



¹ Division of Infection and Global Health Research, School of Medicine, University of St Andrews, St Andrews, UK

² Specialist Virology Laboratory, Royal Infirmary of Edinburgh, Edinburgh, UK and Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, UK

³ Division of Infectious Diseases, Medical University of South Carolina, Charleston, SC, USA

⁴ Laboratory of Emerging and Re-Emerging Viruses, Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, Canada

⁵ School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Correspondence to M Cevik mc349@st-andrews.ac.uk

Cite this as: *BMJ* 2020;371:m3862

<http://dx.doi.org/10.1136/bmj.m3862>

Published: 23 October 2020

CLINICAL UPDATE

Virology, transmission, and pathogenesis of SARS-CoV-2

Muge Cevik,^{1,2} Krutika Kuppalli,³ Jason Kindrachuk,⁴ Malik Peiris⁵

What you need to know

- SARS-CoV-2 is genetically similar to SARS-CoV-1, but characteristics of SARS-CoV-2—eg, 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).¹ 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%).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.

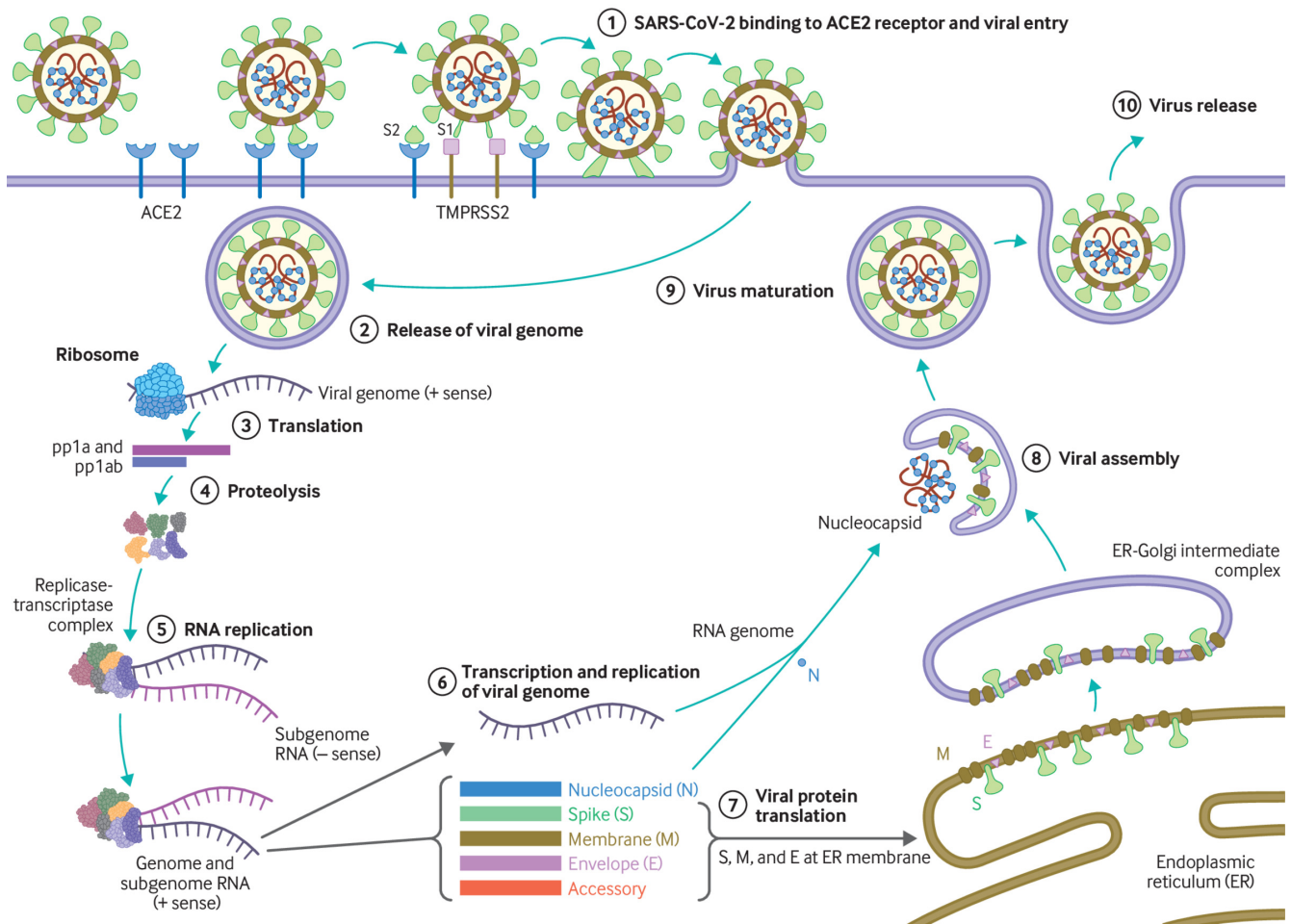


Fig 1 | (1) The virus binds to ACE 2 as the host target cell receptor in synergy with the host's transmembrane serine protease 2 (cell surface protein), which is principally expressed in the airway epithelial cells and vascular endothelial cells. This leads to membrane fusion and releases the viral genome into the host cytoplasm (2). Stages (3-7) show the remaining steps of viral replication, leading to viral assembly, maturation, and virus release

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.³ 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.³ 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 (R_0) than SARS-CoV-1, indicating much more efficient spread.¹ 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 receptor⁴ and greater efficiency at invading host cells.¹ SARS-CoV-2 also has greater affinity (or bonding) for the upper respiratory tract and conjunctiva,⁵ thus can infect the upper respiratory tract and can conduct airways more easily.⁶

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).⁷ 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.⁷

