**MATRIC NO: 16/MHS06/055**

**COURSE TITLE:** INTRODUCTION TO VIROLOGY

**COURSE CODE:** MLS 406

Coronaviruses (CoVs), enveloped positive-sense RNA viruses, are characterized by club-like spikes that project from their surface, an unusually large RNA genome, and a unique replication strategy. Coronaviruses cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease chickens to potentially lethal human respiratory infections. Here we provide a brief introduction to coronaviruses discussing their replication and pathogenicity, and current prevention and treatment strategies. We will also discuss the outbreaks of the highly pathogenic Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the recently identified Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

**ETIOLOGY.**

* 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.[[1]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop1)Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020 Jan 30 [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/32004165?tool=bestpractice.com 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.
* 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.[[16]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop16)Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-33. https://www.nejm.org/doi/full/10.1056/NEJMoa2001017 http://www.ncbi.nlm.nih.gov/pubmed/31978945?tool=bestpractice.com [[17]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop17)Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-74. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32007145?tool=bestpractice.com The full genome has been determined and published in GenBank. [GenBank external link opens in a new window](https://www.ncbi.nlm.nih.gov/genbank/)
* 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 relevance of this finding is unknown at this stage and further research is required.[[18]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop18)Tang X, Wu C, Li X, et al. On the origin and continuing evolution of SARS-CoV-2. Nat Sci Review. 2020 Mar 3 [Epub ahead of print]. https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa036/5775463

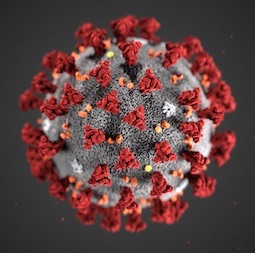


Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopicallyCenters for Disease Control and Prevention *.*

**ORIGIN OF VIRUS.**

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.[[19]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop19)Huang 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/fulltext http://www.ncbi.nlm.nih.gov/pubmed/31986264?tool=bestpractice.com [[20]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop20)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;395(10223):507-13. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32007143?tool=bestpractice.com [[21]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop21)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 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 http://www.ncbi.nlm.nih.gov/pubmed/31995857?tool=bestpractice.com

* 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.[[16]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop16)Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-33. https://www.nejm.org/doi/full/10.1056/NEJMoa2001017 http://www.ncbi.nlm.nih.gov/pubmed/31978945?tool=bestpractice.com [[17]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop17)Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-74. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32007145?tool=bestpractice.com [[22]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop22)Paraskevis D, Kostaki EG, Magiorkinis G, et al. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol. 2020 Jan 29;79:104212. http://www.ncbi.nlm.nih.gov/pubmed/32004758?tool=bestpractice.com [[23]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop23)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?tool=bestpractice.com Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses.[[24]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop24)Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr Biol. 2020 Mar 13 [Epub ahead of print]. https://www.cell.com/current-biology/fulltext/S0960-9822(20)30360-2?\_returnURL http://www.ncbi.nlm.nih.gov/pubmed/32197085?tool=bestpractice.com [[25]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop25)Lam TT, Shum MH, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. Nature. 2020 Mar 26 [Epub ahead of print]. https://www.nature.com/articles/s41586-020-2169-0\_reference.pdf http://www.ncbi.nlm.nih.gov/pubmed/32218527?tool=bestpractice.com

