**What you need to know**

- SARS-CoV-2 is genetically similar to SARS-CoV-1, but characteristics of SARS-CoV-2—e.g., structural differences in its surface proteins and viral load kinetics—may help explain its enhanced rate of transmission.
- In the respiratory tract, peak SARS-CoV-2 load is observed at the time of symptom onset or in the first week of illness, with subsequent decline thereafter, indicating the highest infectiousness potential just before or within the first five days of symptom onset.
- Reverse transcription polymerase chain reaction (RT-PCR) tests can detect viral SARS-CoV-2 RNA in the upper respiratory tract for a mean of 17 days; however, detection of viral RNA does not necessarily equate to infectiousness, and viral culture from PCR positive upper respiratory tract samples has been rarely positive beyond nine days of illness.
- Symptomatic and pre-symptomatic transmission (1-2 days before symptom onset), is likely to play a greater role in the spread of SARS-CoV-2 than asymptomatic transmission.
- A wide range of virus-neutralising antibodies have been reported, and emerging evidence suggests that these may correlate with severity of illness but wane over time.

Since the emergence of SARS-CoV-2 in December 2019, there has been an unparalleled global effort to characterise the virus and the clinical course of disease. Coronavirus disease 2019 (covid-19), caused by SARS-CoV-2, follows a biphasic pattern of illness that likely results from the combination of an early viral response phase and an inflammatory second phase. Most clinical presentations are mild, and the typical pattern of covid-19 more resembles an influenza-like illness—which includes fever, cough, malaise, myalgia, headache, and taste and smell disturbance—rather than severe pneumonia (although emerging evidence about long term consequences is yet to be understood in detail). In this review, we provide a broad update on the emerging understanding of SARS-CoV-2 pathophysiology, including virology, transmission dynamics, and the immune response to the virus. Any of the mechanisms and assumptions discussed in the article and in our understanding of covid-19 may be revised as further evidence emerges.

**What we know about the virus**

SARS-CoV-2 is an enveloped β-coronavirus, with a genetic sequence very similar to SARS-CoV-1 (80%) and bat coronavirus RaTG13 (96.2%). The viral envelope is coated by spike (S) glycoprotein, envelope (E), and membrane (M) proteins (fig 1). Host cell binding and entry are mediated by the S protein. The first step in infection is virus binding to a host cell through its target receptor. The S1 sub-unit of the S protein contains the receptor binding domain that binds to the peptidase domain of angiotensin-converting enzyme 2 (ACE 2). In SARS-CoV-2 the S2 sub-unit is highly preserved and is considered a potential antiviral target. The virus structure and replication cycle are described in figure 1.
Coronaviruses have the capacity for proofreading during replication, and therefore mutation rates are lower than in other RNA viruses. As SARS-CoV-2 has spread globally it has, like other viruses, accumulated some mutations in the viral genome, which contains geographic signatures. Researchers have examined these mutations to study virus characterisation and understand epidemiology and transmission patterns. In general, the mutations have not been attributed to phenotypic changes affecting viral transmissibility or pathogenicity. The G614 variant in the S protein has been postulated to increase infectivity and transmissibility of the virus. Higher viral loads were reported in clinical samples with virus containing G614 than previously circulating variant D614, although no association was made with severity of illness as measured by hospitalisation outcomes. These findings have yet to be confirmed with regards to natural infection.

Why is SARS-CoV-2 more infectious than SARS-CoV-1?

SARS-CoV-2 has a higher reproductive number (R0) than SARS-CoV-1, indicating much more efficient spread. Several characteristics of SARS-CoV-2 may help explain this enhanced transmission. While both SARS-CoV-1 and SARS-CoV-2 preferentially interact with the angiotensin-converting enzyme 2 (ACE 2) receptor, SARS-CoV-2 has structural differences in its surface proteins that enable stronger binding to the ACE 2 receptor and greater efficiency at invading host cells. SARS-CoV-2 also has greater affinity (or bonding) for the upper respiratory tract and conjunctiva, thus can infect the upper respiratory tract and can conduct airways more easily.

