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Coronavirus disease 2019 (COVID-19)

Mark Herbert, PhD

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019, and has resulted in an ongoing pandemic in the world. As of September 22 2020, more than 31.3 million cases have been reported across 188 countries and territories with more than 965,000 deaths, and more than 21.5 million people have recovered. Common symptoms include fever, cough, fatigue, shortness of breath or breathing difficulties loss of smell and loss of taste. While most people have mild symptoms, some people develop acute respiratory distress syndrome possibly precipitated by cytokine storm, multi-organ failure, septic shock and blood clots. The incubation period may range from 1 to 14 days.
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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[10] It was first identified in December 2019, and has resulted in an ongoing pandemic all over the world. As of September 22 2020, more than 31.3 million cases have been reported across 188 countries and territories with more than 965,000 deaths; more than 21.5 million people have recovered.[9] Common symptoms include fever, cough, fatigue, shortness of breath or breathing difficulties, and loss of smell and taste.[7] As most people have mild symptoms, some people develop acute respiratory distress syndrome (ARDS) possibly precipitated by cytokine storm,[11] multi-organ failure, septic shock, and blood clots. The incubation period may range from 1 to 14 days.[12] The contents in article are primarily from Wikipedia, the free encyclopedia (https://en.wikipedia.org/wiki/Coronavirus_disease_2019).

he disease spreads among people most often when they are physically close, which spreads very easily and sustainably through the air, primarily via small droplets or particles such as aerosols, produced after an infected person breathes, coughs, sneezes, talks or sings.[13][14] It may also be transmitted via contaminated surfaces, although this has not been conclusively demonstrated.[14][15][16] It can spread for up to two days prior to symptom onset, and from people who are asymptomatic.[14] People remain infectious in moderate cases for 7–12 days, and up to 2 weeks in severe cases.[14][12] The standard method of diagnosis is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. Chest CT imaging may also be helpful for diagnosis in individuals where there is a high suspicion of infection based on symptoms and risk factors, however guidelines do not recommend using it for routine screening.

Recommended measures to prevent infection include frequent hand washing, social distancing, quarantine, covering coughs, and keeping unwashed hands away from the face.[8] The use of cloth face coverings such as a scarf or a bandana has been recommended by health officials in public settings to minimise the risk of transmissions, with some authorities requiring their use. Health officials also stated that medical-grade face masks, such as N95 masks, should be used only by healthcare workers, first responders, and those who directly care for infected individuals.

There are no proven vaccines or specific treatments for COVID-19 yet, though several are in development. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. The World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern (PHEIC)[17][18] on January 30 2020 and a pandemic on March 11 2020.[19] Local transmission of the disease has occurred in most countries across all

six WHO regions.[20]

Longer-term damage to organs has been observed, and there is concern about a significant number of patients who have recovered from the acute phase of the disease but continue to experience a range of effects including severe fatigue, memory loss and other cognitive issues, low grade fever, muscle weakness, breathlessness and other symptoms for months afterwards.[21][22][23][24][25]

Symptoms of COVID-19.

Symptoms of COVID-19 are variable, but usually include fever and a cough.[27][6] People with the same infection may have different symptoms, and their symptoms may change over time. For example, one person may have a high fever, a cough, and fatigue, and another person may have a low fever at the start of the disease and develop difficulty breathing a week later. All of the symptoms of COVID-19 are non-specific, which means that they are also seen in some other diseases. [26]

Fever is the most common symptom of COVID-19.[27] The fever may be high or low. Most people with COVID-19 develop a fever at some point.[27] Most people with COVID-19 also have a cough, which could be either dry or a productive cough.[27]

Other typical symptoms include fatigue, shortness of breath and muscle and joint pains.[27][6] Some symptoms, such as difficulty breathing, are more common in patients who need hospital care.[6] Shortness of breath tends to develop later in the illness.

About 40% of people temporarily lose their sense of smell, experience changes in how food tastes, or have other disturbances to their normal abilities to smell or taste.[6][28] This symptom, if it is present at all, often appears early in the illness.[28] A disturbance in smell or taste is more commonly found in younger people, and perhaps because of this, it is associated with a lower risk of medical complications.[28] Although most people with COVID-19 do not experience these symptoms, it is an unusual symptom for other respiratory diseases, so it is used for symptom-based screening.[28]

Other symptoms are less common among people with COVID-19. Some people experience gastrointestinal symptoms such as loss of appetite, diarrhoea, or nausea.[6][29] Some people have a sore throat, headache, vertigo, or other symptoms.[27][6]

As is common with infections, there is a delay, known as the incubation period, between the moment a person first becomes infected and the appearance of the first symptoms. The median incubation period for COVID-19 is 4 to 5 days.[30] Most symptomatic people experience symptoms within 2 to 7 days after exposure, and almost all symptomatic people will experience 1 or more symptoms before day 12.[30][31] Some symptoms usually appear sooner than others. In August 2020, scientists at the University of Southern California reported the likely order of initial symptoms of the COVID-19 disease as a fever followed by a cough and muscle pain, and that nausea and vomiting usually appear before diarrhoea.[32] This contrasts with the most common path for influenza where it is common to develop a cough first and fever later.[32]

Some people are infected with the virus but do not develop noticeable symptoms at any point in time.[33] These asymptomatic carriers tend not to get tested, and they can spread the disease.[34][35][33] Other infected people will develop symptoms later or have very mild symptoms, and can also spread the virus.

Cause

COVID-19 is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus strain.

