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Severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**)[2][3] is the strain of coronavirus that causes coronavirus disease 2019 (COVID-19), the respiratory illness responsible for the COVID-19 pandemic. Colloquially known as simply the **coronavirus**, it was previously referred to by its provisional name, **2019 novel coronavirus** (**2019-nCoV**),[4][5][6][7] and has also been called **human coronavirus 2019** (**HCoV-19** or **hCoV-19**).[8][9][10][11] The World Health Organization declared the outbreak a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020.[12][13]

SARS-CoV-2 is a Baltimore class IV[14] positive-sense single-stranded RNA virus[15] that is contagious in humans.[16] As described by the U.S. National Institutes of Health, it is the successor to SARS-CoV-1,[10][17] the strain that caused the 2002–2004 SARS outbreak.

Taxonomically, SARS-CoV-2 is a strain of *severe acute respiratory syndrome-related coronavirus* (SARSr-CoV).[2] It is believed to have zoonotic origins and has close genetic similarity to bat coronaviruses, suggesting it emerged from a bat-borne virus.[18][19][20][9] There is no evidence yet to link an intermediate host, such as a pangolin, to its introduction to humans.[21][22] The virus shows little genetic diversity, indicating that the spillover event introducing SARS-CoV-2 to humans is likely to have occurred in late 2019.[23] In September 2020, based on data analysis, researchers reported the discovery of the genome of the virus's index case.[24][25]

Epidemiological studies estimate each infection results in 5.7 new ones when no members of the community are immune and no preventive measures taken.[26] The virus primarily spreads between people through close contact and via respiratory droplets produced from coughs or sneezes.[27][28] It mainly enters human cells by binding to the receptor angiotensin converting enzyme 2 (ACE2).[18][29][30][31]

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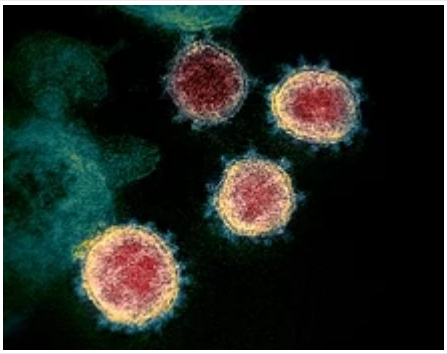

Transmission electron micrograph of SARS-CoV-2 virions with visible coronae

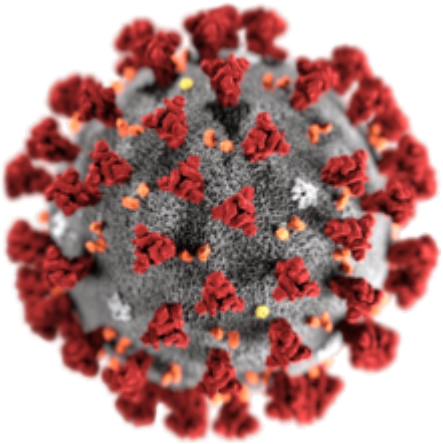

Illustration of a SARS-CoV-2 virion[1]

Red protrusions: spike proteins (S)[1]

Grey coating: the envelope, composed mainly of lipids, which can be destroyed with alcohol or soap[1]

Yellow deposits: envelope proteins (E)[1]

Orange deposits: membrane proteins (M)[1]

Virus classification

- Infection and transmission
- Reservoir and zoonotic origin
- Phylogenetics and taxonomy
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See also

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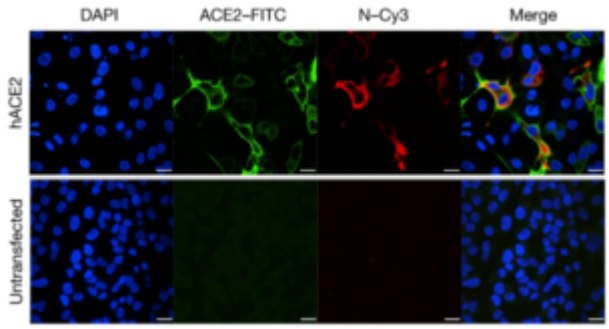
(unranked):	Virus
Realm:	*Riboviria*
Kingdom:	*Orthornavirae*
Phylum:	*Pisuviricota*
Class:	*Pisoniviricetes*
Order:	*Nidovirales*
Family:	*Coronaviridae*
Genus:	*Betacoronavirus*
Subgenus:	*Sarbecovirus*
Species:	*Severe acute respiratory syndrome–related coronavirus*
Strain:	**Severe acute respiratory syndrome coronavirus 2**
Synonyms	
▪ 2019-nCoV	

