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CORONAVIRUS DISEASE.

**Coronavirus disease 2019** (**COVID-19**) is an [infectious disease](https://en.wikipedia.org/wiki/Infectious_disease) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in [Wuhan](https://en.wikipedia.org/wiki/Wuhan), the capital of China's [Hubei](https://en.wikipedia.org/wiki/Hubei) province, and has since spread globally, resulting in the ongoing [2019-20 coronavirus pandemic](https://en.wikipedia.org/wiki/2019%E2%80%9320_coronavirus_pandemic). Common [symptoms](https://en.wikipedia.org/wiki/Symptom) include [fever](https://en.wikipedia.org/wiki/Fever), [cough](https://en.wikipedia.org/wiki/Cough), and [shortness of breath](https://en.wikipedia.org/wiki/Shortness_of_breath). Other symptoms may include fatigue, [muscle pain](https://en.wikipedia.org/wiki/Myalgia), [diarrhea](https://en.wikipedia.org/wiki/Diarrhea), [sore throat](https://en.wikipedia.org/wiki/Sore_throat), [loss of smell](https://en.wikipedia.org/wiki/Loss_of_smell), and abdominal pain.The [time from exposure to onset of symptoms](https://en.wikipedia.org/wiki/Incubation_period) is typically around five days but may range from two to fourteen days. While the majority of cases result in mild symptoms, some progress to viral [pneumonia](https://en.wikipedia.org/wiki/Pneumonia) and [multi-organ failure](https://en.wikipedia.org/wiki/Multi-organ_failure). As of 15 April 2020, more than 1.98 million [cases](https://en.wikipedia.org/wiki/2019%E2%80%9320_coronavirus_pandemic_cases/WHO_situation_reports) have been reported across 210 countries and territories, resulting in over 126,000 [deaths](https://en.wikipedia.org/wiki/2019%E2%80%9320_coronavirus_pandemic_deaths/WHO_situation_reports). More than 486,000 people have recovered.

**Aetiology**

Virology

• 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. Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals 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 SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.The full genome has been determined and published in 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. [Fig-1] 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.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. Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses. Transmission dynamics Person-to-person spread has been confirmed in community and healthcare settings, with local transmission occurring in many countries around the world. An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 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. It is uncertain how easily the virus spreads between people, but transmission in chains involving several links has been recognised. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care. 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). 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. In healthcare settings, the virus is widely distributed in the air and on object surfaces (e.g., floors, rubbish bins, sickbed handrails, and computer mice) in both general wards and intensive care units, with a greater risk of contamination in the intensive care unit. The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, cerebrospinal fluid, urine, saliva, tears, and conjunctival secretions. Faecal-oral transmission may be possible (virus has been detected in the stool samples of almost half of the patients in one meta-analysis), although it has not been reported yet. The presence of virus in these fluids or viral RNA shedding does not necessarily equate with infectivity. • Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series. The majority of healthcare workers with COVID-19 reported contact in the healthcare setting. In a study of over 9000 cases reported in healthcare workers in the US, 55% had contact only in a healthcare setting, 27% only in a household, 13% only in the community, and 5% in more than one setting. 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). Clusters of cases originating from family gatherings have been reported, emphasising the importance of social distancing even within families. The rate of secondary transmission among household contacts of infected patients is approximately 30%. Pre-symptomatic transmission

A small number of studies suggest that some people can be contagious during the incubation period, the time between exposure to the virus and the onset of symptoms. The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 7 days (possibly longer in children). Approximately 97.5% of patients develop symptoms within 11.5 days of infection. Pre-symptomatic transmission has been reported in 12.6% of cases in China. A study in Singapore identified 6.4% of patients among seven clusters of cases in which presymptomatic transmission was likely to have occurred 1 to 3 days before symptom onset. Presymptomatic transmission still requires the virus to be spread by infectious droplets or contact with fomites. Asymptomatic transmission

An asymptomatic case is a laboratory-confirmed case who does not develop symptoms. There is some evidence that spread from asymptomatic carriers is possible, although it is thought that transmission is greatest when people are symptomatic (especially around the time of symptom onset). 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 modelling study found that approximately 700 people with confirmed infection (18%) were asymptomatic. However, a Japanese study of citizens evacuated from Wuhan City estimates the rate to be closer to 31%. Data from a long- term care facility in the US found that 30% of patients with positive test results were asymptomatic (or pre-symptomatic) on the day of testing. Early data from an isolated village of 3000 people in Italy estimates the figure to be higher at 50% to 75%. Other studies ranged from 4% to 80%. A study in a New York obstetric population found that 88% of women who tested positive for SARS- CoV-2 at admission were asymptomatic at presentation. The proportion of asymptomatic cases in children is thought to be significant, and children may play a role in community spread. 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. 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. 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 behavioural and environmental factors. 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. 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.

