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 **THE ETIOLOGY, ORIGIN, STRUCTURE AND PATHOPHYSIOLOGY OF COVID-19**

INTRODUCTION:. The disease caused by an infection with SARS-CoV-2 is called COVID-19, which stands for coronavirus disease 2019. A corona virus is a kind of common virus that causes an infection in your nose, sinuses, or upper throat. Coronavirus disease 2019, or COVID-19, is a disease that can cause what doctors call a respiratory tract infection. It can [affect your upper respiratory tract](https://www.webmd.com/lung/coronavirus-covid-19-affects-body) (sinuses, nose, and throat) or lower respiratory tract (windpipe and lungs). The [COVID-19 outbreak](https://www.webmd.com/cold-and-flu/what-are-epidemics-pandemics-outbreaks) quickly spread around the world. It [spreads the same way other coronaviruses](https://www.webmd.com/lung/coronavirus-transmission-overview) do, mainly through person-to-person contact. Infections range from mild to serious. COVID-19 is one of seven types of coronavirus, including the ones that cause severe diseases like Middle East respiratory syndrome (MERS) and sudden acute respiratory syndrome (SARS). The other coronaviruses cause most of the colds that affect us during the year but aren’t a serious threat for otherwise healthy people.

**ETIOLOGY OF COVID-19:** The COVID-19 novel coronavirus is a new strain of coronavirus affecting humans. Some coronaviruses can cause illness similar to the common cold and others can cause more serious diseases such as Severe Acute Respiratory Syndrome ([SARS](https://www.who.int/csr/sars/en)) and Middle East Respiratory Syndrome ([MERS](https://www.who.int/emergencies/mers-cov/en)). CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes.
Studies to date suggest that the virus that causes COVID-19 is mainly transmitted through contact with respiratory droplets rather than through the air. The main way the disease spreads is through respiratory droplets expelled by someone who is coughing. The risk of catching COVID-19 from someone with no symptoms at all is very low. However, many people with COVID-19 experience only mild symptoms. This is particularly true at the early stages of the disease. It is therefore possible to catch COVID-19 from someone who has, for example, just a mild cough and does not feel ill.

**ORIGIN:** In early 2020, a new virus began generating headlines all over the world because of the unprecedented speed of its transmission. From its origins in a food market in Wuhan, China, in December 2019 to countries as far-flung as the United States and the Philippines, the virus (officially named SARS-CoV-2) has affected hundreds of thousands, with a rising death toll now over 17,000. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus. The severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1 influenza A, H1N1 2009 and Middle East respiratory syndrome coronavirus (MERS-CoV) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China. Only a decade later, another pathogenic coronavirus, known as Middle East respiratory syndrome coronavirus (MERS-CoV) caused an endemic in Middle Eastern countries.

**STRUCTURE**: Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length. COVID-19 (SARS-CoV-2) has approximately 79% sequence identity to SARS-CoV and 50% to MERS-CoV. In addition, homology modeling shows COVID-19 (SARS-CoV-2)  has a similar receptor-binding domain structure as SARS-CoV which suggests COVID-19 (SARS-CoV-2) uses Ace 2 receptors in humans for infection.  The structure of COVID-19 (SARS-CoV-2) consists of the following: a spike protein (S), hemagglutinin-esterease dimer (HE),  a membrane glycoprotein (M), an envelope protein (E) a nucleoclapid protein (N) and RNA.

* Spike protein (S) is heavily glycosylated, utilizes an N-terminal signal sequence to gain access to the ER and mediate attachment to host receptors. It is the largest structure and makes the distinct spikes on the surface of the virus. For most coronaviruses, S protein is cleaved by a host cell furin-like protease into two separate polypeptides S1 and S2.
* RNA is the genome of the virus.
* Nucleocapsid protein (N) binds to RNA in vitro and is heavily phosphorylated. N proteins binds the viral genome in a beads on a string type conformation. This protein likely helps tether the viral genome to replicase-transcriptase complex (RTC), and subsequently package the encapsulated genome into viral particles.
* Envelope protein (E) is found in small quantities in within the virus. It is most likely a transmembrane protein and with ion channel activity. The protein facilitates assembly and release of the virus and has other functions such as ion channel activity. It is not necessary for viral replication but it is for pathogenesis.
* Membrane protein (M) is the most abundant structural protein. It does not contain signal sequence and exists as a dimer in the virion. It may have two different conformations to enable it to promote membrane curvature as well as bind to nucleocapsid.
* Hemagglutinin-esterase dimer protein (HE) is present in a subset of betacoronaviruses. The protein binds sialic acids on surface glycoproteins. The protein activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa.

**PATHOPHYSIOLOGY**: 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.

 In summary; Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response. Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described. Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors. Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs.

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