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.[[19]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop19)Huang 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/fulltext http://www.ncbi.nlm.nih.gov/pubmed/31986264?tool=bestpractice.com [[21]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop21)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 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 http://www.ncbi.nlm.nih.gov/pubmed/31995857?tool=bestpractice.com [[26]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop26)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/fulltext http://www.ncbi.nlm.nih.gov/pubmed/31986261?tool=bestpractice.com [[27]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop27)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?tool=bestpractice.com
* 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).[[28]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop28)van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020 Mar 17 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMc2004973 http://www.ncbi.nlm.nih.gov/pubmed/32182409?tool=bestpractice.com  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.[[29]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop29)World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. March 2020 [internet publication]. https://www.who.int/publications-detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
* 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. Fecal-oral transmission may be possible, although it has not been reported yet.[[30]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop30)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.full [[31]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop31)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(1):386-9. https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1729071 http://www.ncbi.nlm.nih.gov/pubmed/32065057?tool=bestpractice.com [[32]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop32)To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis. 2020 Feb 12 [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/32047895?tool=bestpractice.com [[33]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop33)Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020 Feb 26 [Epub ahead of print]. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25725 http://www.ncbi.nlm.nih.gov/pubmed/32100876?tool=bestpractice.com [[34]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop34)Centre for Evidence-Based Medicine; Ferner RE, Murray PI, Aronson JK. Spreading SARS-CoV-2 through ocular fluids. March 2020 [internet publication]. https://www.cebm.net/spreading-sars-cov-2-through-ocular-fluids/ [[35]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop35)Sun T, Guan J. Novel coronavirus and central nervous system. Eur J Neurol. 2020 Mar 26 [Epub ahead of print]. https://onlinelibrary.wiley.com/doi/epdf/10.1111/ene.14227 http://www.ncbi.nlm.nih.gov/pubmed/32216009?tool=bestpractice.com
* 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. One study of a family cluster of five patients in Shenzhen who had a history of travel to Wuhan City (with one other family member who did not travel to Wuhan City) found that person-to-person spread is possible in both hospital and family settings.[[21]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop21)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 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 http://www.ncbi.nlm.nih.gov/pubmed/31995857?tool=bestpractice.com
* Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series.[[36]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop36)Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7 [Epub ahead of print]. https://jamanetwork.com/journals/jama/fullarticle/2761044 http://www.ncbi.nlm.nih.gov/pubmed/32031570?tool=bestpractice.com
* Widespread transmission has been reported in long-term care facilities and on cruise ships (19% of 3700 passengers and crew were infected aboard the Diamond Princess).[[37]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop37)McMichael TM, Clark S, Pogosjans S, et al. COVID-19 in a long-term care facility: King County, Washington, February 27 – March 9, 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 18 [Epub ahead of print]. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e1.htm?s\_cid=mm6912e1\_w [[38]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop38)Moriarty LF, Plucinski MM, Marston BJ, et al. Public health responses to COVID-19 outbreaks on cruise ships: worldwide, February-March 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):347-52. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e3.htm?s\_cid=mm6912e3\_w http://www.ncbi.nlm.nih.gov/pubmed/32214086?tool=bestpractice.com

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.[[39]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop39)Mizumoto K, Kagaya K, Zarebski A, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020 Mar;25(10). https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180 http://www.ncbi.nlm.nih.gov/pubmed/32183930?tool=bestpractice.com However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%.[[40]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop40)Nishiura H, Kobayashi T, Suzuki A, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020 Mar 13 [Epub ahead of print]. https://www.ijidonline.com/article/S1201-9712(20)30139-9/pdf http://www.ncbi.nlm.nih.gov/pubmed/32179137?tool=bestpractice.com Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%.[[41]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop41)Day M. Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ. 2020 Mar 23;368:m1165. https://www.bmj.com/content/368/bmj.m1165 http://www.ncbi.nlm.nih.gov/pubmed/32205334?tool=bestpractice.com
* The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread.[[42]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop42)Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020 Mar 25 [Epub ahead of print]. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30198-5/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32220650?tool=bestpractice.com
* There is mounting evidence that spread from asymptomatic carriers can occur and this has been observed in endemic areas, although it is thought that transmission is greatest when people are symptomatic.[[43]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop43)Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020 Mar 5;382(10):970-71. https://www.nejm.org/doi/full/10.1056/NEJMc2001468 http://www.ncbi.nlm.nih.gov/pubmed/32003551?tool=bestpractice.com [[44]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop44)Kupferschmidt K. Study claiming new coronavirus can be transmitted by people without symptoms was flawed. February 2020 [internet publication]. https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong [[45]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop45)Tong ZD, Tang A, Li KF, et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang province, China, 2020. Emerg Infect Dis. 2020 May 17;26(5). https://wwwnc.cdc.gov/eid/article/26/5/20-0198\_article http://www.ncbi.nlm.nih.gov/pubmed/32091386?tool=bestpractice.com [[46]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop46)Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020 Mar 4 [Epub ahead of print]. https://link.springer.com/content/pdf/10.1007/s11427-020-1661-4.pdf http://www.ncbi.nlm.nih.gov/pubmed/32146694?tool=bestpractice.com [[47]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop47)Luo SH, Liu W, Liu ZJ, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). Chin Med J (Engl). 2020 Mar 6 [Epub ahead of print]. https://journals.lww.com/cmj/Citation/publishahead/A\_confirmed\_asymptomatic\_carrier\_of\_2019\_novel.99353.aspx http://www.ncbi.nlm.nih.gov/pubmed/32149768?tool=bestpractice.com [[48]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop48)Lu S, Lin J, Zhang Z, et al. Alert for non-respiratory symptoms of Coronavirus Disease 2019 (COVID-19) patients in epidemic period: a case report of familial cluster with three asymptomatic COVID-19 patients. J Med Virol. 2020 Mar 19 [Epub ahead of print]. https://onlinelibrary.wiley.com/doi/pdf/10.1002/jmv.25776 http://www.ncbi.nlm.nih.gov/pubmed/32190904?tool=bestpractice.com Presymptomatic transmission has been reported in 12.6% of cases in one study.[[49]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop49)Du Z, Xu X, Wu Y, et al. Serial interval of COVID-19 among publicly reported confirmed cases. Emerg Infect Dis. 2020 Mar 19;26(6). https://onlinelibrary.wiley.com/doi/pdf/10.1002/jmv.25776 http://www.ncbi.nlm.nih.gov/pubmed/32191173?tool=bestpractice.com

