. However, an initial energy barrier for the conformational transition of HA must be overcome through the aforementioned proteolytic priming and one or more subsequent triggers. These triggers can be receptor binding (e.g., HIV), low pH (e.g., influenza virus), or a combination of the two (e.g., avian leucosis virus). Consequently, membrane fusion occurs either on the host cell surface (e.g., HIV) or in the endosomes (e.g., influenza virus).

PATHOPHYSIOLOGY OF CORONAVIRUS

Coronaviruses infect many species of animals including humans, causing acute and chronic diseases. This focuses primarily on the pathogenies of murine coronavirus mouse (MHV) and severe acute respiratory coronavirus (SARS-CoV). MHV is a collection of strains, which provide models systems for the study of viral tropism and pathogenesis in several organs systems, including the central nervous system, the liver, and the lung, and has been cited as providing one of the few animal models for the study of chronic demynelating such as multiple sclerosis. SARS CoV emerged in the human population in China in 2002, causing a worldwide epidemic with severe morbidity and high mortality rates, particularly in older individuals. We review the pathogenesis of both viruses and the several reverse genetics systems that made much of these studies possible. We also review the functions of coronavirus proteins, structural, enzymatic, and accessory, with an emphasis on roles in pathogenesis. Structural proteins in addition to their roles in Virion structure and morphogenesis also contribute significantly to viral spread *in vivo* and in antagonising host cell responses. Nonstructural proteins include the small accessory proteins that are not at all conserved between MHV and SARS-CoV and the 16 conserved proteins encoded in the replicase locus, many of which have enzyme activities in RNA metabolism or protein processing in addition to functions in antagonising host response.

Clinically, patients with SARS had a triphasic pattern of disease. Patients most frequently initially presented with fever, a nonproductive cough, sore throat, and myalgia, with dyspnea often not becoming a prominent feature until days 7–14 of the illness. During the second phase of the illness, dyspnea and hypoxia, with continued fever and frequently accompanied by diarrhea, became more prominent. Some patient's respiratory status continued to deteriorate and they developed acute respiratory distress syndrome often requiring mechanical respiration by the

third week. Deaths occurred as early as day 4 and as late as 108 days after onset. Virus shedding from the respiratory tract generally peaked around day 10 and subsequently declined. Virus excretion from the GI tract was frequently present. IgG antibodies were detected 10–15 days after onset and their development was associated with decreased virus load. The severity of the disease was correlated with increasing age, with mortality reaching 50% for patients over 60.

The primary pathology observed at autopsy of patients that succumbed to infection was diffuse alveolar damage. The lungs of patients that died in the early phases of the disease contained hyaline membranes, edema, fibrin exudates, small vessel thrombi, loss and sloughing of pneumocytes, and a mixed cellular infiltrate of lymphocytes, macrophages, and polymorphonuclear leukocytes. Multinucleated giant cells that carried markers for macrophages and pneumocytes were frequently present. At later phases of the disease, a histologic picture of an organising pneumonitis and consolidation, with type II pneumocyte hyperplasia, squamous metaplasia, and bronchiolitis obilterans, was found. The association of worsening clinical progression with declining virus loads and the onset of an immunological response, plus the presence of markedly elevated cytokines levels suggested that severe lung damage was largely immunopathological in nature.

Host factors have also been implicated in the pathogenesis of SARS, primarily from work on murine models. Multiple SARS-CoV proteins have been reported to interact with components of the innate immune system to evade an antiviral interferon response, and these are discussed below with the individual proteins that have been implicated in this process. The expression of ACE2, the SARS-CoV receptor, on the surface of cells is down-regulated after infection with SARS-CoV. The mechanism of this down-regulation appears to be due to internalization of ACE2 during SARS-CoV entry and by induction of tumor necrosis factor alpha converting enzyme activity or Adams family metalloproteases which cleave the ACE2 extracellular domain from its transmembrane domain, resulting in shedding of this domain into the media. ACE2 has a pneumoprotective effect on acute lung injury induced by acid injury, and instillation of a recombinant fusion protein containing the SARS S protein RBD increased acute lung injury by acid. These results have led to the hypothesis that the binding of SARS-CoV S protein is a virulence factor for SARS above and beyond its role in viral attachment and entry. Furthermore, in a mouse model, SARS-CoV replication in myocardium during pulmonary infection correlated with down-regulation of ACE2 in the heart. This data combined with the detection of inflammatory lesions and viral replication in myocardial tissue of patients that died of SARS suggests that down-regulation of ACE2 and cardiac infection could contribute to SARS mortality. Several different proteases, including cathepsin L and the serine protease TMPRSS2 have been reported to affect SARS-CoV entry through cleavage of the spike protein and activation of its membrane fusion activity. A large number of noncoding RNAs have also been demonstrated to be differentially regulated during infection of mice with with MA15. About 40% of these noncoding RNAs are similarly regulated during *in vitro* infection of mouse embryonic fibroblasts with mouse-adapted influenza virus and by interferon treatment, suggesting that these noncoding RNAs may play a role

in regulating the host response to virus infection, particularly the innate immune response.

