Accepted word document

TITLE

Advances in the Epidemiology, clinical features, diagnosis, clinical management and prevention of Coronavirus disease 2019 (COVID-19)

AUTHORS:

David SC Hui[+], Alimuddin Zumla*

INSTITUTIONAL AFFILIATIONS:

+Department of Medicine & Therapeutics and Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China.

*Department of Infection, Division of Infection and Immunity, Centre for Clinical Microbiology, University College London, and NIHR Biomedical Research Centre, University College London Hospitals, London, UK

CORRESPONDING AUTHOR:

Professor David Shu Cheong HUI, Department of Medicine & Therapeutics & Stanley Ho Center for Emerging Infectious Diseases, The Chinese University of Hong Kong,
Prince of Wales Hospital,
Shatin, New Territories,
Hong Kong.
Email: dschui@cuhk.edu.hk
Telephone: +852 35053128

Word count: 2529 words

Purpose of review:

This article reviews the latest information on the epidemiology, clinical features, diagnostics, clinical management and prevention of COVID-19.

Recent findings:

Atypical pneumonia due to SARS-COV2 emerged in Dec 2019 in a market in Wuhan, China and rapidly evolved into a pandemic in March 2020. Viral loads of patients with COVID-19 peak in the first week of illness around day 2 to 4 and hence there is very high transmission potential causing community outbreaks. Asymptomatic and pre-symptomatic transmission is a hallmark of COVID-19. Several variants of concern have emerged over the last 2 years and Omicron is the predominant variant in many countries. PCR is the standard diagnostic test while rapid antigen test is a useful supplementary test. Serology tests provide indirect evidence of infection 1–2 weeks after the onset of symptoms. Molnupiravir and paxlovid are oral antiviral agents that may reduce the risk of hospitalization and deaths if administered early to high risk subjects. Remdesivir, baricitinib, anti-IL6 tocilizumab and dexamethasone are frequently used for treatment of patients with respiratory failure.

Summary: COVID-19 pandemic progresses relentlessly with substantial morbidity and mortality especially in unvaccinated subjects. Mass COVID-19 vaccinations are the most important measure for control of the COVID-19 pandemic.

Word count = 202

KEYWORDS: COVID-19; epidemiology; clinical features; diagnostics; management; prevention

INTRODUCTION

Coronaviruses (CoVs) have over the past two decades caught global scientific and political attention as an important group of respiratory pathogens following the outbreaks due to Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) in 2003[1], Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012[2], and the novel coronavirus (SARS-CoV-2) which emerged in Wuhan, China, in late 2019, and spread rapidly to all continents through international travel [3]. As of 14 February 2022, over 410 million confirmed cases and over 5.8 million deaths have been reported globally [4]. The COVID-19 pandemic has posed enormous and unprecedented health, economic and social challenges to many countries. This article provides an update on the epidemiology, clinical features, diagnostics, clinical management and prevention of COVID-19.

EPIDEMIOLOGY

Unusual clusters of pneumonia in Wuhan, China were reported by the Chinese National Commission of Health to the World Health Organization (WHO) on 31 Dec 2019 [5]. The virus was initially tentatively named 2019 novel coronavirus (2019-nCoV). On 7 Jan 2020, scientists in China discovered a novel CoV as the aetiology of this outbreak, and the virus was later named by the International Committee of Taxonomy of Viruses as SARS-CoV-2[5].

SARS-CoV-2 is classified under the genus *Betacoronavirus* (subgenus *Sarbecovirus*) of the family *Coronaviridae*. It is the seventh CoV identified that is known to infect humans (HCoV) while four of these viruses (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1) are seasonal, endemic and generally cause mild respiratory disease [6]. The other two viruses are the more virulent zoonotic MERS-CoV [2] and SARS-CoV-1[1]. SARS-CoV-2 is genetically similar to SARS-CoV-1, and both viruses belong to the subgenus *Sarbecovirus* within the genus *Betacoronavirus*.

Before the lockdown of Wuhan city on 23 Jan 2020, travelers from Wuhan quickly spread the infection within China and internationally to many other countries. On 30 January 2020, the outbreak was declared by the WHO as a Public Health Emergency of International Concern and the new CoV disease was named as COVID-19 on 11 Feb 2020. On 11 March 2020, the WHO announced the scale of the global outbreak of COVID-19 as having reached a status of being pandemic [5].

Variants of concern (VOC)

The current global epidemiology of SARS-CoV-2 is characterized by the emergence and continued rapid global spread of the Omicron variant [7]. All other variants, including VOCs (Alpha, Beta, Gamma and Delta) and VOIs (Lambda and Mu) have continued to decline in all six WHO regions [8].