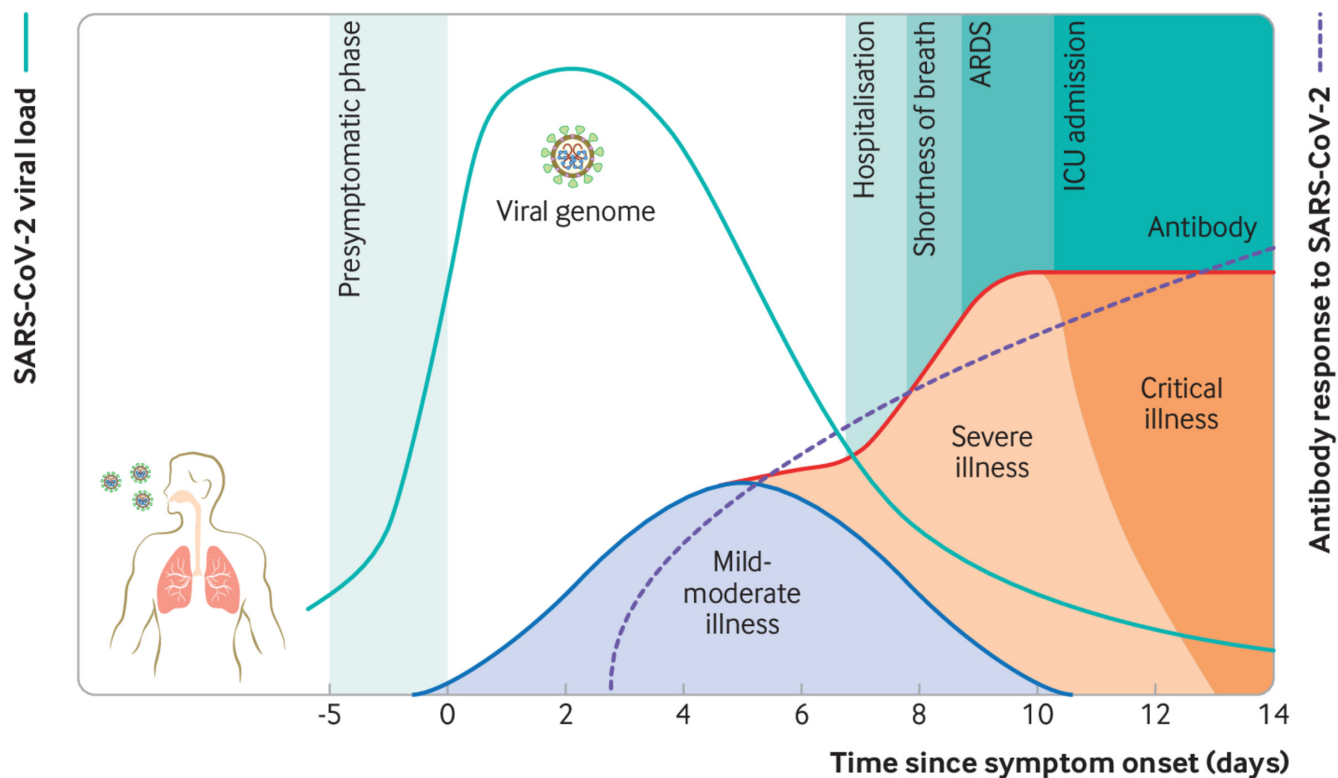


Fig 2 | After the initial exposure, patients typically develop symptoms within 5-6 days (incubation period). SARS-CoV-2 generates a diverse range of clinical manifestations, ranging from mild infection to severe disease accompanied by high mortality. In patients with mild infection, initial host immune response is capable of controlling the infection. In severe disease, excessive immune response leads to organ damage, intensive care admission, or death. The viral load peaks in the first week of infection, declines thereafter gradually, while the antibody response gradually increases and is often detectable by day 14 (figure adapted with permission from <https://www.sciencedirect.com/science/article/pii/S009286742030475X>; [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30230-7/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30230-7/fulltext))

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.⁷ 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.⁵ 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.⁸ 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.⁹⁻¹¹ 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-2.⁷ Symptomatic and pre-symptomatic transmission (one to two days before symptom onset) is likely to play a greater role in the spread of SARS-CoV-2.^{10,12} 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.⁶ 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.⁶

Transmission risk depends on factors such as contact pattern, environment, infectiousness of the host, and socioeconomic factors, as described elsewhere.¹² Most transmission occurs through close range contact (such as 15 minutes face to face and within 2 m),¹³ and spread is especially efficient within households and through gatherings of family and friends.¹² 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%.¹² 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.¹² Other activities identified as high risk include dining in close proximity with the infected person, sharing food, and taking part in group activities.¹² The risk of infection substantially increases in enclosed environments compared with outdoor settings.¹² For example, a systematic review of transmission clusters found that most superspreading events occurred indoors.¹¹ Aerosol transmission can still factor during prolonged stay in crowded, poorly ventilated indoor settings (meaning transmission could occur at a distance > 2 m).^{12,14-17}

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).^{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 samples⁷; however, virus isolation has rarely been successful from the stool.^{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.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.¹ Active replication and release of the virus in the lung cells lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms.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-19.²¹ 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.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.^{1 23} 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.²⁴ In patients who develop severe disease, SARS-CoV-2 elicits an aberrant host immune response.^{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).^{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.²⁸ This is potentially caused by the overproduction of pro-inflammatory cytokines that accumulate in the lungs, eventually damaging the lung parenchyma.²⁴

Some patients also experience septic shock and multi-organ dysfunction.²⁴ 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.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.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.^{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,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

Underlying condition

- Older age
- Hypertension
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Obesity
- Malignancy

Presentation

- Higher fever ($\geq 39^{\circ}\text{C}$ on admission)
- Dyspnoea on admission
- Higher qSOFA score

Laboratory markers

- Neutrophilia/lymphopenia
- Raised lactate and lactate dehydrogenase
- Raised C reactive protein
- Raised ferritin
- Raised IL-6
- Raised ACE2
- D-dimer $> 1 \mu\text{g/mL}$

Sex-related differences in immune response have been reported, revealing that men had higher plasma innate immune cytokines and chemokines at baseline than women.³¹ 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

as older age and male sex is associated with increased risk of severe disease and mortality.