REFERENCES

Almazan et al., 2000
F. Almazan, J.M. Gonzalez, Z. Penzes, A. Izeta, E. Calvo, J. Plana-Duran, L. Enjuanes
Engineering the largest RNA virus genome as an infectious bacterial artificial chromosome
Proc. Natl. Acad. Sci. USA, 97 (2000), pp. 5516-5521
View Record in ScopusGoogle Scholar
Almazan et al., 2006
F. Almazan, M.L. Dediego, C. Galan, D. Escors, E. Alvarez, J. Ortego, I. Sola, S. Zuniga, S. Alonso, J.L. Moreno, A. Nogales, C. Capiscol, *et al.*
Construction of a severe acute respiratory syndrome coronavirus infectious cDNA clone and a replicon to study coronavirus RNA synthesis
J. Virol., 80 (2006), pp. 10900-10906
CrossRefView Record in ScopusGoogle Scholar
Almeida et al., 2007
M.S. Almeida, M.A. Johnson, T. Herrmann, M. Geralt, K. Wuthrich
Novel beta-barrel fold in the nuclear magnetic resonance structure of the replicase nonstructural protein 1 from the severe acute respiratory syndrome coronavirus
J. Virol., 81 (2007), pp. 3151-3161
CrossRefView Record in ScopusGoogle Scholar
Alvarez et al., 2010
E. Alvarez, M.L. DeDiego, J.L. Nieto-Torres, J.M. Jimenez-Guardeno, L. Marcos-Villar, L. Enjuanes
The envelope protein of severe acute respiratory syndrome coronavirus interacts with the non-structural protein 3 and is ubiquitinated
Virology, 402 (2010), pp. 281-291
ArticleDownload PDFView Record in ScopusGoogle Scholar
An et al., 1999
S. An, C.J. Chen, X. Yu, J.L. Leibowitz, S. Makino
Induction of apoptosis in murine coronavirus-infected cultured cells and demonstration of E protein as an apoptosis inducer
J. Virol., 73 (1999), pp. 7853-7859
CrossRefView Record in ScopusGoogle Scholar
Arbely et al., 2004
E. Arbely, Z. Khattari, G. Brotons, M. Akkawi, T. Salditt, I.T. Arkin
A highly unusual palindromic transmembrane helical hairpin formed by SARS coronavirus E protein

Ksiazek TG, **Erdman D**, **Goldsmith CS**, **Zaki SR**, **Peret T**, et al. **2003**. A novel coronavirus associated with severe acute respiratory syndrome. N. Engl. J. Med. 348:1953–66
CrossrefMedlineWeb of Science ®Google Scholar

Peiris JSM, **Lai ST**, **Poon LLM**, **Guan Y**, **Yam LYC**, et al. **2003**. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361:1319–25
CrossrefMedlineWeb of Science ®Google Scholar

Marra MA, **Jones SJM**, **Astell CR**, **Holt RA**, **Brooks-Wilson A**, et al. **2003**. The genome sequence of the SARS-associated coronavirus. Science 300:1399–404.

N. Zhong, B. Zheng, Y. Li, L. Poon, Z. Xie, K. Chan, *et al.*
Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003
The Lancet, 362 (9393) (2003), pp. 1353-1358
ArticleDownload PDFView Record in ScopusGoogle Scholar

N. Wang, X. Shi, L. Jiang, S. Zhang, D. Wang, P. Tong, *et al.*
Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4
Cell Res, 23 (8) (2013), p. 986
CrossRefView Record in ScopusGoogle Scholar

J. Cui, F. Li, Z.-L. Shi
Origin and evolution of pathogenic coronaviruses
Nat Rev Microbiol, 17 (3) (2019), pp. 181-192
CrossRefView Record in ScopusGoogle Scholar

C.-C. Lai, T.-P. Shih, W.-C. Ko, H.-J. Tang, P.-R. Hsueh
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges
Int J Antimicrob Agents, 105924 (2020)
Google Scholar

Organization WH. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. World Health Organization, 2020.
Google Scholar

J. Peiris, Y. Guan, K. Yuen
Severe acute respiratory syndrome
Nat Med, 10 (12) (2004), pp. S88-S97
CrossRefView Record in ScopusGoogle Scholar

K. Pyrc, B. Berkhout, L. Van Der Hoek
Identification of new human coronaviruses
Expert Review of Anti-infective Therapy, 5 (2) (2007), pp. 245-253
CrossRefView Record in ScopusGoogle Scholar

A. Rahman, A. Sarkar
Risk factors for fatal middle east respiratory syndrome coronavirus infections in Saudi Arabia: analysis of the WHO Line List, 2013–2018
Am J Public Health, 109 (9) (2019), pp. 1288-1293
CrossRefView Record in ScopusGoogle Scholar

Z.A. Memish, A.I. Zumla, R.F. Al-Hakeem, A.A. Al-Rabeeah, G.M. Stephens

Family cluster of Middle East respiratory syndrome coronavirus infections
N Engl J Med, 368 (26) (2013), pp. 2487-2494
CrossRefView Record in ScopusGoogle Scholar
C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao
A novel coronavirus outbreak of global health concern
The Lancet (2020)
Google Scholar