PATHOGENESIS.

# INTRODUCTION

Coronaviruses, a family of viruses within the Nidovirus superfamily, were divided into three groups (1, 2, 3), originally based on antigenic reactivity, later confirmed by genome sequencing. Recently, a new taxonomic nomenclature was adapted by the International Committee on Taxonomy of Viruses (2009) ([http://talk.ictvonline.org/media/g/vertebrate-2008/default.aspx)](http://talk.ictvonline.org/media/g/vertebrate-2008/default.aspx). As such, coronaviruses are divided into three genera (alpha, beta and gammacoronaviruses), corresponding to groups 1, 2, 3, within the subfamily coronavirinae, within the family of coronaviridae, and within the order or superfamily of nidovirales.

Coronaviruses cause diseases in a variety of domestic and wild animals as well as in humans. Probably the most well-studied coronavirus is the betacoronavirus, murine coronavirus (MuCoV), mouse hepatitis virus (commonly referred to as MHV) that has long provided model systems for the study of central nervous system (CNS) diseases such as encephalitis and multiple sclerosis (MS) and acute hepatitis. While most coronavirus infections cause the common cold in humans, the emergence of the agent for severe acute respiratory syndrome (SARS), the SARS-associated coronavirus (SARS-CoV), also a betacoronavirus, demonstrated the potential for further significant human diseases to result from coronavirus infections. Indeed, shortly after the identification of the SARS-associated human coronavirus (HCoV), new coronavirus were identified in association with more severe infections in humans, NL63 an alphacoronavirus, believed to cause bronchiolitis in children, and HKU1, a betacoronavirus, associated with chronic respiratory disease in the elderly (Pyrc et al., 2007). This review will concentrate on the model MuCoV and the human SARS-CoV.