Transmission

COVID-19 is a new disease, and how it spreads remains under investigation.[15][13][12] It spreads from person to person, most often when they are physically close, but also over longer distances, especially indoors.[13][14] It spreads through the air, mainly after an infected person breathes, coughs, sneezes, talks or sings.[13][14][36][37] It transmits very easily and sustainably, with 1 infected person generally infecting between 2 and 3 others.[14][13] This is more infectious than influenza, but less so than measles.[14][13] It can transmit when people are symptomatic, also for up to 2 days prior to developing symptoms, and even if a person never shows symptoms, but it is unclear how often this happens.[7][13][12][15][14] A July 2020 systematic review found that the proportion of asymptomatic cases ranges from 6% to 41%.[16]

People remain infectious in moderate cases for 7-12 days, and up to 2 weeks in severe cases.[14]

Airborne transmission occurs particularly in crowded and less ventilated indoor spaces, which are particularly effective for transmitting the virus, such as restaurants, nightclubs, public transport and gatherings such as funerals.[37][38][14]

It may be possible that people may be infected if they contaminated surfaces and then their eyes, nose or mouth with unwashed hands, but this has not been conclusively demonstrated.[16][14] Surfaces are easily decontaminated with household disinfectants which destroy the virus outside the human body or on the hands.[7] Disinfectants or bleach are not a medical treatment for COVID-19, and cause health problems when not used properly, such as when used inside the human body.[39]

Sputum and saliva carry large amounts of virus.[7][13][12][40] Although COVID-19 is not a sexually transmitted infection, direct contact such as kissing, intimate contact, and fecal–oral routes are suspected to

transmit the virus.[41][42] The virus may occur in breast milk, but whether it is transmittable to the baby is unknown.[43][44] The WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed.[45][16]

Estimates of the number of people infected by one person with COVID-19, the R0, have varied. The WHO's initial estimates of R0 were 1.4–2.5; however, a review in early April 2020 found the *basic* R0 to be higher at 3.28 and the median R0 to be 2.79.[46] However, a CDC study from the same month found that the median R0 of the virus was 5.7, with a basic R0 potentially as high as 8.9 without control measures, with a 95% confidence interval.[47]

Virology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel severe acute respiratory syndrome coronavirus. It was first isolated from three people with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan.[48] All features of the novel SARS-CoV-2 virus occur in related coronaviruses in nature.[49]

Outside the human body, the virus is destroyed by household soap, which bursts its protective bubble.[50]

SARS-CoV-2 is closely related to the original SARS-CoV.[51] It is thought to have an animal origin. Genetic analysis has revealed that the coronavirus genetically clusters with the genus *Betacoronavirus*, in subgenus *Sarbecovirus* together with two bat-derived strains. It is 96% identical at the whole genome level to other bat coronavirus samples.[52]

Pathophysiology

COVID-19 can affect the upper respiratory tract and the lower respiratory tract.[53] The lungs are the organs most affected by COVID-19 because the virus accesses host cells via the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of the lungs.[54] The virus uses a special surface glycoprotein called a spike to connect to ACE2 and enter the host cell.[55] The density of ACE2 in each tissue correlates with the severity of the disease in that tissue and some have suggested decreasing ACE2 activity might be protective,[56][57] though another view is that increasing ACE2 using angiotensin II receptor blocker medications could be protective.[58] As the alveolar disease progresses, respiratory failure might develop and death may follow.[57]

SARS-CoV-2 may also cause respiratory failure through affecting the brainstem as other coronaviruses have been found to invade the central nervous system (CNS). While virus has been detected in cerebrospinal fluid of autopsies, the exact mechanism by which it invades the CNS remains unclear and may first involve invasion of peripheral nerves given the low levels of ACE2 in the brain.[59][60]

The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium[61] as well as endothelial cells and enterocytes of the small intestine.[62]

The virus can cause acute myocardial injury and chronic damage to the cardiovascular system.[63] An acute cardiac injury was found in 12% of infected people admitted to the hospital in Wuhan, China,[64] and is more frequent in severe disease.[65] Rates of cardiovascular symptoms are high, owing to the systemic inflammatory response and immune system disorders during disease progression, but acute myocardial injuries may also be related to ACE2 receptors in the heart.[63] ACE2 receptors are highly expressed in the heart and are involved in heart function.[63][66] A high incidence of thrombosis (31%) and venous thromboembolism (25%) have been found in ICU patients with COVID-19 infections, and may be related to poor prognosis.[67] Blood vessel dysfunction and clot formation (as suggested by high D-dimer levels) are thought to play a significant role in mortality, incidences of clots leading to pulmonary embolisms, and ischaemic events within the brain have been noted as complications leading to death in patients infected with SARS-CoV-2. Infection appears to set off a chain of vasoconstrictive responses within the body, constriction of blood vessels within the pulmonary circulation has also been posited as a mechanism in which oxygenation decreases alongside the presentation of viral pneumonia.[69]

Another common cause of death is complications related to the kidneys.[69] Early reports show that up to 30% of hospitalized patients both in China and in New York have experienced some injury to their kidneys, including some persons with no previous kidney problems.[70]

Autopsies of people who died of COVID-19 have found diffuse alveolar damage (DAD), and lymphocyte-containing inflammatory infiltrates within the lung.[71]

Immunopathology

Although SARS-CoV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract, patients with severe COVID-19 have symptoms of systemic hyperinflammation. Clinical laboratory findings of elevated IL-2, IL-7, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), and tumour necrosis factor-α (TNF-α) indicative of cytokine release syndrome (CRS) suggest an underlying immunopathology.[64]

Additionally, people with COVID-19 and acute

respiratory distress syndrome (ARDS) have classical serum biomarkers of CRS, including elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin.[72]

Systemic inflammation results in vasodilation, allowing inflammatory lymphocytic and monocytic infiltration of the lung and the heart. In particular, pathogenic GM-CSF-secreting T-cells were shown to correlate with the recruitment of inflammatory IL-6-secreting monocytes and severe lung pathology in COVID-19 patients. Lymphocytic infiltrates have also been reported at autopsy.[71]