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.[[50]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop50)Frieden TR, Lee CT. Identifying and interrupting superspreading events-implications for control of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis. 2020 Mar 18;26(6). https://wwwnc.cdc.gov/eid/article/26/6/20-0495\_article http://www.ncbi.nlm.nih.gov/pubmed/32187007?tool=bestpractice.com
* Superspreaders can pass the infection on to large numbers of contacts, including healthcare workers. This phenomenon is well documented for infections such as severe acute respiratory syndrome (SARS), Ebola virus infection, and MERS.[[51]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop51)Stein RA. Super-spreaders in infectious diseases. Int J Infect Dis. 2011 Aug;15(8):e510-3. https://www.ijidonline.com/article/S1201-9712(11)00024-5/fulltext http://www.ncbi.nlm.nih.gov/pubmed/21737332?tool=bestpractice.com [[52]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop52)Hui DS. Super-spreading events of MERS-CoV infection. Lancet. 2016 Sep 3;388(10048):942-3. https://www.ijidonline.com/article/S1201-9712(11)00024-5/fulltext http://www.ncbi.nlm.nih.gov/pubmed/27402382?tool=bestpractice.com
* Some of these individuals are also supershedders of virus, but the reasons underlying superspreader events are often more complex than just excess virus shedding and can include a variety of behavioral and environmental factors.[[51]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop51)Stein RA. Super-spreaders in infectious diseases. Int J Infect Dis. 2011 Aug;15(8):e510-3. https://www.ijidonline.com/article/S1201-9712(11)00024-5/fulltext http://www.ncbi.nlm.nih.gov/pubmed/21737332?tool=bestpractice.com