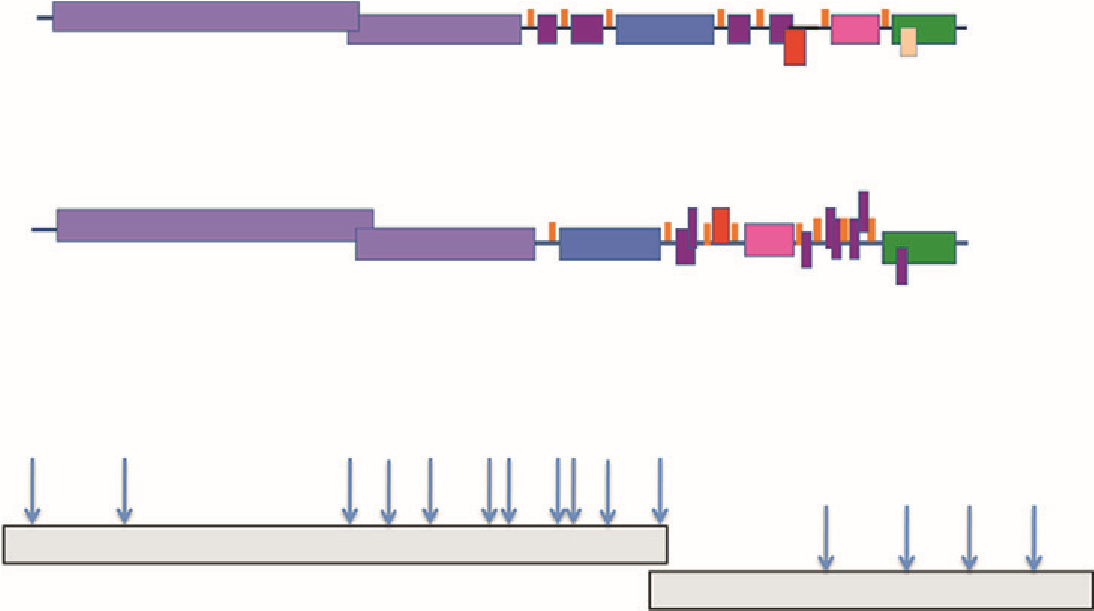
# II. GENOME AND VIRION

Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genomes, of 30–32 kb (Fig. 1). All coronavirus genomes are arranged similarly with the replicase locus encoded within the 50 end and the structural proteins encoded in the 30 third of the genome arranged in the order hemagglutinin esterase (HE), if present (HE is only present in some betacoronaviruses), spike (S), small membrane (E), membrane (M) and nucleocapsid (N) and internal (I) protein, encoded within the N gene (Fig. 1). The nucleocapsid protein complexes with the genome RNA to form a helical capsid structure found within the viral envelope. Trimers of the spike protein form the peplomers embedded in the envelope giving the virion its corona or crown-like morphology. In some coronavirus virions, the HE protein forms smaller spikes on the membrane. M and E are also transmembrane proteins involved in virus assembly (Fig. 2).

The 50 end of the coronavirus genome encodes the replicase gene, containing two very large open reading frames (orfs), orf1a and orf1b, encompassing about 20 kb or two-thirds of the genome. The replicase is translated as two large polyproteins (pp) 1a and 1ab, with pp1ab expressed via a translational frame shift encoded near the end of orf1a. These replicase polyproteins are cotranslationally cleaved into 16 proteins, many of which have enzymatic activities, including two or three proteases, several RNA modification enzymes as well as a polymerase and helicase, as will be discussed below. Intermingled with the structural genes are a variable number of accessory nonstructural genes encoding

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A



MHV-JHM.SD

L

L

SARS-CoV

nsp

1

b

b

1

2

a

HE

E

E

M

M

N

N

I

S

S

3

3

2

1

45

6

7

89

10

11

12

13

14

1516

4

5

a

6

6

7

a/3b

3

a/7b

7

8

a/8b

b

9

orf1a

orf1b

a

1

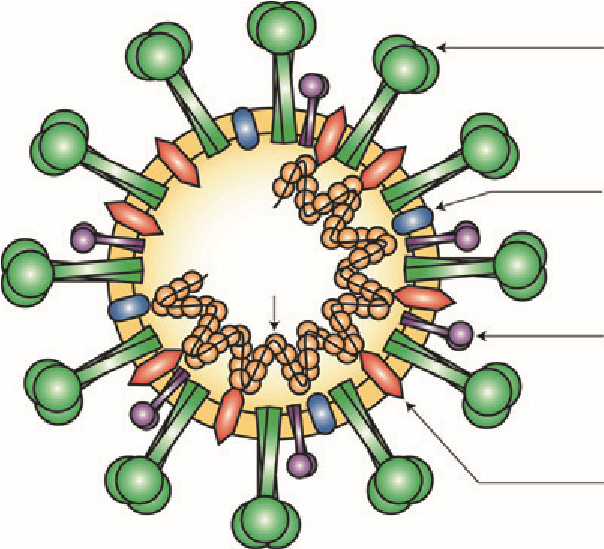
1

a

B

FIGURE 1 Genome organization and replicase encoded nonstructural proteins. (A) The genomes of MHV-JHM.SD and SARS-CoV are diagrammed. L, leader; ORF1a/1b, replicase; structural genes: HE, hemagglutinin-esterase; S, spike; E, small membrane envelope; M, membrane; N, nucleocapsid; I, internal. orfs encoding accessory genes are designated with numbers. (B). Arrows indicate cleavage sites for orf1a, orf1ab encoded polypeptides and numbers indicate individual nsp cleavage products.

S



RNA

N

E

HE

M

FIGURE 2 Coronavirus virion structure. The genome RNA is complexed with the N protein to form a helical cased within the viral membrane, HE, hemagglutinin-esterase; S, spike; E, small membrane envelope; M, membrane are all transmembrane proteins. (Reproduced from Finlay and Hancock, 2004).

usually small, accessory proteins not essential for replication in cell culture. These proteins differ in number, sequence, and function among coronavirus groups and between MHV and SARS-CoV. It has beenwidely speculated that these proteins mediate virus host interactions, and there are some new data suggesting important functions for some of these proteins, as will be discussed below.