Several lineages have been identified ever since B.1.1.529 was designated as a VOC on 26 November 2021. These include Pango lineages BA.1, BA.1.1, BA.2 and BA.3, which are all being monitored by the WHO under the umbrella of 'Omicron'. BA.2 shares many mutations with BA.1, but also has a number of differences, including in the Spike protein – critically, it does not carry the Spike 69-70 deletion associated with S-gene target failure, used as a proxy for detecting BA.1, BA.1.1, B.1.1.529 and BA.3. BA.1.1 carries an additional R346K mutation, which is suspected to provide additional immune escape potential. Phenotypic impacts of various VOCs are summarized in table 1[8].

Omicron appears to have a greater replication rate than Delta and may escape humoral immunity, with a higher risk of reinfection in individuals previously infected with a different strain. There is a lower hospital admission risk for adult cases with Omicron compared with Delta variants [e.g. adjusted hazard ratio 0.25 (0.23-0.28) in 60-69 years old] but there is no difference in hospital admission risk between children under the age of 10 years with Omicron compared with Delta with an adjusted hazard ratio 1.00 (0.85-1.18) [9].

Clinical features

Common presenting symptoms of COVID-19 include fever (44% on admission and then increased to 89% during hospitalization), cough mainly non-productive (67.8%) while diarrhoea is uncommon (3.8%). The median incubation period is 4 days (interquartile range, 2 to 7) [10]. Absence of fever in a high proportion of patients makes it difficult to detect these cases in the community in the early stage of infection. Nevertheless, there is evidence that patients in the pre-symptomatic stage and those with mild disease may transmit infection to others [11]. Similar to SARS and MERS, children infected with SARS-CoV2 generally have mild disease [12]. Published data regarding pregnancy outcomes in COVID-19 have shown that maternal outcomes are similar to non-pregnant adults, while vertical transmission and neonatal infection are rare. However, pregnant women are at risk of severe disease requiring intensive care [13]. Viral kinetic studies have shown that the viral load peaks on day 2 to 4 of the patient's illness [14] and this explains the high potential of SARS-CoV-2 in causing community transmission among close contacts. Serology response starts on day 7 of illness while PCR positivity in deep throat saliva could last for at least 3 weeks in one third of patients [15].

Extra-pulmonary manifestations of COVID-19 include acute kidney injury, gastrointestinal symptoms, hepatocellular injury, thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications. As ACE2, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in numerous extrapulmonary tissues, direct viral tissue damage is a plausible mechanism of injury [16].

COVID-19 is a multisystem disease and can present with a wide clinical spectrum of clinical manifestations, ranging from asymptomatic or pre-symptomatic stage, mild, moderate, severe to critical disease with definitions as summarized in table 2 [17].

While the majority of patients with COVID-19 develop mild (40%) or moderate (40%) disease, about 15% develop severe disease requiring supplemental oxygen, while 5% progress to critical disease with complications such as ARDS, sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury prior to the emergence of Omicron variant [18]. Age older than 60 years, cigarette smoking and underlying comorbid diseases, such as diabetes mellitus, hypertension, cardiac disease, chronic lung disease and malignancy, have been reported as risk factors associated with severe disease and death. Multivariable analyses have confirmed older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1 µg/L on admission were associated with higher mortality. This study also observed a median duration of viral RNA detection of 20.0 days (IQR 17.0–24.0) in survivors, while COVID-19 viral RNA was detectable until death in fatal cases [19,20]. Observational data suggest that the risk of severe disease with Omicron infection is relatively lower than with other variants.

The median incubation period for COVID-19 is 4 days (IQR 2-7 days), but can be up to 14 days [9]. During the "pre-symptomatic" period, some infected persons can be infectious, from 1–3 days before symptom onset [21]. It is important to recognize that pre-symptomatic transmission occurs via infectious respiratory droplets or by direct or indirect contact with bodily fluids from an infected person while asymptomatic transmission can also occur [22]. Various studies have shown that transmission from symptomatic people to others predominantly occurs by close contact with respiratory droplets, by direct contact with infected persons, or via contact with contaminated surfaces and objects [23,24]. Short range airborne transmission may occur in settings with poor air ventilation [25].