Viral load dynamics and duration of infectiousness

Viral load kinetics could also explain some of the differences between SARS-CoV-2 and SARS-CoV-1. In the respiratory tract, peak SARS-CoV-2 load is observed at the time of symptom onset or in the first week of illness, with subsequent decline thereafter, which indicates the highest infectiousness potential just before or within the first five days of symptom onset (fig 2). In contrast, in SARS-CoV-1 the highest viral loads were detected in the upper respiratory tract in the second week of illness, which explains its minimal contagiousness in the first week after symptom onset, enabling early case detection in the community.

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Quantitative reverse transcription polymerase chain reaction (qRT-PCR) technology can detect viral SARS-CoV-2 RNA in the upper respiratory tract for a mean of 17 days (maximum 83 days) after symptom onset. However, detection of viral RNA by qRT-PCR does not necessarily equate to infectiousness, and viral culture from PCR positive upper respiratory tract samples has been rarely positive beyond nine days of illness. This corresponds to what is known about transmission based on contact tracing studies, which is that transmission capacity is maximal in the first week of illness, and that transmission after this period has not been documented. Severely ill or immune-compromised patients may have relatively prolonged virus shedding, and some patients may have intermittent RNA shedding; however, low level results close to the detection limit may not constitute infectious viral particles. While asymptomatic individuals (those with no symptoms throughout the infection) can transmit the infection, their relative degree of infectiousness seems to be limited. People with mild symptoms (paucisymptomatic) and those whose symptom have not yet appeared still carry large amounts of virus in the upper respiratory tract, which might contribute to the easy and rapid spread of SARS-CoV-2. A combination of preventive measures, such as physical distancing and testing, tracing, and self-isolation, continue to be needed.

**Route of transmission and transmission dynamics**

Like other coronaviruses, the primary mechanism of transmission of SARS-CoV-2 is via infected respiratory droplets, with viral infection occurring by direct or indirect contact with nasal, conjunctival, or oral mucosa, when respiratory particles are inhaled or deposited on these mucous membranes. Target host receptors are found mainly in the human respiratory tract epithelium, including the oropharynx and upper airway. The conjunctiva and gastrointestinal tracts are also susceptible to infection and may serve as transmission portals.

Transmission risk depends on factors such as contact pattern, environment, infectiousness of the host, and socioeconomic factors, as described elsewhere. Most transmission occurs through close range contact (such as 15 minutes face to face and within 2 m), and spread is especially efficient within households and through gatherings of family and friends. Household secondary attack rates (the proportion of susceptible individuals who become infected within a group of susceptible contacts with a primary case) ranges from 4% to 35%. Sleeping in the same room as, or being a spouse of an infected individual increases the risk of infection, but isolation of the infected person away from the family is related to lower risk of infection. Other activities identified as high risk include dining in close proximity with the infected person, sharing food, and taking part in group activities. The risk of infection substantially increases in enclosed environments compared with outdoor settings. For example, a systematic review of transmission clusters found that most superspreading events occurred indoors. Aerosol transmission can still factor during prolonged stay in crowded, poorly ventilated indoor settings (meaning transmission could occur at a distance >2 m).
The role of faecal shedding in SARS-CoV-2 transmission and the extent of fomite (through inanimate surfaces) transmission also remain to be fully understood. Both SARS-CoV-2 and SARS-CoV-1 remain viable for many days on smooth surfaces (stainless steel, plastic, glass) and at lower temperature and humidity (eg, air conditioned environments).\textsuperscript{18, 19} Thus, transferring infection from contaminated surfaces to the mucosa of eyes, nose, and mouth via unwashed hands is a possible route of transmission. This route of transmission may contribute especially in facilities with communal areas, with increased likelihood of environmental contamination. However, both SARS-CoV-1 and SARS-CoV-2 are readily inactivated by commonly used disinfectants, emphasising the potential value of surface cleaning and handwashing. SARS-CoV-2 RNA has been found in stool samples and RNA shedding often persists for longer than in respiratory samples\textsuperscript{7}; however, virus isolation has rarely been successful from the stool.\textsuperscript{5, 7} No published reports describe faecal-oral transmission. In SARS-CoV-1, faecal-oral transmission was not considered to occur in most circumstances; but, one explosive outbreak was attributed to aerosolisation and spread of the virus across an apartment block via a faulty sewage system.\textsuperscript{20} It remains to be seen if similar transmission may occur with SARS-CoV-2.