III. CORONAVIRUS-INDUCED DISEASES

# A. MHV pathogenesis

The MHV is a collection of strains with different organ tropisms. MHV strains may be divided into two major biotypes, based on general patterns of tropism. One group is enterotropic and includes MHV-D, -Y, -RI, -S/ CDC, LIVIM, and DVIM; these viruses are the frequent cause of MHV outbreaks in housed rodent colonies (Homberger et al., 1998). The other biotype, the polytropic strains are those generally studied as models of human disease. Various strains from this group provide model systems for diseases of several organ systems. Neurotropic MHV strains induce acute encephalitis and chronic demyelinating diseases, serving as one of the few recognized mouse models for MS. Hepatotropic strains provide one of the few small animal models for viral hepatitis, and the pneumotropic MHV-1 strain induces severe pneumonitis and reproduces the pathology of SARS. Curiously, despite the very different organ tropisms, all MHV strains use the same cellular receptor, carcinoembryonic antigen molecule (CEACAM)-1, with no known requirements for coreceptors, suggesting that MHV tropism is in part determined by postviral entry events.

## 1. Central nervous system disease

The most frequently studied MHV strains are the neurotropic ones, primarily JHM and A59. The original JHM isolate, recovered from a paralyzed mouse, was highly neurovirulent, inducing encephalomyelitis with extensive demyelination (Bailey et al., 1949; Cheever et al., 1949). It was subsequently passaged multiple times through mouse brains (Lavi et al., 1984a; Weiner, 1973; Weiner et al., 1973). From this mouse brain-adapted stock, various clones with very different pathogenic phenotypes were isolated and used in many labs, all under the name JHM, causing confusion as to the actual phenotype of JHM. More recently, attempts have been made to differentiate among the JHM isolates, as described further below (Table I). Among the various JHM isolates, some induce severe encephalitis and high mortality and others induce more mild acute disease followed by chronic demyelination; the origins and pathogenic phenotypes of the various strains has been reviewed recently (Bender and Weiss, 2010; Weiss and Leibowitz, 2008). The A59 strain is a relatively

HISTOPATHOLOGICAL FEATURES

This is the first study to describe the pathology of disease caused by SARS-CoV-2, or COVID-19 pneumonia, since no autopsy or biopsies had been performed thus far,” senior author Xiao said. “Since both patients did not exhibit symptoms of pneumonia at the time of surgery, these changes likely represent an early phase of the lung pathology of COVID-19 pneumonia … This would be the only descriptions of early phase pathology of the disease due to this rare coincidence. There would be no other circumstance that this will happen. Autopsies will only show late or end stage changes of the disease.” The team’s paper is titled, “[Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer](http://dx.doi.org/10.1016/j.jtho.2020.02.010).”

Although there have been several studies describing clinical features of COVID-19 and characteristic radiographic findings (mainly chest CT scans) no pathologic studies have been conducted based on autopsies or biopsies, the authors noted. “Some of the reasons for the lack of autopsies and biopsies include the suddenness of the outbreak, the vast patient volume in hospitals, shortage of healthcare personnel, and the high rate of transmission, which makes invasive diagnostic procedures less of a clinical priority.”

The researchers were given an unexpected opportunity to examine what is most likely the early lung pathology of COVID-19 when, “fortunately and unfortunately,” they write, they encountered two patients who underwent surgery for lung cancer and were later found to have been infected with SARS-CoV-2 at the time the operations were carried out. As the team explained, “The surgical specimens overlapped in time with the infection, which offered us the necessary specimens to examine the histopathology of COVID-19 pneumonia … To our knowledge, the pathologic findings reported here represent the first for SARS-CoV-2 pneumonia, or 2019 coronavirus infection disease (COVID-19).”

As described in the published paper, the first case was a female patient aged 84 years who was admitted for treatment evaluation of a tumor in the right middle lobe of the lung, which had been discovered on chest CT scan at an outside hospital. She had a past medical history of hypertension for 30 years, as well as type 2 diabetes. Although she was given comprehensive treatment, assisted oxygenation, and other supportive care, the patient’s condition deteriorated, and she died. Subsequent clinical information confirmed that she had been exposed to another patient in the same room who was subsequently found to be infected with the SARS-CoV-2.

The second case was a male patient of 73 years of age, who presented for elective surgery for lung cancer, in the form of a small in the right lower lobe of the lung. He had a past medical history of hypertension for 20 years, which had been adequately managed. Nine days after lung surgery, he developed a fever with dry cough, chest tightness, and muscle pain. A nucleic acid test for SARS-CoV-2 came back as positive. He gradually recovered and was discharged after twenty days of treatment in the infectious disease unit.