Perinatal transmission

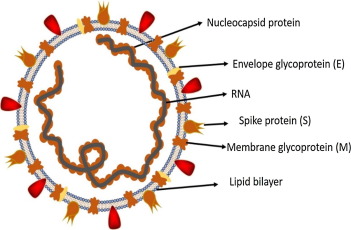
* It is unknown whether perinatal transmission (including transmission via breastfeeding) is possible. Retrospective reviews of pregnant women with COVID-19 found that there is no evidence for intrauterine infection in women with COVID-19.[[53]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop53)Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020 Mar 7;395(10226):809-15. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30360-3/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32151335?tool=bestpractice.com [[54]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop54)Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020 Mar 17 [Epub ahead of print]. https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2020-0901-SA http://www.ncbi.nlm.nih.gov/pubmed/32180426?tool=bestpractice.com However, vertical transmission cannot be ruled out. 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.[[55]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop55)Wang S, Guo L, Chen L, et al. A case report of neonatal COVID-19 infection in China. Clin Infect Dis. 2020 Mar 12 [Epub ahead of print]. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa225/5803274 http://www.ncbi.nlm.nih.gov/pubmed/32161941?tool=bestpractice.com [[56]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop56)Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020 Feb;9(1):51-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7036645/ http://www.ncbi.nlm.nih.gov/pubmed/32154135?tool=bestpractice.com [[57]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop57)Zeng H, Xu C, Fan J, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA 2020 Mar 26 [Epub ahead of print]. https://jamanetwork.com/journals/jama/fullarticle/2763854 http://www.ncbi.nlm.nih.gov/pubmed/32215589?tool=bestpractice.com [[58]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop58)Dong L, Tian J, He S, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020 Mar 26 [Epub ahead of print]. https://jamanetwork.com/journals/jama/fullarticle/2763853 http://www.ncbi.nlm.nih.gov/pubmed/32215581?tool=bestpractice.com [[59]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop59)Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr. 2020 Mar 26 [Epub ahead of print]. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2763787 http://www.ncbi.nlm.nih.gov/pubmed/32215598?tool=bestpractice.com

**STRUCTURE OF THE VIRUS.**

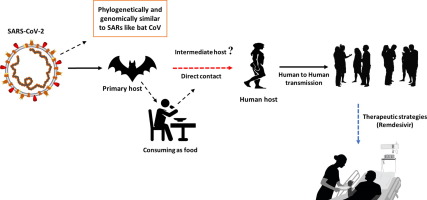
Key features and entry mechanism of human coronaviruses

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 [32]. 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 [33]. The entire mechanism of pathogenicity of SARS-CoV-2, from attachment to replication is well mentioned in Figure below;



Fig(1). The life cycle of SARS-CoV-2 in host cells; begins its life cycle when S protein binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment.

Fig(2)

Genomic variations in SARS-CoV-2

The genome of the SARS-CoV-2 has been reported over 80% identical to the previous human coronavirus (SARS-like bat CoV) . The Structural proteins are encoded by the four structural genes, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes. The orf1ab is the largest gene in SARS-CoV-2 which encodes the pp1ab protein and 15 nsps. The orf1a gene encodes for pp1a protein which also contains 10 nsps . According to the evolutionary tree, SARS-CoV-2 lies close to the group of SARS-coronaviruses (Fig. 5). Recent studies have indicated notable variations in SARS-CoV and SARS-CoV-2 such as the absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c protein in SARS-CoV-2 [34] (Fig. 4). It is also reported that Spike glycoprotein of the Wuhan coronavirus is modified via homologous recombination. The spike glycoprotein of SARS-CoV-2 is the mixture of bat SARS-CoV and a not known Beta-CoV . In a fluorescent study, it was confirmed that the SARS-CoV-2 also uses the same ACE2 (angiotensin-converting enzyme 2) cell receptor and mechanism for the entry to host cell which is previously used by the SARS-CoV. The single N501T mutation in SARS-CoV-2's Spike protein may have significantly enhanced its binding affinity for ACE2.