Diagnosis

The WHO has published several testing protocols for the disease.[74] The standard method of testing is real-time reverse transcription polymerase chain reaction (rRT-PCR).[75] The test is typically done on respiratory samples obtained by a nasopharyngeal swab; however, a nasal swab or sputum sample may also be used.[76][77] Results are generally available within a few hours to two days.[78][79] Blood tests can be used, but these require two blood samples taken two weeks apart, and the results have little immediate value.[80] Chinese scientists were able to isolate a strain of the coronavirus and publish the genetic sequence so laboratories across the world could independently develop polymerase chain reaction (PCR) tests to detect infection by the virus.[81][82][83] As of April 4 of 2020, antibody tests (which may detect active infections and whether a person had been infected in the past) were in development, but not yet widely used.[84][85][86] Antibody tests may be most accurate 2–3 weeks after a person's symptoms start.[87] The Chinese experience with testing has shown the accuracy is only 60 to 70%.[88] The US Food and Drug Administration (FDA) approved the first point-of-care test on March 21 of 2020 for use at the end of that month.[89] The absence or presence of COVID-19 signs and symptoms alone is not reliable enough for an accurate diagnosis.[90] Different clinical scores were created based on symptoms, laboratory parameters and imaging to determine patients with probable SARS-CoV-2 infection or more severe stages of COVID-19.[91][92]

Diagnostic guidelines released by Zhongnan Hospital of Wuhan University suggested methods for detecting infections based upon clinical features and epidemiological risk. These involved identifying people who had at least two of the following symptoms in addition to a history of travel to Wuhan or contact with other infected people: fever, imaging features of pneumonia, normal or reduced white blood cell count, or reduced lymphocyte count.[93]

A study asked hospitalised COVID-19 patients to cough into a sterile container, thus producing a saliva sample, and detected the virus in eleven of twelve patients using RT-PCR. This technique has the potential of being quicker than a swab and involving less risk to health care workers (collection at home or in the car).[40]

Along with laboratory testing, chest CT scans may be helpful to diagnose COVID-19 in individuals with a high clinical suspicion of infection but are not recommended for routine screening.[50][94] Bilateral multilobar ground-glass opacities with a peripheral, asymmetric, and posterior distribution are common in early infection.[50] Subpleural dominance, crazy paving (lobular septal thickening with variable alveolar filling), and consolidation may appear as the disease progresses.[50][95]

In late 2019, the WHO assigned emergency ICD-10 disease codes U07.1 for deaths from lab-confirmed SARS-CoV-2 infection and U07.2 for deaths from clinically or epidemiologically diagnosed COVID-19 without lab-confirmed SARS-CoV-2 infection.[96]

Pathology

Few pieces of data were available in spring 2020 about microscopic lesions and the pathophysiology of COVID-19.[97][98] The main pathological findings at autopsy are:

- Macroscopy: pleurisy, pericarditis, lung consolidation and pulmonary oedema
- Four types of severity of viral pneumonia can be observed:
  - minor pneumonia: minor serous exudation, minor fibrin exudation
  - mild pneumonia: pulmonary oedema, pneumocyte hyperplasia, large atypical pneumocytes, interstitial inflammation with lymphocytic infiltration and multinucleated giant cell formation
  - severe pneumonia: diffuse alveolar damage (DAD) with diffuse alveolar exudates. DAD is the cause of acute respiratory distress syndrome (ARDS) and severe hypoxemia.
  - healing pneumonia: organisation of exudates in alveolar cavities and pulmonary interstitial fibrosis
  - plasmocytosis in BAL[99]
- Blood: disseminated intravascular coagulation (DIC);[100] leukoerythroblastic reaction[101]
- Liver: microvesicular steatosis

Prevention

Without pandemic containment measures—such as social distancing, vaccination, and use of face masks—pathogens can spread exponentially.[102] This graphic shows how early adoption of containment measures tends to protect wider swaths of the population.

Progressively stronger mitigation efforts to reduce the number of active cases at any given time—flattening the curve—allows healthcare services to better manage the same volume of patients.[103][104][105] Likewise, progressively greater increases in healthcare

capacity—called *raising the line*—such as by increasing bed count, personnel, and equipment, helps to meet increased demand.[106]

Mitigation attempts that are inadequate in strictness or duration—such as premature relaxation of distancing rules or stay-at-home orders—can allow a resurgence after the initial surge and mitigation.[104][107]

A COVID-19 vaccine is not expected until 2021 at the earliest.[108] The US National Institutes of Health guidelines do not recommend any medication for prevention of COVID-19, before or after exposure to the SARS-CoV-2 virus, outside the setting of a clinical trial.[109][110] Without a vaccine, other prophylactic measures, or effective treatments, a key part of managing COVID-19 is trying to decrease and delay the epidemic peak, known as flattening the curve.[104] This is done by slowing the infection rate to decrease the risk of health services being overwhelmed, allowing for better treatment of current cases, and delaying additional cases until effective treatments or a vaccine become available.[104][107]

Preventive measures to reduce the chances of infection include staying at home, wearing a mask in public, avoiding crowded places, keeping distance from others, washing hands with soap and water often and for at least 20 seconds, practising good respiratory hygiene, and avoiding touching the eyes, nose, or mouth with unwashed hands.[111][112][113][114] Those diagnosed with COVID-19 or who believe they may be infected are advised by the CDC to stay home except to get medical care, call ahead before visiting a healthcare provider, wear a face mask before entering the healthcare provider's office and when in any room or vehicle with another person, cover coughs and sneezes with a tissue, regularly wash hands with soap and water and avoid sharing personal household items.[115][116]

Personal protective equipment

For healthcare professionals who may come into contact with COVID-19 positive bodily fluids, using personal protective coverings on exposed body parts improves protection from the virus.[117] Breathable personal protective equipment improves user-satisfaction and may offer a similar level of protection from the virus.[117] In addition, adding tabs and other modifications to the protective equipment may reduce the risk of contamination during donning and doffing.[117] Implementing an evidence-based donning and doffing protocol such as a one-step glove and gown removal technique, giving oral instructions while donning and doffing, double gloving, and the use of glove disinfection may also improve protection for healthcare professionals.[117]