Pathologic examinations revealed that, apart from the tumors, the lungs of both patients exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. Fibroblastic plugs were noted in airspaces. The presence of early lung lesions days before the patients developed symptoms corresponds to the long incubation period — generally 3–14 days — of COVID-19.

Although the female patient was never febrile, her CBC profile, especially from post-op day 1, showed “high WBC counts and lymphocytopenia, which is consistent with COVID-19,” the authors stated. “This may be a good clue for early diagnosis in the future.” Case 2 developed a fever a few days after the CT findings, suggesting a delay in symptom development in these patients.” The investigators point out that the time for the early lung lesions or COVID-19 to become severe enough to cause clinical symptoms is “rather long.” Even among patients who do present with fever, commonly used pharyngeal swab PCR tests may still be negative, they suggested, due to the lack of virus in the upper respiratory tract, and despite the presence of pneumonia.

The authors believe that the two incidences they report also typify what commonly occurred during the earlier phase of the SARS-CoV-2 outbreak, when a significant number of healthcare providers became infected in hospitals in Wuhan, and patients in the same room were cross-infected. During this period prevention of transmission was difficult, as many healthcare workers in Wuhan became infected as they were tending to patients without sufficient protection, Xiao noted. Just this week it has been reported that 3,387 health workers in China have been infected with COVID-19, more than 90% of whom in the stricken Hubei province. More than 15 doctors in Wuhan, including young, healthy individuals, have now died of COVID-19 infections contracted while they were taking care of patients.

“The two cases reported here represent ‘accidental’ sampling of the COVID-19, in which surgeries were performed for tumors in the lungs at a time when the superimposed infections were not recognized,” the researchers stated. “These provided the first opportunities for studying the pathology of COVID-19.” Xiao added, “We believe it is imperative to report the findings of routine histopathology for better understanding of the mechanism by which the SARS-CoV-2 causes lung injury in the unfortunate tens and thousands of patients in Wuhan and worldwide.” Further studies are ongoing by the team and collaborators to assess COVID-19 pathology through post-mortem biopsies, and their findings should provide new information on the late changes of this disease.

“It would be beneficial if RT-PCR and/or immunohistochemical stains could be performed on these two cases to further confirm the presence of the viruses that may be associated with the pneumonia,” the investigators further commented. “Unfortunately, these tests are currently under development, and adaptation to tissue specimens is not yet available. Nevertheless, we believe it is imperative to report the findings of routine histopathology for better understanding of the mechanism by which the SARS-CoV-2 causes lung injury in the unfortunate tens and thousands of patients in Wuhan and worldwide.”

neuroattenuated, yet moderately hepatovirulent strain that was isolated in 1961 from a mouse with leukemia (Manaker et al., 1961).

The general paradigm for neurotropic MHV infection can be summarized as follows. Following intracranial or intranasal inoculation, neurotropic MHV infects all of the major CNS cell types including neurons, the most frequently infected cell type, and glial cells, astrocytes, oligodendrocytes, and microglia. Viral titers typically peak in the CNS at day 5 postinfection and then begin to decline (Leparc-Goffart et al., 1998), with infectious virus becoming undetectable by approximately 2 weeks postinfection (Matthews et al., 2002). Infected mice develop mild to severe encephalomyelitis, characterized by infiltration of a variety of inflammatory cells. Innate immune responses are detectable within the first few days postinfection, followed by the development of an adaptive immune response (Bergmann et al., 2006; Savarin and Bergmann, 2008). Virus is cleared primarily by CD8þ T-cells with help from CD4þ T-cells

(Williamson et al., 1991). However, despite clearance of infectious virus, viral RNA, both genome and mRNA persist in the CNS and demyelination, largely immune-mediated, develops, peaking at approximately 1 month postinfection (Lavi et al., 1984a,b; Marten et al., 2001).