Diagnostics

There are three types of diagnostic tests that are important for clinical management: a) molecular

or nucleic acid amplification tests (NAAT) [eg, reverse transcription polymerase chain reaction (RT-PCR) tests] that detect viral RNA; b) rapid antigen tests that detect viral proteins (eg, spike or nucleocapsid proteins); and c) serology tests that detect host antibodies in response to infection, or vaccination, or both. While PCR and rapid antigen tests can be used to diagnose acute infection, serology tests provide indirect evidence of infection 1–2 weeks after the onset of symptoms and are better applied for surveillance (table 3)[26].

For all suspected COVID-19 cases, at minimum the collection of respiratory specimens for NAAT, for example RT-PCR. Repetitive testing of upper respiratory tract (URT) and/or lower respiratory tract (LRT) might be needed to establish a diagnosis. Additional samples that might aid the diagnosis of COVID-19 include faecal specimens (if appropriately validated by the receiving laboratory) [17]. Sometimes bronchoscopy is needed if the URT and faecal specimens fail to ascertain the aetiology in patients with progressive pneumonia [27]. Based on 1,070 specimens from 205 patients with COVID-19, the positive detection rates using RT-PCR were 93% in broncho-alveolar lavage, 72% in sputum, 63% in nasal swabs, 32% in pharyngeal swabs and 29% in faecal samples [28].

The duration of viral RNA detection in many survivors of COVID-19 was about 37 days [19,20]. However, patients with severe immunosuppression after receiving cellular therapies or undergoing haematopoietic stem cell transplantation may shed viable SARS-CoV2 for more than 2 months [29]. Another prospective study in New York using nasopharyngeal swab samples for patients with SARS-CoV2 by real-time RT-PCR has shown a significant independent association between viral load and mortality (HR 1.07 [95% CI 1.03-1.11], p=0.014), with a 7% increase in hazard for each log transformed copy per ml [30].

Based on analysis of the relationship between in vitro neutralization levels and the observed protection from SARS-CoV-2 infection using data from seven vaccines and from convalescent

cohorts, Khoury DS et al. [31] estimated the neutralization level for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level (95% confidence interval (CI) = 14.4–28.4%) while the estimated neutralization level required for 50% protection from severe infection was significantly lower (3% of the mean convalescent level; 95% CI = 0.7–13%, $P = 0.0004$). Until there is better understanding of the correlates of protection, clinical indications for serologic testing in health-care settings are inadequate.

Clinical Management

A) General management:

It is important to screen and triage for early recognition of suspected COVID-19 patients and rapid implementation of source control measures. Healthcare workers should apply standard precautions for all patients while contact and droplet precautions are needed for suspected or confirmed COVID-19 patients. Airborne precautions should be implemented when performing aerosol-generating procedures such as bronchoscopy [27]. At a healthcare facility, after screening and isolation, triage patients with suspected COVID-19 using a standardized triage tool (such as the WHO/IFRC Interagency Integrated Triage Tool); and evaluate the patient to determine disease severity [17].

B) **Drug treatment**

a) *For patients with severe or critical COVID-19:* The WHO has recommended: a) a strong recommendation for systemic corticosteroids; b) a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab); c) a strong recommendation for the use of baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids; d) a conditional recommendation for casirivimab-imdevimab, for those having seronegative status; e) a conditional recommendation against the use of ruxolitinib and tofacitinib; f) a recommendation against convalescent plasma,

except in the context of a clinical trial [32].

b) *For patients with non-severe COVID-19*, the following medications are recommended: a) a conditional recommendation for casirivimab-imdevimab, for those at highest risk of severe disease but not recommended for patients with non-severe COVID-19: b) a conditional recommendation against systemic corticosteroids; c) a strong recommendation against convalescent plasma; d) a conditional recommendation for the use of sotrovimab in patients, conditional for those at highest risk of hospitalization [32].

c) The following are not recommended, regardless of COVID-19 disease severity: a) a conditional recommendation against remdesivir; b) a strong recommendation against hydroxychloroquine; c) a strong recommendation against lopinavir/ritonavir; d) a recommendation against ivermectin, except in the context of a clinical trial [32]. Nevertheless remdesivir may be most effective if administered within 10 days of symptom onset in patients requiring supplemental oxygen [33].

d) For outpatients with mild symptoms, molnupiravir [34] and paxlovid [35] are oral antiviral agents that may reduce the risks of hospitalization by 30% and 89% respectively if administered within 5 days of symptom onset.