Face masks

The World Health Organization (WHO) and most government health agencies, such as the US Centers for Disease Control and Prevention (CDC), the UK National Health Service (NHS), or the New Zealand Ministry of Health (NZMH) recommend individuals wear non-medical face coverings in public settings where there is an increased risk of transmission and where social distancing measures are difficult to maintain.[118][119][120][121][122] This recommendation is meant to reduce the spread of the disease by asymptomatic and pre-symtomatic individuals and is complementary to established preventive measures such as social distancing.[119][123] Face coverings limit the volume and travel distance of expiratory droplets dispersed when talking, breathing, and coughing.[119][123] Many countries and local jurisdictions encourage or mandate the use of face masks or cloth face coverings by members of the public to limit the spread of the virus.[124][125][126][127]

Masks are also strongly recommended for those who may have been infected and those taking care of someone who may have the disease.[128]

Social distancing

Social distancing strategies aim to reduce contact of infected persons with large groups by closing schools and workplaces, restricting travel, and cancelling large public gatherings.[129] Distancing guidelines also include that people stay at least 2 metres (6.6 ft) apart.[130] After the implementation of social distancing and stay-at-home orders, many regions have been able to sustain an effective transmission rate ("R_t") of less than one, meaning the disease is in remission in those areas.[131]

Hand-washing and hygiene

When not wearing a mask, the CDC, WHO, and NHS recommends covering the mouth and nose with a tissue when coughing or sneezing and recommends using the inside of the elbow if no tissue is available.[112][121][132] Proper hand hygiene after any cough or sneeze is encouraged.[112][121] The WHO also recommends that individuals wash hands often with soap and water for at least 20 seconds, especially after going to the toilet or when hands are visibly dirty, before eating and after blowing one's nose.[132] The CDC recommends using an alcohol-based hand sanitiser with at least 60% alcohol, but only when soap and water are not readily available.[121] For areas where commercial hand sanitisers are not readily available, the WHO provides two formulations for local production. In these formulations, the antimicrobial activity arises from ethanol or isopropanol. Hydrogen peroxide is used to help eliminate bacterial spores in the alcohol; it is not an active substance for hand antisepsis. Glycerol is added as a humectant.[133]

Sanitizing of frequently touched surfaces is also recommended or required by regulation for businesses and public facilities; the United States Environmental

Protection Agency maintains a list of products expected to be effective.[134]

Management

People are managed with supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.[135][136][137] The CDC recommends those who suspect they carry the virus wear a simple face mask.[115] Extracorporeal membrane oxygenation (ECMO) has been used to address the issue of respiratory failure, but its benefits are still under consideration.[138] Personal hygiene and a healthy lifestyle and diet have been recommended to improve immunity.[139] Supportive treatments may be useful in those with mild symptoms at the early stage of infection.[140]

The WHO, the Chinese National Health Commission, and the United States' National Institutes of Health have published recommendations for taking care of people who are hospitalised with COVID-19.[109][141][142] Intensivists and pulmonologists in the US have compiled treatment recommendations from various agencies into a free resource, the IBCC.[143][144]

Prognosis

The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover.[150] Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.[52]

Children make up a small proportion of reported cases, with about 1% of cases being under 10 years and 4% aged 10–19 years.[12] They are likely to have milder symptoms and a lower chance of severe disease than adults. In those younger than 50 years the risk of death is less than 0.5%, while in those older than 70 it is more than 8%.[151][152][153] Pregnant women may be at higher risk of severe COVID-19 infection based on data from other similar viruses, like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), but data for COVID-19 is lacking.[154][155] According to scientific reviews smokers are more likely to require intensive care or die compared to non-smokers,[156][157] air pollution is similarly associated with risk factors,[157] and obesity contributes to an increased health risk of COVID-19.[157][158][159]

A European multinational study of hospitalized children published in *The Lancet* on June 25 of 2020 found that about 8% of children admitted to a hospital needed intensive care. Four of those 582 children (0.7%) died, but the actual mortality rate could be substantially lower since milder cases that did not seek medical help were not included in the study.[160]

Comorbidities

Most of those who die of COVID-19 have pre-existing (underlying) conditions, including hypertension, diabetes mellitus, and cardiovascular disease.[207] The Istituto Superiore di Sanità reported that out of 8.8% of deaths where medical charts were available, 97% of people had at least one comorbidity with the average person having 2.7 diseases.[208] According to the same report, the median time between the onset of symptoms and death was ten days, with five being spent hospitalised. However, people transferred to an ICU had a median time of seven days between hospitalisation and death.[208] In a study of early cases, the median time from exhibiting initial symptoms to death was 14 days, with a full range of six to 41 days.[209] In a study by the National Health Commission (NHC) of China, men had a death rate of 2.8% while women had a death rate of 1.7%.[210] In 11.8% of the deaths reported by the National Health Commission of China, heart damage was noted by elevated levels of troponin or cardiac arrest.[211] According to March data from the United States, 89% of those hospitalised had preexisting conditions.[212]

Most critical respiratory comorbidities according to the CDC are: moderate or severe asthma, pre-existing COPD, pulmonary fibrosis, cystic fibrosis.[213] Evidence stemming from meta-analysis of several smaller research papers also suggests that smoking can be associated with worse patient outcomes.[214][215] When someone with existing respiratory problems is infected with COVID-19, they might be at greater risk for severe symptoms.[216] COVID-19 also poses a greater risk to people who misuse opioids and methamphetamines, insofar as their drug use may have caused lung damage.[217]

Complications

Complications may include pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and death.[81][218][219][220]

Cardiovascular complications may include heart failure, arrhythmias, heart inflammation, and blood clots.[221][222][223][224]