Among the highly neurovirulent isolates are JHM.SD (San Diego, formerly called MHV-4; Dalziel et al., 1986; Ontiveros et al., 2003), JHM.IA (Iowa), JHM.WU (Wurzburg, previously called Wb3; Schwarz et al., 1990), JHM-DL (Stohlman et al., 1982; Wang et al., 1992), and JHM-cl2 (Taguchi et al., 1995). These isolates kill weanling mice with a lethal dose (LD)50 of <10 pfu following intracranial inoculation. There are subtle phenotypic differences among these isolates which map to the spike gene as well as to other viral genes, as discussed further below. The most neurovirulent strains (e.g., JHM.SD, JHM-cl2) are able to spread cell to cell in the absence of the only known MHV receptor, CEACAM1a (Gallagher and Buchmeier, 2001). JHM 2.2-V-1 (Fleming et al., 1986; Wang et al., 1992), an attenuated monoclonal antibody escape variant, is glialtropic and nonlethal in immunocompetent mice; however, JHM 2.2-V-1 infection along with A59 infection provides useful models to demyelination, in that mice do not die of acute encephalitis (Bergmann et al., 2001; Lavi et al., 1984a,b). JHM.IA infection of suckling mice, passively immunized, provides another model that has been used to study MHV-induced demyelination (Pewe etal.,1996).

**Passive antibody therapy**

Transferring purified and concentrated [antibodies](https://en.wikipedia.org/wiki/Immunoglobulin_therapy) produced by the [immune systems](https://en.wikipedia.org/wiki/Immune_system) of those who have recovered from COVID-19 to people who need them is being investigated as a non-vaccine method of [passive immunisation](https://en.wikipedia.org/wiki/Passive_immunity). This strategy was tried for SARS with inconclusive results.[[308]](https://en.wikipedia.org/wiki/Coronavirus_disease_2019#cite_note-pmid-32167489-310) [Viral neutralisation](https://en.wikipedia.org/wiki/Neutralisation_(immunology)) is the anticipated [mechanism of action](https://en.wikipedia.org/wiki/Mechanism_of_action) by which passive antibody therapy can mediate defence against SARS-CoV-2. Other mechanisms however, such as [antibody-dependent cellular cytotoxicity](https://en.wikipedia.org/wiki/Antibody-dependent_cellular_cytotoxicity) and/or [phagocytosis](https://en.wikipedia.org/wiki/Phagocytosis), may be possible. Other forms of passive antibody therapy, for example, using manufactured monoclonal antibodies, are in development. Production of [convalescent serum](https://en.wikipedia.org/wiki/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.

**Management**

People are managed with [supportive care](https://en.wikipedia.org/wiki/Supportive_care), which may include fluid therapy, [oxygen support](https://en.wikipedia.org/wiki/Oxygen_support), and supporting other affected vital organs. The CDC recommends that those who suspect they carry the virus wear a simple face mask. [Extracorporeal membrane oxygenation](https://en.wikipedia.org/wiki/Extracorporeal_membrane_oxygenation) (ECMO) has been used to address the issue of respiratory failure, but its benefits are still under consideration.

The WHO and [Chinese National Health Commission](https://en.wikipedia.org/wiki/National_Health_Commission) have published recommendations for taking care of people who are hospitalised with COVID-19. [Intensivists](https://en.wikipedia.org/wiki/Critical_care_medicine) and [pulmonologists](https://en.wikipedia.org/wiki/Pulmonology) in the U.S. have compiled treatment recommendations from various agencies into a free resource, the [IBCC](https://en.wikipedia.org/wiki/EMCrit).

**Medications**

As of April 2020, there is no specific treatment for COVID-19. For symptoms, some medical professionals recommend [paracetamol](https://en.wikipedia.org/wiki/Paracetamol) (acetaminophen) over [ibuprofen](https://en.wikipedia.org/wiki/Ibuprofen) for first-line use. The WHO does not oppose the use of [non-steroidal anti-inflammatory drugs](https://en.wikipedia.org/wiki/Non-steroidal_anti-inflammatory_drugs) (NSAIDs) such as ibuprofen for symptoms, and the [FDA](https://en.wikipedia.org/wiki/Food_and_Drug_Administration) says currently there is no evidence that NSAIDs worsen COVID-19 symptoms.

While theoretical concerns have been raised about [ACE inhibitors](https://en.wikipedia.org/wiki/ACE_inhibitors) and [angiotensin receptor blockers](https://en.wikipedia.org/wiki/Angiotensin_receptor_blocker), as of 19 March 2020, these are not sufficient to justify stopping these medications. [Steroids](https://en.wikipedia.org/wiki/Steroids), such as [methylprednisolone](https://en.wikipedia.org/wiki/Methylprednisolone), are not recommended unless the disease is complicated by [acute respiratory distress syndrome](https://en.wikipedia.org/wiki/Acute_respiratory_distress_syndrome).