Terminology

During the initial outbreak in Wuhan, China, various names were used for the virus; some names used by different sources included the "coronavirus" or "Wuhan coronavirus".[32][33] In January 2020, the World Health Organisation recommended "2019 novel coronavirus" (2019-nCov)[34][5] as the provisional name for the virus. This was in accordance with WHO's 2015 guidance[35] against using geographical locations, animal species, or groups of people in disease and virus names.[36][37]

On 11 February 2020, the International Committee on Taxonomy of Viruses adopted the official name "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2).[21] To avoid confusion with the disease SARS, the WHO sometimes refers to SARS-CoV-2 as "the COVID-19 virus" in public health communications[38][39] and the name HCoV-19 was included in some research articles.[8][9][10]

The name "2019-nCoV" in use in a trilingual sign at a Lisbon health facility in February 2020.



HeLa cells engineered to express ACE2 become susceptible to SARS-CoV-2 infection.

The general public often call both the virus, and the disease it causes, "coronavirus". U.S. President Donald Trump referred to the virus as the "Chinese virus" in tweets, interviews, and White House press briefings, which drew some criticism that he was stigmatizing the disease with racial or nationalistic overtones.[40][41][42]

Virology

Infection and transmission

Human-to-human transmission of SARS-CoV-2 was confirmed on 20 January 2020, during the COVID-19 pandemic.[16][43][44][45] Transmission was initially assumed to occur primarily via respiratory droplets from coughs and sneezes within a range of about 1.8 metres (6 ft).[28][46] Laser light scattering experiments suggest speaking— as an additional mode of transmission.[47][48] Other studies have suggested that the virus may be airborne as well, with aerosols potentially being able to transmit the virus.[49][50][51]

Indirect contact via contaminated surfaces is another possible cause of infection.[52] Preliminary research indicates that the virus may remain viable on plastic (polypropylene) and stainless steel (AISI 304) for up to three days, but does not survive on cardboard for more than one day or on copper for more than four hours;[10] the virus is inactivated by soap, which destabilises its lipid bilayer.[53][54] Viral RNA has also been found in stool samples and semen from infected individuals.[55][56]

The degree to which the virus is infectious during the incubation period is uncertain, but research has indicated that the pharynx reaches peak viral load approximately four days after infection[57][58] or the first week of symptoms, and declines after.[59] On 1 February 2020, the World Health Organization (WHO) indicated that "transmission from asymptomatic cases is likely not a major driver of transmission".[60] However, an epidemiological model of the beginning of the outbreak in China suggested that "pre-symptomatic shedding may be typical among documented infections" and that subclinical infections may have been the source of a majority of infections.[61] That may explain how out of 217 on board a cruise liner that docked at Montevideo, only 24 of 128 who tested positive for viral RNA showed symptoms.[62] Similarly, a study of ninety-four patients hospitalized in January and February 2020 estimated patients shed the greatest amount of virus two to three days before symptoms appear and that "a substantial proportion of transmission probably occurred before first symptoms in the index case".[63]

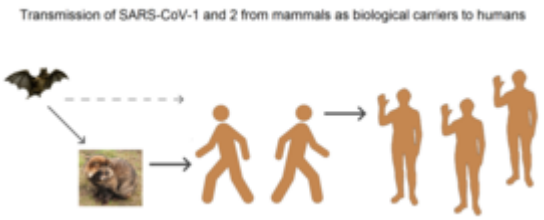
A study by a team of researchers from the University of North Carolina found that the nasal cavity is seemingly the dominant initial site for infection with subsequent aspiration-mediated virus seeding into the lungs in SARS-CoV-2 pathogenesis.[64] They found that there was an infection gradient from high in proximal towards low in distal pulmonary epithelial cultures, with a focal infection in ciliated cells and type 2 pneumocytes in the airway and alveolar regions respectively.[64]