Approximately 20–30% of people who present with COVID-19 have elevated liver enzymes reflecting liver injury.[225][110]

Neurologic manifestations include seizure, stroke, encephalitis, and Guillain–Barré syndrome.[226][227] Following the infection, children may develop paediatric multisystem inflammatory syndrome, which has symptoms similar to Kawasaki disease, which can be fatal.[228][229]

Longer-term effects

Concerns have been raised about long-term sequelae of the disease, while patients with a severe form of the acute disease may also suffer from post-intensive care syndrome following recovery.[230]

The University of Leicester and the University Hospitals of Leicester NHS Trust are undertaking a major study into the long-term health effects of COVID-19 as of August 2020.[25]

Immunity

The immune response by humans to CoV-2 virus occurs as a combination of the cell-mediated immunity and antibody production,[231] just as with most other infections.[232] However, it remains unknown if the immunity is long-lasting in people who recover from the disease. [*needs update*][233] Cases in which recovery from COVID-19 was followed by positive tests for coronavirus at a later date have been reported.[234] However, these cases are believed to be lingering infection rather than reinfection,[234] or false positives due to remaining RNA fragments. [*medical citation needed*] Some other coronaviruses circulating in people are capable of reinfection after roughly a year.[235]

History

The virus is thought to be natural and has an animal origin,[49] through spillover infection.[236] A study of the first 41 cases of confirmed COVID-19, published in January 2020 in *The Lancet*, reported the earliest date of onset of symptoms as December 1 of 2019.[237][238][239] Official publications from the WHO reported the earliest onset of symptoms as December 8 of 2019.[240] Human-to-human transmission was confirmed by the WHO by January 20 of 2020.[241][242] These were mostly linked to the live animals.[243] In May 2020, Gao Fu, the director of the Chinese Center for Disease Control and Prevention, said animal samples collected from the seafood market had tested negative for the virus, indicating that the market was the site of an early superspreading event, but it was not the site of the initial outbreak.[244] Traces of the virus have been found in wastewater that was collected from Milan and Turin, Italy, on December 18 of 2019.[245]

There are several theories about where the very first case (patient zero) originated.[246] According to an unpublicised report, the first case can be traced back to 17 November 2019; the person was a 55-year old citizen in the Hubei province. There were four men and five women reported to be infected in November, but none of them were patient zero. By December 2019, the spread of infection was almost entirely driven by human-to-human transmission.[146][247] The number of coronavirus cases in Hubei gradually increased, reaching 60 by December 20[248] and at least 266 by December 31.[249] On December 24, Wuhan Central Hospital sent a bronchoalveolar lavage fluid (BAL) sample from an unresolved clinical case to sequencing company Vision Medicals. On December 27 and 28, Vision Medicals informed the Wuhan Central Hospital and the Chinese CDC of the results of the test, showing a new coronavirus.[250] A pneumonia cluster of unknown cause was observed on December 26 and treated by the doctor Zhang Jixian in Hubei Provincial Hospital, who informed the Wuhan Jianghan CDC on December 27.[251] On December 30, a test report addressed to Wuhan Central Hospital, from company CapitalBio Medlab, stated an erroneous positive result for SARS, causing a group of doctors at Wuhan Central Hospital to alert their colleagues and relevant hospital authorities of the result. That evening, the Wuhan Municipal Health Commission issued a notice to various medical institutions on the treatment of pneumonia of unknown cause.[252][253][254]

The Wuhan Municipal Health Commission made the first public announcement of a pneumonia outbreak of unknown cause on December 31, confirming 27 cases[255][256][257] enough to trigger an investigation.[258]

During the early stages of the outbreak, the number of cases doubled approximately every seven and a half days.[259] In early and mid-January 2020, the virus spread to other Chinese provinces, helped by the Chinese New Year migration and Wuhan being a transport hub and major rail interchange.[52] On January 20, China reported nearly 140 new cases in one day, including two people in Beijing and one in Shenzhen.[260] Later official data shows 6,174 people had already developed symptoms by then,[261] and more may have been infected.[262] A report in *The Lancet* on January 24 indicated human transmission, strongly recommended personal protective equipment for health workers, and said testing for the virus was essential due to its pandemic potential.[64][263] On January 30, the WHO declared the coronavirus a public health emergency of international concern.[262] By this time, the outbreak spread by a factor of 100 to 200 times.[264]

On January 31 2020, Italy had its first confirmed cases.[265] As of March 13 2020, WHO considered Europe the active centre of the pandemic.[266] On March 19 2020, Italy overtook China as the country with the most deaths.[267] By March 26, the United States had overtaken Italy and China with the highest number of confirmed cases in the world.[268] Research on coronavirus genomes indicates the majority of COVID-19 cases in New York came from European travellers, rather than directly from China or any other Asian country.[269] Retesting of prior samples found a person in France who had the virus on December 27 2019[270][271] and a person in the United States who died from the disease on February 6 2020.[272]

On June 11 2020, after 55 days without a locally transmitted case,[273] Beijing reported the first COVID-19 case, followed by two more cases on June 12 2020.[274] By June 15 2020m 79 cases were officially confirmed.[275] Most of these patients went to Xinfadi Wholesale Market.[273][276]

Epidemiology

Several measures are commonly used to quantify mortality.[277] These numbers vary by region and over time and are influenced by the volume of testing, healthcare system quality, treatment options, time since the initial outbreak, and population characteristics such as age, sex, and overall health.[278]

The death-to-case ratio reflects the number of deaths divided by the number of diagnosed cases within a given time interval. Based on Johns Hopkins University statistics, the global death-to-case ratio is 3.1% (965,575/31,358,115) as of September 22 2020.[9] The number varies by region.[279]