COVID-19 vaccines

A range of COVID-19 vaccines have been developed, evaluated and rolled out at an unprecedented speed [36]. There have been three leading strategies of COVID-19 vaccine development, mRNA vaccines, adenoviral vector vaccines and recombinant nanoparticles. The emergence of SARS-CoV-2 variants has negative impact on the effectiveness of the most widely implemented vaccines. A WHO tracker and landscape compiles detailed information of

each COVID-19 vaccine candidate in development by closely monitoring their progress through the pipeline.

Prevention

A) Community level

People in the community are advised to practice social distancing by avoiding crowds and maintaining a physical distance of at least 1 meter from others in public areas. In particular, individuals should avoid close contact with ill subjects. Individuals are encouraged to wear properly fitted masks when physical distancing is not possible and in poorly ventilated settings, in addition to paying attention to hand hygiene and respiratory etiquette. It is important to ensure good ventilation indoor and disinfect frequently touched objects and surfaces. Testing and quarantine are important strategies to promptly identify any secondary infections in an exposed individual and reduce the risk of exposing others before an infection is finally recognized. Vaccination is the most important public health measure for controlling the pandemic [37].

B) Hospital setting

The following healthcare infection prevention control (IPC) strategies and measures are required to prevent or limit SARS-CoV-2 transmission in healthcare facilities, including having the following in place: an IPC programme or at least a dedicated and trained IPC focal point, engineering and environmental controls, administrative controls, standard and transmission based precautions, screening and triage for early identification of cases and source control, robust surveillance and vaccination of healthcare workers [38].

Health facilities should adhere to key WHO recommended IPC measures, in particular, adhering to respiratory etiquette and hand hygiene best practices, contact, droplet and airborne

precautions, adequate environmental cleaning and disinfection; ensuring adequate ventilation; isolation facilities of COVID-19 patients; in addition, where possible, maintaining a physical distance among all individuals in health facilities of at least 1 metre (increasing it whenever feasible), especially in indoor settings[38].

Universal masking should be adopted by all patients, staff, caregivers and visitors within a health facility should be implemented in health facilities in areas where there is known or suspected community or cluster transmission of SARS-CoV-2. Targeted continuous masking should be implemented in clinical areas of health facilities in areas with known or suspected sporadic transmission. IPC precautions should be applied for COVID-19 vaccine administration. Mask use by vaccinators and recipients of the vaccine should be according to local or national guidance [38].

Conclusions

Atypical pneumonia due to SARS-COV2 emerged in Dec 2019 in a market in Wuhan, China and rapidly evolved into a pandemic in March 2020. Viral loads of patients with COVID-19 peak in the first week of illness with a very high transmission potential causing community outbreaks. Asymptomatic and pre-symptomatic transmission is a hallmark of COVID-19. Several variants of concern have emerged over the last 2 years and Omicron is the currently predominant variant in many countries. PCR is the standard diagnostic test while rapid antigen test is a useful supplementary test. Serology tests provide indirect evidence of infection 1–2 weeks after the onset of symptoms and are best used for surveillance. Molnupiravir and paxlovid are oral antiviral agents that may reduce the risk of hospitalization and/or deaths. Remdesivir, baricitinib, anti-IL6 tocilizumab and dexamethasone are frequently used for treatment of patients with respiratory failure.

Summary: COVID-19 pandemic is ongoing with substantial morbidity and mortality

especially in unvaccinated elderly subjects with chronic illness. Mass COVID-19 vaccinations are the most important measure for control of the COVID-19 pandemic.