There is some evidence of human-to-animal transmission of SARS-CoV-2, including examples in felids.[65][66] Some institutions have advised those infected with SARS-CoV-2 to restrict contact with animals.[67][68]

There are still a lot of questions about reinfection and long-term immunity.[69] It is not known how common reinfection is, but reports have indicated that it is occurring with variable severity.[69] The first reported case of reinfection was a 33-year-old man from Hong Kong who first tested positive on 26 March 2020, was discharged on 15 April 2020 after two negative tests, and tested positive again on 15 August 2020 (142 days later), which was confirmed by whole genome sequencing showing that the viral genomes between the episodes belong to different clades.[70] The findings had the implications that herd immunity may not eliminate the virus if reinfection is not an uncommon occurrence and that vaccines may not be able to provide lifelong protection against the virus.[70] Another case study described a 25-year-old man from Nevada who tested positive for SARS-CoV-2 on 18 April 2020 and on 5 June 2020 (separated by two negative tests). Since genomic analyses showed significant genetic differences between

the SARS-CoV-2 variant sampled on those two dates, the case study authors determined this was a reinfection.[71] The man's second infection was symptomatically more severe than the first infection, but the mechanisms that could account for this is not known.[71]

Reservoir and zoonotic origin



Transmission of SARS-CoV-1 and SARS-CoV-2 from mammals as biological carriers to humans

The first known infections from the SARS-CoV-2 strain were discovered in Wuhan, China.[18] The original source of viral transmission to humans remains unclear, as does whether the strain became pathogenic before or after the spillover event.[23][72][9] Because many of the first individuals found to be infected by the virus were workers at the Huanan Seafood Market,[73][74] it has been suggested that the strain might have originated from the market.[9][75] However, other research indicates that visitors may have introduced the virus to the market, which then facilitated rapid expansion of the infections.[23][76] A phylogenetic network analysis of 160 early coronavirus genomes sampled from December 2019 to February 2020 revealed that the virus type most closely related to the bat coronavirus was most abundant in Guangdong, China, and designated type "A". The predominant type among samples from Wuhan, "B", is more distantly related to the bat coronavirus than the ancestral type "A".[77][78]

Research into the natural reservoir of the virus strain that caused the 2002–2004 SARS outbreak has resulted in the discovery of many SARS-like bat coronaviruses, most originating in the *Rhinolophus* genus of horseshoe bats. Phylogenetic analysis indicates that samples taken from *Rhinolophus sinicus* show a resemblance of 80% to SARS-CoV-2.[20][79][80] Phylogenetic analysis also indicates that a virus from *Rhinolophus affinis*, collected in Yunnan province and designated RaTG13, has a 96% resemblance to SARS-CoV-2.[18][81]

Samples taken from *Rhinolophus sinicus*, a species of horseshoe bats, show an 80% resemblance to SARS-CoV-2.

Bats are considered the most likely natural reservoir of SARS-CoV-2,[82][83] but differences between the bat coronavirus and SARS-CoV-2 suggest that humans were infected via an intermediate host.[75] Although studies have suggested some likely candidates, the number and identities of intermediate hosts remain uncertain.[84] Nearly half of the strain's genome has a phylogenetic lineage distinct from known relatives.[85]

A phylogenetics study published in 2020 indicates that pangolins are a reservoir host of SARS-CoV-2-like coronaviruses.[87] However, there is no direct evidence to link pangolins as an intermediate host of SARS-CoV-2 at this moment.[88] While there is scientific consensus that bats are the ultimate source of coronaviruses, the pangolin CoV is sister to both RaTG13 as well as SARS-CoV-2. Based on whole genome sequence similarity, a pangolin coronavirus candidate strain was found to be less similar than RaTG13, but more similar than other bat coronaviruses to SARS-CoV-2. Therefore, based on maximum parsimony and current

The pangolin coronavirus has up to 92% resemblance to SARS-CoV-2.[86]

sample data, a specific population of bats is more likely to have directly transmitted SARS-CoV-2 to humans than a pangolin, while an evolutionary ancestor to bats was the source of general coronaviruses.[86]