Other measures include the case fatality rate (CFR), which reflects the percentage of *diagnosed* individuals who die from a disease, and the infection fatality rate (IFR), which reflects the percentage of *infected* individuals (diagnosed and undiagnosed) who die from a disease. These statistics are not time-bound and follow a specific population from infection through case resolution. Many academics have attempted to calculate these numbers for specific populations.[280]

Outbreaks have occurred in prisons due to crowding and an inability to enforce adequate social distancing.[281][282] In the United States, the prisoner population is aging and many of them are at high risk for poor outcomes from COVID-19 due to high rates of coexisting heart and lung disease, and poor access to high-quality healthcare.[281]

Infection fatality rate

Infection fatality rate or infection fatality ratio (IFR) is distinguished from case fatality rate (CFR). The CFR for a disease is the proportion of deaths from the disease compared to the total number of people *diagnosed* with the disease. The IFR, in contrast, is the proportion of deaths among all the *infected* individuals. IFR, unlike CFR, attempts to account for all asymptomatic and undiagnosed infections. [283] [284]

Our World in Data states that, as of March 25 2020, the IFR for coronavirus cannot be accurately calculated.[285] In February, WHO reported estimates of IFR between 0.3% and 1%.[286][287] On July 2, The WHO's Chief Scientist reported that the average IFR estimate presented at a two-day WHO expert forum was about 0.6%.[288][289]

The CDC estimated for planning purposes that the IFR is 0.7% and that 40% of infected individuals are asymptomatic, suggesting a fatality rate among those who are symptomatic of 1.1%.[290][291] Studies incorporating data from broad serology testing in Europe show IFR estimates converging at approximately 0.5-1%.[292] According to the University of Oxford Centre for Evidence-Based Medicine (CEBM), random antibody testing in Germany suggested a national IFR of 0.4% (0.1% to 0.9%).[293][294][295]

Firm lower limits of IFRs have been established in a number of locations such as New York City and Bergamo in Italy since the IFR cannot be less than the population fatality rate. As of July 10 2020, in New York City, with a population of 8.4 million, 23,377 individuals have died with COVID-19 (0.3% of the population).[296] May antibody testing in New York City suggested an IFR of 0.9%.[297] In Bergamo province, 0.6% of the population has died.[298]

Sex differences

Early reviews of epidemiologic data showed greater impact of the pandemic and a higher mortality rate in men in Italy and China.[299][2][300] The Chinese Center for Disease Control and Prevention reported the death rate was 2.8% for men and 1.7% for women.[301] Later reviews in June 2020 indicated that there is no significant difference in susceptibility or in CFR between genders.[302][303] One review acknowledges the different mortality rates in Chinese men, suggesting that it may be attributable to lifestyle choices such as smoking and drinking alcohol rather than genetic factors.[304] Sex-based immunological differences, lesser prevalence of smoking in women and men developing co-morbid conditions such as hypertension at a younger age than women could have contributed to the higher mortality in men.[305] In Europe, 57% of the infected people were men and 72% of those died with COVID-19 were men.[306] As of April 2020, the US government is not tracking sex-related data of COVID-19 infections.[307] Research has shown that viral illnesses like Ebola, HIV, influenza and SARS affect men and women differently.[307]

Ethnic differences

In the US, a greater proportion of deaths due to COVID-19 have occurred among African Americans.[309] Structural factors that prevent African Americans from practicing social distancing include their concentration in crowded substandard housing and in essential occupations such as public transit and health care. Greater prevalence of lacking health insurance and care and of underlying conditions such as diabetes, hypertension and heart disease also increase their risk of death.[310] Similar issues affect Native American and Latino communities.[309] According to a US health policy non-profit, 34% of American Indian and Alaska Native People (AIAN) non-elderly adults are at risk of serious illness compared to 21% of white non-elderly adults.[311] The source attributes it to disproportionately high rates of many health conditions that may put them at higher risk as well as living conditions like lack of access to clean water.[312] Leaders have called for efforts to research and address the disparities.[313]

In the U.K., a greater proportion of deaths due to COVID-19 have occurred in those of a Black, Asian,

and other ethnic minority background.[314][315][316] Several factors such as poverty, poor nutrition and living in overcrowded properties, may have caused this.

Society and culture

Name

The virus and disease were commonly referred to as coronavirus.[317][318][319][320][321][323]

In January 2020, WHO recommended 2019-nCov[324] and 2019-nCoV acute respiratory disease[325] as interim names for the virus and disease per 2015 guidance and international guidelines against using geographical locations, animal species.[326][327][328]

The official names COVID-19 and SARS-CoV-2 were issued by the WHO on February 11 2020.[329] WHO chief Tedros Adhanom Ghebreyesus explained: CO for *corona*, VI for *virus*, D for *disease* and 19 for when the outbreak was first identified (December 31 20*19*).[330] The WHO additionally uses "the COVID-19 virus" and "the virus responsible for COVID-19" in public communications.[329]

Misinformation

After the initial outbreak of COVID-19, misinformation and disinformation regarding the origin, scale, prevention, treatment, and other aspects of the disease rapidly spread online.[331][332][333]

Other health issues

The pandemic has had many impacts on global health beyond those caused by the COVID-19 disease itself. It has led to a reduction in hospital visits for other reasons. There have been 38% fewer hospital visits for heart attack symptoms in the United States and 40% fewer in Spain.[334][335] There is also concern that people with strokes and appendicitis are not seeking timely treatment.[335] Shortages of medical supplies have impacted people with various conditions.[336] However, some other diseases are reduced by the concerns of the COVID-19. In some countries and districts there has been a marked reduction of spread of sexually transmitted infections, including HIV, attributable to COVID-19 quarantines and social distancing needed.[337][338] Similarly, in some places, rates of transmission of influenza and other respiratory viruses significantly decreased during the COVID-19 pandemic.[339][340][341] The pandemic has negatively impacted mental health globally, including increased loneliness resulting from social distancing.[342]