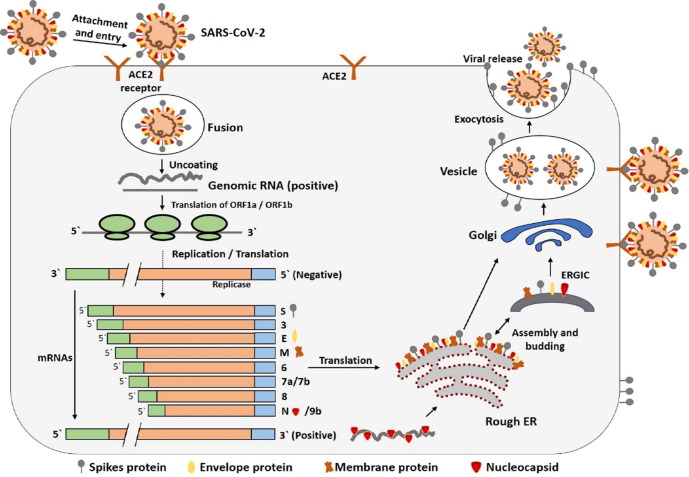


Fig. 4. Betacoronaviruses genome organization; The Betacoronavirus for human (SARS-CoV-2, SARS-CoV and MERS-CoV) genome comprises of the 5′-untranslated region (5′-UTR), open reading frame (orf) 1a/b (green box) encoding non-structural proteins (nsp) for replication, structural proteins including spike (blue box), envelop (maroon box), membrane (pink box), and nucleocapsid (cyan box) proteins, accessory proteins (light gray boxes) such as orf 3, 6, 7a, 7b, 8 and 9b in the SARS-CoV-2 genome, and the 3′-untranslated region (3′-UTR). The doted underlined in red are the protein which shows key variation between SARS-CoV-2 and SARS-CoV. The length of nsps and orfs are not drawn in scale. (For interpretation of the references to colour in this figure legend.

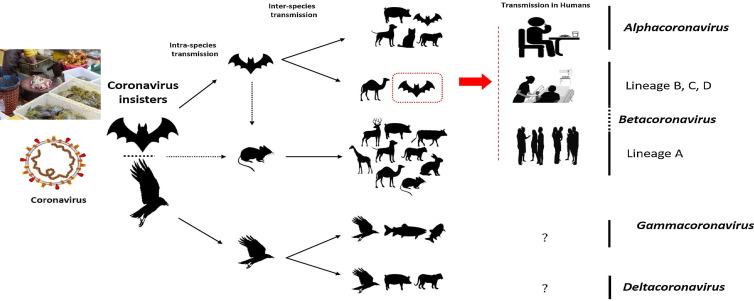


Fig. 5. Phylogenetic tree of coronaviruses (content in red is the latest addition of newly emerged SARS-CoV-2 and WSFMP Wuhan-Hu-1 is used as a reference in the tree); The phylogenetic tree showing the relationship of Wuhan-Hu-1 (denoted as red) to selected coronavirus is based on nucleotide sequences of the complete genome. The viruses are grouped into four genera (prototype shown): Alphacoronavirus (sky blue), Betacoronavirus (pink), Gammacoronavirus (green) and Deltacoronavirus (light blue). Subgroup clusters are labeled as 1a and 1b for the Alphacoronavirus and 2a, 2b, 2c, and 2d for the Betacoronavirus. This tree is based on the published trees of Coronavirinae [3], [41] and reconstructed with sequences of the complete RNA- dependent RNA polymerase- coding region of the representative novel coronaviruses (maximum likelihood method using MEGA 7.2 software). severe acute respiratory syndrome coronavirus (SARS- CoV); SARS- related coronavirus (SARSr- CoV); the Middle East respiratory syndrome coronavirus (MERS- CoV); porcine enteric diarrhea virus (PEDV); Wuhan seafood market pneumonia (Wuhan-Hu-1). Bat CoV RaTG13 Showed high sequence identity to SARS-CoV-2 [42]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**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.[[60]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop60)World Health Organization. Novel coronavirus (2019-nCoV) situation report - 6. January 2020 [internet publication]. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200126-sitrep-6-2019--ncov.pdf [[61]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop61)Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): symptoms. February 2020 [internet publication]. https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html
* The median incubation period has been estimated to be approximately 5 days.[[21]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop21)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 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 http://www.ncbi.nlm.nih.gov/pubmed/31995857?tool=bestpractice.com [[62]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop62)Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020 Mar 10 [Epub ahead of print]. https://annals.org/aim/fullarticle/2762808/ http://www.ncbi.nlm.nih.gov/pubmed/32150748?tool=bestpractice.com 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).[[63]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop63)Jiang X, Niu Y, Li X, et al. Is a 14-day quarantine period optimal for effectively controlling coronavirus disease 2019 (COVID-19)? March 2020 [internet publication]. https://www.medrxiv.org/content/10.1101/2020.03.15.20036533v1
* Transmission may be possible during the incubation period.[[64]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop64)Yu P, Zhu J, Zhang Z, et al. A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. J Infect Dis. 2020 Feb 18 [Epub ahead of print]. https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa077/5739751 http://www.ncbi.nlm.nih.gov/pubmed/32067043?tool=bestpractice.com