**Mechanical ventilation**

Most cases of COVID-19 are not severe enough to require [mechanical ventilation](https://en.wikipedia.org/wiki/Mechanical_ventilation) or alternatives, but a percentage of cases are. The type of respiratory support for individuals with COVID-19 related [respiratory failure](https://en.wikipedia.org/wiki/Respiratory_failure) is being actively studied for people in hospital, with some evidence that [intubation](https://en.wikipedia.org/wiki/Tracheal_intubation) can be avoided with a [high flow nasal cannula](https://en.wikipedia.org/wiki/Heated_humidified_high-flow_therapy) or [bi-level positive airway pressure](https://en.wikipedia.org/wiki/Positive_airway_pressure). Whether either of these two leads to the same benefit for people who are critically ills is not known. Some doctors prefer staying with invasive [mechanical ventilation](https://en.wikipedia.org/wiki/Mechanical_ventilation) when available because this technique limits the spread of [aerosol](https://en.wikipedia.org/wiki/Airborne_disease) particles compared to a [high flow nasal cannula](https://en.wikipedia.org/wiki/Heated_humidified_high-flow_therapy).

Severe cases are most common in older adults (those older than 60 years, and especially those older than 80 years). Many developed countries do not have enough [hospital beds per capita](https://en.wikipedia.org/wiki/List_of_countries_by_hospital_beds), which limits a [health system](https://en.wikipedia.org/wiki/Health_system)'s capacity to handle a sudden spike in the number of COVID-19 cases severe enough to require hospitalisation. This limited capacity is a significant driver behind calls to “[flatten the curve](https://en.wikipedia.org/wiki/Flatten_the_curve)” — to lower the speed at which new cases occur and thus keep the number of persons sick at any one time lower. One study in China found 5% were admitted to [intensive care units](https://en.wikipedia.org/wiki/Intensive_care_unit), 2.3% needed mechanical support of ventilation, and 1.4% died. In China, approximately 30% of people in hospital with COVID-19 are eventually admitted to ICU.

**Acute respiratory distress syndrome**

*Main article:* [*Acute respiratory distress syndrome*](https://en.wikipedia.org/wiki/Acute_respiratory_distress_syndrome)

[Mechanical ventilation](https://en.wikipedia.org/wiki/Mechanical_ventilation) becomes more complex as [acute respiratory distress syndrome](https://en.wikipedia.org/wiki/Acute_respiratory_distress_syndrome) (ARDS) develops in COVID-19 and oxygenation becomes increasingly difficult. Ventilators capable of [pressure control modes](https://en.wikipedia.org/wiki/Modes_of_mechanical_ventilation) and high [PEEP](https://en.wikipedia.org/wiki/PEEP) are needed to maximise oxygen delivery while minimising the risk of [ventilator-associated lung injury](https://en.wikipedia.org/wiki/Ventilator-associated_lung_injury) and [pneumothorax](https://en.wikipedia.org/wiki/Pneumothorax). High PEEP may not be available on older ventilators.

|  |  |
| --- | --- |
| Options for ARDS | |
| **Therapy** | **Recommendations** |
| [High-flow nasal oxygen](https://en.wikipedia.org/wiki/Nasal_cannula) | For [SpO2](https://en.wikipedia.org/wiki/Oxygen_saturation) <93%. May prevent the need for intubation and ventilation |
| [Tidal volume](https://en.wikipedia.org/wiki/Tidal_volume) | 6mL per kg and can be reduced to 4mL/kg |
| [Plateau airway pressure](https://en.wikipedia.org/wiki/Plateau_pressure) | Keep below 30 [cmH2O](https://en.wikipedia.org/wiki/Centimetre_of_water) if possible (high [respiratory rate](https://en.wikipedia.org/wiki/Respiratory_rate) (35 per minute) may be required) |
| [Positive end-expiratory pressure](https://en.wikipedia.org/wiki/Positive_end-expiratory_pressure) | Moderate to high levels |
| [Prone positioning](https://en.wikipedia.org/wiki/Prone_position) | For worsening oxygenation |
| [Fluid management](https://en.wikipedia.org/wiki/Fluid_replacement) | Goal is a negative balance of 0.5–1[L](https://en.wikipedia.org/wiki/Liter) per day |
| [Antibiotics](https://en.wikipedia.org/wiki/Antibiotics) | For secondary bacterial infections |
| [Glucocorticoids](https://en.wikipedia.org/wiki/Glucocorticoids) | Not recommended |

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