Pathogenesis

Viral entry and interaction with target cells

SARS-CoV-2 binds to ACE 2, the host target cell receptor.\textsuperscript{7} Active replication and release of the virus in the lung cells lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms.\textsuperscript{1} In an experimental hamster model, the virus causes transient damage to the cells in the olfactory epithelium, leading to olfactory dysfunction, which may explain temporary loss of taste and smell commonly seen in covid-19.\textsuperscript{21} The distribution of ACE 2 receptors in different tissues may explain the sites of infection and patient symptoms. For example, the ACE 2 receptor is found on the epithelium of other organs such as the intestine and endothelial cells in the kidney and blood vessels, which may explain gastrointestinal symptoms and cardiovascular complications.\textsuperscript{22} Lymphocytic endotheliitis has been observed in postmortem pathology examination of the lung, heart, kidney, and liver as well as liver cell necrosis and myocardial infarction in patients who died of covid-19.\textsuperscript{1, 12} These findings indicate that the virus directly affects many organs, as was seen in SARS-CoV-1 and influenzae.

Much remains unknown. Are the pathological changes in the respiratory tract or endothelial dysfunction the result of direct viral infection, cytokine dysregulation, coagulopathy, or are they multifactorial? And does direct viral invasion or coagulopathy directly contribute to some of the ischaemic complications such as ischaemic infarcts? These and more, will require further work to elucidate.

Immune response and disease spectrum (figure 2)

After viral entry, the initial inflammatory response attracts virus-specific T cells to the site of infection, where the infected cells are eliminated before the virus spreads, leading to recovery in most people.\textsuperscript{23} In patients who develop severe disease, SARS-CoV-2 elicits an aberrant host immune response.\textsuperscript{24, 25} For example, postmortem histology of lung tissues of patients who died of covid-19 have confirmed the inflammatory nature of the injury, with features of bilateral diffuse alveolar damage, hyaline-membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation consistent with acute respiratory distress syndrome (ARDS), and is similar to the lung pathology seen in severe Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).\textsuperscript{26-27} A distinctive feature of covid-19 is the presence of mucus plugs with fibrinous exudate in the respiratory tract, which may explain the severity of covid-19 even in young adults.\textsuperscript{28} This is potentially caused by the overproduction of pro-inflammatory cytokines that accumulate in the lungs, eventually damaging the lung parenchyma.\textsuperscript{24}

Some patients also experience septic shock and multi-organ dysfunction.\textsuperscript{26} For example, the cardiovascular system is often involved early in covid-19 disease and is reflected in the release of highly sensitive troponin and natriuretic peptides.\textsuperscript{29} Consistent with the clinical context of coagulopathy, focal intra-alveolar haemorrhage and presence of platelet-fibrin thrombi in small arterial vessels is also seen.\textsuperscript{27} Cytokines normally mediate and regulate immunity, inflammation, and haematopoiesis; however, further exacerbation of immune reaction and accumulation of cytokines in other organs in some patients may cause extensive tissue damage, or a cytokine release syndrome (cytokine storm), resulting in capillary leak, thrombus formation, and organ dysfunction.\textsuperscript{24, 30}

Mechanisms underlying the diverse clinical outcomes

Clinical outcomes are influenced by host factors such as older age, male sex, and underlying medical conditions,\textsuperscript{1} as well as factors related to the virus (such as viral load kinetics), host-immune response, and potential cross-reactive immune memory from previous exposure to seasonal coronaviruses (box 1).