Other animals

Humans appear can spread the virus to animals. A domestic cat in Liège, Belgium, tested positive after it started showing symptoms (diarrhoea, vomiting, shortness of breath) a week later than its owner, who was also positive.[343] Tigers and lions at the US New York Bronx Zoo were tested positive for the coronavirus and showed symptoms of COVID-19, including a dry cough and loss of appetite.[344] Minks at two farms in the Netherlands also tested positive for COVID-19.[345]

Different races have different responses to the COVID-19 virus depending on the genetic background. A study on domesticated animals inoculated with the virus found that cats and ferrets appear to be highly susceptible to the disease, while dogs appear to be less susceptible, with lower levels of viral replication. The study failed to find evidence of viral replication in pigs, ducks, and chickens.[346]

In March 2020, researchers from the University of Hong Kong have shown that Syrian hamsters could be a model organism for COVID-19 researches.[347]

As of August 2020, dozens of domestic cats and dogs had tested positive, though according to the U.S. CDC, there was no evidence they transmitted the virus to humans.[348] CDC guidance recommends potentially infected people avoid close contact with pets.[348]It is possible for the animals to infect COVID-19 to people.

Research

No medication or vaccine other than remdesivir is approved with the specific indication to treat the disease in any country.[349] In Australia and the European Union, remdesivir (Veklury) is indicated for the treatment of COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen.[350][351][352] International research on vaccines and medicines in COVID-19 is underway by government organisations, academic groups, and industry researchers.[353][354] In March 2020, WHO initiated the Solidarity Trial to assess the treatment effects of four existing antiviral compounds with the most promise of efficacy.[355] WHO suspended hydroxychloroquine from its global drug trials for COVID-19 treatments on May 26 2020 due to safety concerns. It had previously enrolled 3,500 patients from 17 countries in the Solidarity Trial.[356] France, Italy and Belgium also banned the use of hydroxychloroquine as a COVID-19 treatment.[357]

Modelling research has been conducted with several objectives, including predictions of the dynamics of transmission,[358] diagnosis and prognosis of infection,[359] estimation of the impact of interventions,[360][361] or allocation of resources.[362] Modelling studies are mostly based on epidemiological models,[363] estimating the number of infected people over time under given conditions. Several other types of models have been developed and used during the COVID-19 including computational fluid dynamics models to study the flow physics of COVID-19,[364] retrofits of crowd movement models to study occupant exposure,[365] mobility-data based models to investigate transmission,[366] or the use of macroeconomic models to assess the economic impact of the pandemic.[367]

There has been a great deal of COVID-19 research, involving accelerated research processes and publishing shortcuts to meet the global demand. To minimise the harm from misinformation, medical professionals and the public are advised to expect rapid changes to available information, and to be attentive to retractions and other updates.[368]

Vaccine

There is no available vaccine, but various agencies are actively developing vaccine candidates. Previous work on SARS-CoV is being used because both SARS-CoV and SARS-CoV-2 use the ACE2 receptor to enter human cells.[369] Nine vaccine platforms are being investigated (as of August 2020),[370] with 24 candidate vaccines being tested in clinical trials.[371][372] First, researchers aim to build a whole virus vaccine. The use of such inactive virus aims to elicit a prompt immune response of the human body to a new infection with COVID-19.[373] A second strategy, subunit vaccines, aims to create a vaccine that sensitises the immune system to certain subunits of the virus.[373] In the case of SARS-CoV-2, such research focuses on the S-spike protein that helps the virus intrude the ACE2 enzyme receptor. A third strategy is that of the nucleic acid vaccines (DNA or RNA vaccines, a novel technique for creating a vaccination).[373] Fourthly, scientists are attempting to use viral vectors to deliver the SARS-CoV-2 antigen gene into the cell. These can be replicating or non-replicating.[373] Experimental vaccines from any of these strategies would have to be tested for safety and efficacy.[374]

Antibody-dependent enhancement represents a significant potential challenge for vaccine development for SARS-COV-2.[375]

Two vaccines have received partial approval. The Gamaleya Research Institute's adenovirus 5 and adenovirus 26 vectored vaccine and the CanSino BIO's adenovirus 5 vectored vaccine have been approved in Russia and China respectively. Neither of these have undergone Phase III trials for efficacy.[376]

Medications

At least 29 Phase II–IV efficacy trials in COVID-19 were concluded in March 2020, or scheduled to provide results in April from hospitals in China.[377][378] There are more than 300 active clinical trials underway as of April 2020.[110] Seven trials were evaluating already approved treatments, including four studies on hydroxychloroquine or chloroquine.[378] Repurposed antiviral drugs make up most of the research, with nine Phase III trials on remdesivir across several countries due to report by the end of April.[377][378] Other candidates in trials include vasodilators, corticosteroids, immune therapies, lipoic acid, bevacizumab, and recombinant angiotensin-converting enzyme 2.[378]

The COVID-19 Clinical Research Coalition has goals to 1) facilitate rapid reviews of clinical trial proposals by ethics committees and national regulatory agencies, 2) fast-track approvals for the candidate therapeutic compounds, 3) ensure standardised and rapid analysis of emerging efficacy and safety data and 4) facilitate sharing of clinical trial outcomes before publication.[379][380]

Several existing medications are being evaluated for the treatment of COVID-19,[349] including remdesivir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, and lopinavir/ritonavir combined with interferon beta.[355][381] There is tentative evidence for efficacy by remdesivir, and on May 1 2020, the United States Food and Drug Administration (FDA) gave the drug an emergency use authorization (EUA) for people hospitalized with severe COVID-19.[382] On August 28 2020, the FDA broadened the EUA for remdesivir to include all hospitalized patients with suspected or laboratory-confirmed COVID-19, irrespective of the severity of their disease.[383][384][385] Phase III clinical trials for several drugs [*which?*] are underway in several countries, including the US, China, and Italy.[349][377][386]