A metagenomics study published in 2019 had previously revealed that SARS-CoV, the strain of the virus that causes SARS, was the most widely distributed coronavirus among a sample of Sunda pangolins.[89] On 7 February 2020, South China Agricultural University in Guangzhou announced that researchers discovered a pangolin sample with a particular coronavirus – a single nucleic acid sequence of the virus was "99% similar" to that of a protein-coding RNA of SARS-CoV-2.[90] The authors state that "the receptor-binding domain of the S protein [that binds to the cell surface receptor during infection] of the newly discovered Pangolin-CoV is virtually identical to that of 2019-nCoV, with one amino acid difference."[91] Microbiologists and geneticists in Texas have independently found evidence of reassortment in coronaviruses suggesting involvement of pangolins in the origin of SARS-CoV-2.[92] The majority of the viral RNA is related to a variation of bat coronaviruses.[93] The spike protein appears to be a notable exception, however, possibly acquired through a more recent recombination event with a pangolin coronavirus.[94] SARS-CoV-2's entire receptor binding motif appears to have been introduced through recombination from coronaviruses of pangolins.[95] Such a recombination event may have been a critical step in the evolution of SARS-CoV-2's capability to infect humans.[95] Recombination events have been key steps in the viral evolutionary process that lead to the emergence of new human diseases.[96] Structural analysis of the receptor binding domain (RBD) and human angiotensin-converting enzyme 2 (ACE2) complex[97] revealed key mutations on the RBD, such as F486 and N501, which form contacts with ACE2.[98] These residues are found in the pangolin coronavirus.[98]

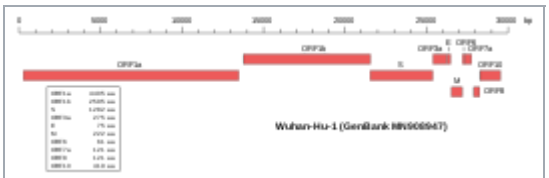
Pangolins are protected under Chinese law, but their poaching and trading for use in traditional Chinese medicine remains common in the black market.[99][100] Deforestation, wildlife farming and trade in unsanitary conditions increases the risk of new zoonotic diseases.[101][102][103][104]

All available evidence suggests that SARS-CoV-2 has a natural animal origin and is not genetically engineered.[105] Nevetheless, laboratory origin of SARS-CoV-2 can not be ruled out.[106] According to computational simulations on protein folding, the RBD of the spike protein of SARS-CoV-2 should have unremarkable binding affinity. In actuality, however, it has very efficient binding to the human ACE2 receptor. To expose the RBD for fusion, furin proteases must first cleave the S protein. Furin proteases are abundant in the respiratory tract and lung epithelial cells. Additionally, the backbone of the virus does not resemble any previously described in scientific literature used for genetic modification. The possibility that the virus could have gained the necessary adaptations through cell culture in a laboratory setting is challenged by scientists who assert that "the generation of the predicted O-linked glycans... suggest[s] the involvement of an immune system."[107][9]

Phylogenetics and taxonomy

SARS-CoV-2 belongs to the broad family of viruses known as coronaviruses.[33] It is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. Other coronaviruses are capable of causing illnesses ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS, fatality rate ~34%). It is the seventh known coronavirus to infect people, after 229E, NL63, OC43, HKU1, MERS-CoV, and the original SARS-CoV.[108]

Genomic information



Genomic organisation of isolate Wuhan-Hu-1, the earliest sequenced sample of SARS-CoV-2

NCBI	86693 (https://www.ncbi.nl

genome ID	m.nih.gov/genome/?term=86693)
Genome size	29,903 bases
Year of completion	2020
Genome browser (https://genome.ucsc.edu/cgi-bin/hgTracks?db=wuhCor1) (UCSC)	

Like the SARS-related coronavirus strain implicated in the 2003 SARS outbreak, SARS-CoV-2 is a member of the subgenus *Sarbecovirus* (beta-CoV lineage B).[109][110] Its RNA sequence is approximately 30,000 bases in length.[15] SARS-CoV-2 is unique among known betacoronaviruses in its incorporation of a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses.[9][111][112]