Increased levels of pro-inflammatory cytokines correlate with severe pneumonia and increased ground glass opacities within the lungs.^{30 32} In people with severe illness, increased plasma concentrations of inflammatory cytokines and biomarkers were observed compared with people with non-severe illness.^{30 33 34}

Emerging evidence suggests a correlation between viral dynamics, the severity of illness, and disease outcome.⁷ Longitudinal characteristics of immune response show a correlation between the severity of illness, viral load, and IFN- α , IFN- γ , and TNF- α

response.³⁴ In the same study many interferons, cytokines, and chemokines were elevated early in disease for patients who had severe disease and higher viral loads. This emphasises that viral load may drive these cytokines and the possible pathological roles associated with the host defence factors. This is in keeping with the pathogenesis of influenza, SARS, and MERS whereby prolonged viral shedding was also associated with severity of illness.^{7 35}

Given the substantial role of the immune response in determining clinical outcomes, several immunosuppressive therapies aimed at limiting immune-mediated damage are currently in various phases of development (table 1).

Table 1 | Therapeutics currently under investigation

Entry to the cell	Viral replication	Host immune response
ACE receptor inhibitors	RNA polymerase inhibitors	Immunomodulators
Angiotensin II receptor blockers	Remdesivir	Tocilizumab
Fusion inhibitors	Ribavirin	Sarilumab
Uminefovir	Favipiravir	Adalimumab (TNF inhibitor)
Baricitinib	Protease inhibitors	IFN
Monoclonal antibodies	Lopinavir	Corticosteroids
	Darunavir	

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.³⁶ A wide range of virus-neutralising antibodies have been reported, and emerging evidence suggests that these may correlate with severity but wane over time.³⁷ The duration and protectivity 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.³⁸

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.

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?

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.

Author contributions: MC, KK, JK, MP drafted the first and subsequent versions of the manuscript and all authors provided critical feedback and contributed to the manuscript.

Competing interests *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: none.

Further details of *The BMJ* policy on financial interests are here: <https://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests>

Provenance and peer review: commissioned; externally peer reviewed.