There are mixed results as of April 3 2020, as to the effectiveness of hydroxychloroquine as a treatment for COVID-19, with some studies showing little or no improvement.[387][388] One study has shown an association between hydroxychloroquine or chloroquine use with higher death rates along with other side effects.[389][390] A retraction of this study by its authors was published by *The Lancet* on June 4 2020.[391] The studies of chloroquine and hydroxychloroquine with or without azithromycin have major limitations that have prevented the medical community from embracing these therapies without further study.[110] On June 15 2020, the FDA updated the fact sheets for the emergency use authorization of remdesivir to warn that using chloroquine or hydroxychloroquine with remdesivir may reduce the antiviral activity of remdesivir.[392]

In June 2020, initial results from a randomised trial in the United Kingdom showed that dexamethasone reduced mortality by one third for patients who are critically ill on ventilators and one fifth for those receiving supplemental oxygen.[393] Because this is a well tested and widely available treatment this was welcomed by the WHO that is in the process of updating treatment guidelines to include dexamethasone or other steroids.[394][395] Based on those preliminary results, dexamethasone treatment has been recommended by the National Institutes of Health for patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen but not in patients with COVID-19 who do not require supplemental oxygen.[396]

In September 2020, the WHO released updated guidance on using corticosteroids for COVID-19.[397] The WHO recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of people with severe and critical COVID-19.[397] The WHO suggests not to use corticosteroids in the treatment of people with non-severe COVID-19.[397] The updated guidance was based on a meta-analysis of clinical trials of critically ill COVID-19 patients.[398][399]

In September 2020, the European Medicines Agency (EMA) endorsed the use of dexamethasone in adults and adolescents who require supplemental oxygen therapy.[400] Dexamethasone can be taken by mouth or given as an injection or infusion drip into a vein.[400]

Cytokine storm

A cytokine storm can be a complication in the later stages of severe COVID-19. There is preliminary evidence that hydroxychloroquine may be useful in controlling cytokine storms in late-phase severe forms of the disease.[401]

Tocilizumab has been included in treatment guidelines by China's National Health Commission after a small study was completed.[402][403] It is undergoing a Phase II non-randomised trial at the national level in Italy after showing positive results in people with severe disease.[404][405] Combined with a serum ferritin blood test to identify a cytokine storm, it is meant to counter such developments, which are thought to be the cause of death in some affected people.[406][407][408] The interleukin-6 receptor antagonist was approved by the FDA to undergo a Phase III clinical trial assessing its effectiveness on COVID-19 based on retrospective case studies for the treatment of steroid-refractory cytokine release syndrome induced by a different cause, CAR T cell therapy, in 2017.[409] There is no randomised, controlled evidence that tocilizumab is an efficacious treatment for CRS. Prophylactic tocilizumab has been shown to increase serum IL-6 levels by saturating the IL-6R, driving IL-6 across the blood-brain barrier, and exacerbating neurotoxicity while having no effect on the incidence of CRS.[410]

Lenzilumab, an anti-GM-CSF monoclonal antibody, is protective in murine models for CAR T cell-induced CRS and neurotoxicity and is a viable therapeutic option due to the observed increase of pathogenic GM-CSF secreting T-cells in hospitalised patients with COVID-19.[411]

The Feinstein Institute of Northwell Health announced in March 2020 a study on a human antibody that may prevent the activity of IL-6.[412]

Passive antibodies

Transferring purified and concentrated antibodies produced by the immune systems of those who have recovered from COVID-19 to people who need them is being investigated as a non-vaccine method of passive immunisation.[413][414] The safety and effectiveness of convalescent plasma as a treatment option requires further research.[414] This strategy was tried for SARS with inconclusive results.[413] Viral neutralization is the anticipated mechanism of action by which passive antibody therapy can mediate defence against SARS-CoV-2. The spike protein of SARS-CoV-2 is the primary target for neutralizing antibodies.[415] As of August 8 2020, eight neutralizing antibodies targeting the spike protein of SARS-CoV-2 have entered clinical studies.[416] It has been proposed that selection of broad-neutralizing antibodies against SARS-CoV-2 and SARS-CoV might be useful for treating not only COVID-19 but also future SARS-related CoV infections.[415] Other mechanisms, however, such as antibody-dependent cellular cytotoxicity and phagocytosis, may be possible.[413] Other forms of passive antibody therapy, for example, using manufactured monoclonal antibodies, are in development.[413] Production of convalescent serum, which consists of the liquid portion of the blood from recovered patients and contains antibodies specific to this virus, could be increased for quicker deployment.[417]

Laminoid antibodies

Peru announced in April 2020 that it would begin working towards creating a vaccine, with the pharmaceutical company Farvet and Universidad Peruana Cayetano Heredia (UPCH) announcing plans to jointly develop a vaccine in Chincha.[418] Peru's Experimental Station for Scientific Research and Genetic Improvement of Alpacas belonging to the Inca Group, selected on June 5 2020 four alpacas for the development of a new vaccine that it had been developing in conjunction with Farvet and UPCH. They also indicated that alpacas have the ability to generate some types of antibodies known as nanobodies, which are very small and have a greater potential to treat pathogens.[419] According to Andina, research from the United States, Belgium, and Chile showed that antibodies from laminoid animals could possibly be formulated into inhaler or injection treatments for those infected with coronaviruses, with Teodosio Huanca of Peru's National Institute of Agricultural Innovation (INIA) National Camelid Program stating that Peruvian camelidae share the same genetic roots and antibodies.[420]

On August 7, the Peruvian National Institute of Health (INS) announced that it would begin the development of a possible treatment for COVID-19 utilizing recombinant nanoantibodies from a llama named Tito.[421] According to the INIA, Peru holds the only germplasm bank of South American camelids in the world, with 1,700 samples of alpacas and 1,200 of

llamas".[421]

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