With a sufficient number of sequenced genomes, it is possible to reconstruct a phylogenetic tree of the mutation history of a family of viruses. By 12 January 2020, five genomes of SARS-CoV-2 had been isolated from Wuhan and reported by the Chinese Center for Disease Control and Prevention (CCDC) and other institutions;[15][113] the number of genomes increased to 42 by 30 January 2020.[114] A phylogenetic analysis of those samples showed they were "highly related with at most seven mutations relative to a common ancestor", implying that the first human infection occurred in November or December 2019.[114] As of 7 May 2020, 4,690 SARS-CoV-2 genomes sampled on six continents were publicly available.[115]

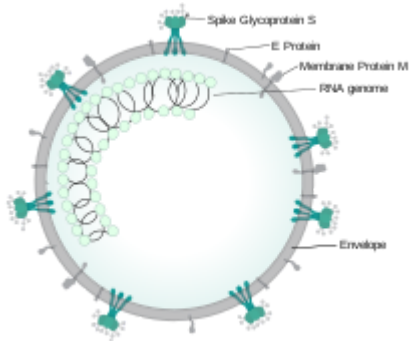
On 11 February 2020, the International Committee on Taxonomy of Viruses announced that according to existing rules that compute hierarchical relationships among coronaviruses on the basis of five conserved sequences of nucleic acids, the differences between what was then called 2019-nCoV and the virus strain from the 2003 SARS outbreak were insufficient to make them separate viral species. Therefore, they identified 2019-nCoV as a strain of *Severe acute respiratory syndrome-related coronavirus*.[2]

In July 2020, scientists report that a more infectious SARS-CoV-2 variant with spike protein variant G614 has replaced D614 as the dominant form in the pandemic.[116][117]

In October 2020, researchers discovered a possible overlapping gene named *ORF3d*, in the Covid-19 virus genome. It is unknown if the protein produced by *ORF3d* has any function, but it provokes a strong immune response. *ORF3d* has been identified before, in a variant of coronavirus that infects pangolins.[118][119]

Structural biology

Each SARS-CoV-2 virion is 50–200 nanometres in diameter.[74] Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope.[120] The spike protein, which has been imaged at the atomic level using cryogenic electron microscopy,[121][122] is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell;[120] specifically, its S1 subunit catalyzes attachment, the S2 subunit fusion.[123]



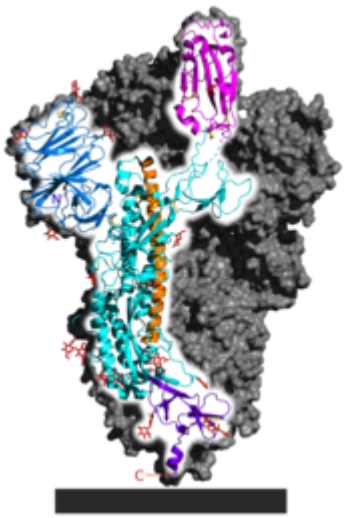
Structure of a SARSr-CoV virion

Protein modeling experiments on the spike protein of the virus soon suggested that SARS-CoV-2 has sufficient affinity to the receptor angiotensin converting enzyme 2 (ACE2) on human cells to use them as a mechanism of cell entry.[124] By 22 January 2020, a group in China working with the full virus genome and a group in the United States using reverse genetics

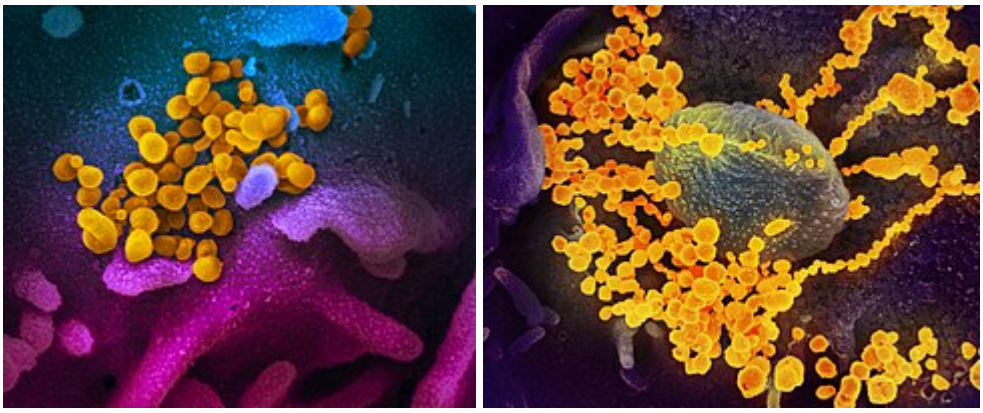
methods independently and experimentally demonstrated that ACE2 could act as the receptor for SARS-CoV-2.[18][125][29][126] Studies have shown that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS virus strain.[121][127] SARS-CoV-2 may also use basigin to assist in cell entry.[128]

Initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2) is essential for entry of SARS-CoV-2.[30] After a SARS-CoV-2 virion attaches to a target cell, the cell's protease TMPRSS2 cuts open the spike protein of the virus, exposing a fusion peptide in the S2 subunit, and the host receptor ACE2.[123] After fusion, an endosome forms around the virion, separating it from the rest of the host cell. The virion escapes when the pH of the endosome drops or when cathepsin, a host cysteine protease, cleaves it.[123] The virion then releases RNA into the cell and forces the cell to produce and disseminate copies of the virus, which infect more cells.[129]

SARS-CoV-2 produces at least three virulence factors that promote shedding of new virions from host cells and inhibit immune response.[120] Whether they include downregulation of ACE2, as seen in similar coronaviruses, remains under investigation (as of May 2020).[87]



SARS-CoV-2 spike homotrimer with one protein subunit highlighted. The ACE2 binding domain is magenta.



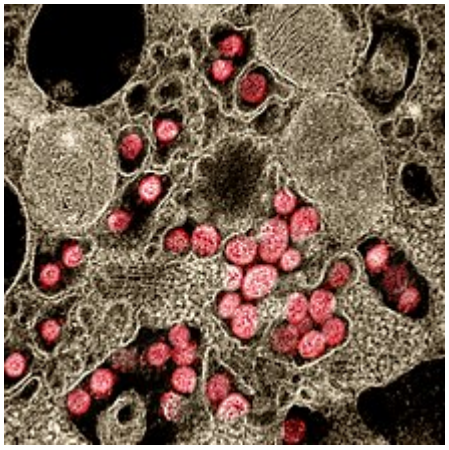
Digitally colourised scanning electron micrographs of SARS-CoV-2 virions (yellow) emerging from human cells cultured in a laboratory

Epidemiology

Based on the low variability exhibited among known SARS-CoV-2 genomic sequences, the strain is thought to have been detected by health authorities within weeks of its emergence among the human population in late 2019.[23][130] The earliest case of infection currently known is dated back to 17 November 2019 or possibly 1 December 2019.[131] The virus subsequently spread to all provinces of China and to more than 150 other countries in Asia, Europe, North America, South America, Africa, and Oceania.[132] Human-to-human transmission of the virus has been confirmed in all these regions.[133] On 30 January 2020, SARS-CoV-2 was designated a Public Health Emergency of International Concern by the WHO,[134][12] and on 11 March 2020 the WHO declared it a pandemic.[13][135]

The basic reproduction number (R_0) of the virus has been estimated to be around 5.7.[26] This means each infection from the virus is expected to result in 5.7 new infections when no members of the community are immune and no preventive measures are taken. The reproduction number may be higher in densely populated conditions such as those found on cruise ships.[136] Many forms of preventive

efforts may be employed in specific circumstances to reduce the propagation of the virus.[137]



Transmission electron micrograph of SARS-CoV-2 virions (red) isolated from a patient during the COVID-19 pandemic

There have been about 82,000 confirmed cases of infection in mainland China.[132] While the proportion of infections that result in confirmed cases or progress to diagnosable disease remains unclear,[138] one mathematical model estimated that 75,815 people were infected on 25 January 2020 in Wuhan alone, at a time when the number of confirmed cases worldwide was only 2,015.[139] Before 24 February 2020, over 95% of all deaths from COVID-19 worldwide had occurred in Hubei province, where Wuhan is located.[140][141] As of 24 November 2020, the percentage had decreased to 0.23%.[132]

As of 24 November 2020, there have been 59,131,816 total confirmed cases of SARS-CoV-2 infection in the ongoing pandemic.[132] The total number of deaths attributed to the virus is 1,395,865.[132] Many recoveries from confirmed infections go unreported, but at least 37,852,903 people have recovered from confirmed infections.[132]

See also

- Cluster 5, a mutated variant of the SARS-CoV-2 virus

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