- 1 Cevik M, Bamford CGG, Ho A. COVID-19 pandemic—a focused review for clinicians. *Clin Microbiol Infect* 2020;26:842-7. doi: 10.1016/j.cmi.2020.04.023 pmid: 32344166
- 2 Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 2020;367:1444-8. doi: 10.1126/science.abb2762 pmid: 32132184
- 3 Korber B, Fischer WM, Gnanakaran S, et al. Sheffield COVID-19 Genomics Group. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the covid-19 virus. *Cell* 2020;182:812-827.e19. doi: 10.1016/j.cell.2020.06.043 pmid: 32697968
- 4 Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260-3. doi: 10.1126/science.abb2507 pmid: 32075877
- 5 Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581:465-9. doi: 10.1038/s41586-020-2196-x pmid: 32235945
- 6 Hui KPY, Cheung MC, Perera RAPM, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *Lancet Respir Med* 2020;8:687-95. doi: 10.1016/S2213-2600(20)30193-4 pmid: 32386571
- 7 Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral load dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis. *Lancet Microbe* 2020; (forthcoming).
- 8 Cheng H-Y, Jian S-W, Liu D-P, Ng TC, Huang WT, Lin HHT. Taiwan COVID-19 Outbreak Investigation Team. Contact tracing assessment of covid-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med* 2020;180:1156-63. doi: 10.1001/jamainternmed.2020.2020 pmid: 32356867
- 9 Meyerowitz E, Richterman A, Bogoch I, Low N, Cevik M. Towards an accurate and systematic characterization of persistently asymptomatic infection with SARS-CoV-2. *Lancet Infect Dis* 2020; (forthcoming).
- 10 Qiu X, Nergiz AI, Maraolo AE, et al. Defining the role of asymptomatic SARS-CoV-2 transmission: a living systematic review. *MedRxiv* [Preprint] 2020. doi: 10.1101/2020.09.01.20135194
- 11 Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Med* 2020;17:e1003346. doi: 10.1371/journal.pmed.1003346 pmid: 32960881
- 12 Cevik M, Marcus J, Buckee C, Smith T. SARS-CoV-2 transmission dynamics should inform policy. *Clin Infect Dis*;2020. doi: 10.1093/cid/ciaa1442.
- 13 European Centre for Disease Prevention and Control. Surveillance definitions for COVID-19. 2020. <https://www.ecdc.europa.eu/en/covid-19/surveillance/surveillance-definitions>.
- 14 Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. *JAMA* 2020;324:441-2. doi: 10.1001/jama.2020.12458 pmid: 32749495
- 15 Centers for Disease Control and Prevention. How COVID-19 spreads. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html>
- 16 Centers for Disease Control and Prevention. Scientific brief: SARS-CoV-2 and potential airborne transmission. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html>
- 17 Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med* 2004;350:1731-9. doi: 10.1056/NEJMoa032867 pmid: 15102999
- 18 Chin AWH, Chu JTS, Perera MRA, et al. Stability of SARS-CoV-2 in different environmental conditions. *Lancet Microbe* 2020;1:e10. doi: 10.1016/S2666-5247(20)30003-3 pmid: 32835322
- 19 van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020;382:1564-7. doi: 10.1056/NEJMc2004973 pmid: 32182409
- 20 Kang M, Wei J, Yuan J, et al. Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. *Ann Intern Med* 2020. doi: 10.7326/M20-0928. pmid: 32870707
- 21 Sia SF, Yan LM, Chin AWH, et al. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature* 2020;583:834-8. doi: 10.1038/s41586-020-2342-5 pmid: 32408338
- 22 Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020;181:905-913.e7. doi: 10.1016/j.cell.2020.04.004 pmid: 32333836
- 23 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. *Lancet* 2020;395:1417-8. doi: 10.1016/S0140-6736(20)30937-5 pmid: 32325026
- 24 Mangalmurti N, Hunter CA. Cytokine Storms: understanding COVID-19. *Immunity* 2020;53:19-25. doi: 10.1016/j.immuni.2020.06.017 pmid: 32610079
- 25 Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced host response to SARS-CoV-2 drives development of covid-19. *Cell* 2020;181:1036-1045.e9. doi: 10.1016/j.cell.2020.04.026 pmid: 32416070
- 26 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420-2. doi: 10.1016/S2213-2600(20)30076-X pmid: 32085846
- 27 Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;20:1135-40. doi: 10.1016/S1473-3099(20)30434-5 pmid: 32526193
- 28 Wang C, Xie J, Zhao L, et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. *EBioMedicine* 2020;57:102833. doi: 10.1016/j.ebiom.2020.102833 pmid: 32574956
- 29 Liu PP, Blet A, Smyth D, Li H. The science underlying covid-19: implications for the cardiovascular system. *Circulation* 2020;142:68-78. doi: 10.1161/CIRCULATIONAHA.120.047549 pmid: 32293910
- 30 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934-43. doi: 10.1001/jamainternmed.2020.0994 pmid: 32167524
- 31 Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020. <https://pubmed.ncbi.nlm.nih.gov/32846427/>
- 32 Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020;20:656-7. doi: 10.1016/S1473-3099(20)30232-2 pmid: 32199493
- 33 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5 pmid: 31986264
- 34 Lucas C, Wong P, Klein J, et al. Yale IMPACT Team. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020;584:463-9. doi: 10.1038/s41586-020-2588-y pmid: 32717743
- 35 Wang Y, Guo Q, Yan Z, et al. CAP-China Network. Factors associated with prolonged viral shedding in patients with avian influenza A (H7N9) virus infection. *J Infect Dis* 2018;217:1708-17. doi: 10.1093/infdis/jiy115 pmid: 29648602
- 36 Perera RA, Mok CK, Tsang OT, et al. Serological assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), March 2020. *Euro Surveill* 2020;25:2000421. doi: 10.2807/1560-7917.ES.2020.25.16.2000421 pmid: 32347204
- 37 Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *Nat Microbiol* 2020. doi: 10.1038/s41564-020-00813-8
- 38 Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with covid-19 disease and unexposed individuals. *Cell* 2020;181:1489-1501.e15. doi: 10.1016/j.cell.2020.05.015 pmid: 32473127

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.