Box 1: Risk factors associated with the development of severe disease, admission to intensive care unit, and mortality

<table>
<thead>
<tr>
<th>Underlying condition</th>
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<tbody>
<tr>
<td>Older age</td>
<td></td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Cardiovascular disease</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Diabetes</td>
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<td>Obesity</td>
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<tr>
<td>Malignancy</td>
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<table>
<thead>
<tr>
<th>Presentation</th>
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<tbody>
<tr>
<td>Higher fever (≥39°C on admission)</td>
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<tr>
<td>Dyspnoea on admission</td>
</tr>
<tr>
<td>Higher qSOFA score</td>
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<table>
<thead>
<tr>
<th>Laboratory markers</th>
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<tbody>
<tr>
<td>Neutrophilia/lymphopenia</td>
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<tr>
<td>Raised lactate and lactate dehydrogenase</td>
</tr>
<tr>
<td>Raised C reactive protein</td>
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<tr>
<td>Raised ferritin</td>
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<tr>
<td>Raised IL-6</td>
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<tr>
<td>Raised ACE2</td>
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<tr>
<td>D-dimer &gt;1 μg/mL</td>
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Sex-related differences in immune response have been reported, revealing that men had higher plasma innate immune cytokines and chemokines at baseline than women.\textsuperscript{21} In contrast, women had notably more robust T cell activation than men, and among male participants T cell activation declined with age, which was sustained among female patients. These findings suggest that adaptive immune response may be important in defining the clinical outcome...
Immune response to the virus and its role in protection

Covid-19 leads to an antibody response to a range of viral proteins, but the spike (S) protein and nucleocapsid are those most often used in serological diagnosis. Few antibodies are detectable in the first four days of illness, but patients progressively develop them, with most achieving a detectable response after four weeks. A wide range of virus-neutralising antibodies have been reported, and emerging evidence suggests that these may correlate with severity but wane over time. The duration and protective role of antibody and T cell responses remain to be defined through studies with longer follow-up. CD-4 T cell responses to endemic human coronaviruses appear to manifest cross-reactivity with SARS-CoV-2, but their role in protection remains unclear.

Unanswered questions

Further understanding of the pathogenesis for SARS-CoV-2 will be vital in developing therapeutics, vaccines, and supportive care modalities in the treatment of covid-19. More data are needed to understand the determinants of healthy versus dysfunctional response and immune markers for protection and the severity of disease. Neutralising antibodies are potential correlates of protection, but other protective antibody mechanisms may exist. Similarly, the protective role of T cell immunity and duration of both antibody and T cell responses and the correlates of protection need to be defined. In addition, we need optimal testing systems and technologies to support and inform early detection and clinical management of infection. Greater understanding is needed regarding the long term consequences following acute illness and multisystem inflammatory disease, especially in children.

Questions for future research

- What is the role of the cytokine storm and how could it inform the development of therapeutics, vaccines, and supportive care modalities?
- What is the window period when patients are most infectious?
- Why do some patients develop severe disease while others, especially children, remain mildly symptomatic or do not develop symptoms?
- What are the determinants of healthy versus dysfunctional response, and the biomarkers to define immune correlates of protection and disease severity for the effective triage of patients?
- What is the protective role of T cell immunity and duration of both antibody and T cell responses, and how would you define the correlates of protection?

How patients were involved in the creation of this article

No patients were directly involved in the creation of this article.

How this article was created

We searched PubMed from 2000 to 18 September 2020, limited to publications in English. Our search strategy used a combination of key words including “COVID-19,” “SARS-CoV-2,” “SARS,” “MERS,” “Coronavirus,” “Novel Coronavirus,” “Pathogenesis,” “Transmission,” “Cytokine Release,” “Immune response,” “antibody response.” These sources were supplemented with systematic reviews. We also reviewed technical documents produced by the Centers for Disease Control and Prevention and World Health Organization technical documents.

Education into practice

How would you describe SARS-CoV-2 transmission routes and ways to prevent infection? How would you describe to a patient why cough, anosmia, and fever occur in covid-19?