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.[[21]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop21)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 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMoa2001316 http://www.ncbi.nlm.nih.gov/pubmed/31995857?tool=bestpractice.com [[65]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop65)Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Euro Surveill. 2020 Jan;25(4). https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.4.2000058 http://www.ncbi.nlm.nih.gov/pubmed/32019669?tool=bestpractice.com However, as the situation is still evolving, the R₀ may actually be higher or lower.
* The secondary attack rate for SARS-CoV-2 is estimated to be 0.45% for close contacts of US patients.[[27]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop27)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?tool=bestpractice.com

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.[[17]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop17)Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-74. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32007145?tool=bestpractice.com [[66]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop66)Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. Science. 2020 Mar 4 [Epub ahead of print]. https://science.sciencemag.org/content/early/2020/03/03/science.abb2762 http://www.ncbi.nlm.nih.gov/pubmed/32132184?tool=bestpractice.com 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.[[67]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop67)Chen Y, Guo Y, Pan Y, et al. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020 Feb 17. pii: S0006-291X(20)30339-9 [Epub ahead of print]. https://www.sciencedirect.com/science/article/pii/S0006291X20303399?via%3Dihub http://www.ncbi.nlm.nih.gov/pubmed/32081428?tool=bestpractice.com A furin-like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS-like coronaviruses.[[68]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop68)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 Res. 2020 Feb 10;176:104742. http://www.ncbi.nlm.nih.gov/pubmed/32057769?tool=bestpractice.com
* 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.[[69]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop69)Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020 Mar 12 [Epub ahead of print]. https://link.springer.com/content/pdf/10.1007/s11684-020-0754-0.pdf http://www.ncbi.nlm.nih.gov/pubmed/32170560?tool=bestpractice.com
* 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.[[70]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop70)Hanff TC, Harhay MO, Brown TS, et al. Is there an association between COVID-19 mortality and the renin-angiotensin system: a call for epidemiologic investigations. Clin Infect Dis. 2020 Mar 26 [Epub ahead of print]. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa329/5811880 http://www.ncbi.nlm.nih.gov/pubmed/32215613?tool=bestpractice.com

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.[[71]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop71)Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020 Feb 19 [Epub ahead of print]. https://www.nejm.org/doi/full/10.1056/NEJMc2001737 http://www.ncbi.nlm.nih.gov/pubmed/32074444?tool=bestpractice.com [[72]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop72)To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020 Mar 23 [Epub ahead of print]. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30196-1/fulltext http://www.ncbi.nlm.nih.gov/pubmed/32213337?tool=bestpractice.com
* 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.[[73]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop73)Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11 [Epub ahead of print]. https://www.thelancet.com/pb-assets/Lancet/pdfs/S014067362305663.pdf http://www.ncbi.nlm.nih.gov/pubmed/32171076?tool=bestpractice.com [[74]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop74)Chang, Mo G, Yuan X, et al. Time kinetics of viral clearance and resolution of symptoms in novel coronavirus infection. Am J Respir Crit Care Med. 2020 Mar 23 [Epub ahead of print]. https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0524LE http://www.ncbi.nlm.nih.gov/pubmed/32200654?tool=bestpractice.com [[75]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop75)Chen C, Gao G, Xu Y, et al. SARS-CoV-2 positive sputum and feces after conversion of pharyngeal samples in patients with COVID-19. Ann Intern Med. 2020 Mar 30 [Epub ahead of print]. https://annals.org/aim/fullarticle/2764036/sars-cov-2-positive-sputum-feces-after-conversion-pharyngeal-samples [[76]](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop76)Zhang T, Cui X, Zhao X, et al. Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. J Med Virol. 2020 Mar 29 [Epub ahead of print]. https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25795 http://www.ncbi.nlm.nih.gov/pubmed/32222992?tool=bestpractice.com

**Classification**

**World Health Organization: clinical classification of COVID-19**[**[5]**](https://newbp.bmj.com/topics/en-us/3000168/aetiology#referencePop5)**World Health Organization. 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**

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.