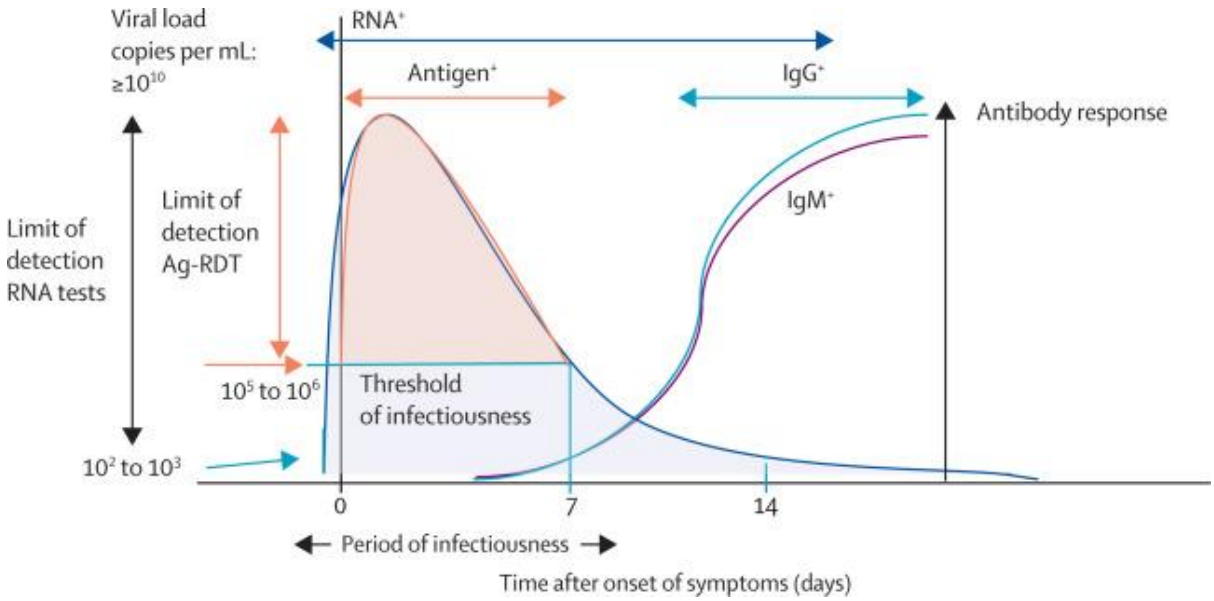
Acknowledgement: DSH is supported by the Health and Medical Research Fund Commissioned Research on the Novel Coronavirus Disease (COVID-19), Hong Kong SAR (COVID1903003; COVID190126) and RGC theme-based research schemes (T11-712/19-N and T11-705/21-N).

Conflicts of interest: Nil

Figure legend:

Figure 1. A schematic of the viral dynamics of, and antibody response to, SARS-CoV-2 infection in a patient who is symptomatic, and the optimal timeframe for deployment of different types of tests **[26].**

Footnote: The optimal timeframe during which molecular and antigen tests can be used for confirming the clinical diagnosis in a patient infected with SARS-CoV-2, based on the lower limits of virus detection for these tests, the dynamics of viral shedding, and the period of infectiousness over the course of infection. Serology tests to detect host response to infection are usually used 7 days or more after symptom onset to determine exposure or past or recent infection and are primarily used for surveillance. Ag-RDT=antigen rapid detection test.



REFERENCES

• *of special interest*

•• *of outstanding interest*

1. Lee N, Hui DS, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986-1994.
2. Zaki AM, van Boheeman S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814-1820.
3. Hui DS, Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-266.
4. WHO Coronavirus (COVID-19) Dashboard. Accessed 14 Feb 2022. Available at: https://covid19.who.int/
5. WHO. Listings of WHO's response to COVID-19. *Last updated 29 January 2021.* Accessed 14 Feb 2022. Available at: https://www.who.int/news/item/29-06-2020-covidtimeline
6. Zumla A, Chan JF, Azhar EI, et al. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15:327-347.
7. Petersen E, Ntoumi F, Hui DS, et al Emergence of new SARS-CoV-2 Variant of Concern Omicron (B.1.1.529) - highlights Africa's research capabilities, but exposes major knowledge gaps, inequities of vaccine distribution, inadequacies in global COVID-19 response and control efforts. Int J Infect Dis. 2022 Jan;114:268-272. doi: 10.1016/j.ijid.2021.11.040.
   ***This viewpoint highlights the emergence of Omicron VOC Omicron in Africa and emphasize that vaccine development must adapt and evolve over time and exposes major knowledge gaps, inequities of vaccine distribution, inadequacies in global COVID-19 response and control efforts*
8. WHO. Weekly epidemiological update on COVID-19 - 8 February 2022. Accessed 14

Feb 2022. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-february-2022

9. COVID-19 hospitalisation risk for Omicron compared with Delta VOCs, by age group. MRC Biostatistics Unit, University of Cambridge and UKHSA COVID-19 Epidemiology Cell. 19 Jan 2022. Accessed 14 Feb 2022. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1052451/S1501_Omicron_severity_2022-01-Cambridge.pdf
10. Guan W-J, Ni Z-Y, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708–1720.

    •• An excellent paper examining the clinical features of COVID-19
11. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA. 2020;323:1406-1407.
12. Ludvigsson JF. Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. Acta Paediatr. 2020;109:1088-1095.
13. Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020 May;2(2):100107. doi: 10.1016/j.ajogmf.2020.100107.
14. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020;382:1177-1179.

    • A nice paper on the viral kinetics of COVID-19
15. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020;20:565-574.

16. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017-1032.
17. WHO. Living guidance for clinical management of COVID-19. 23 November 2021. Accessed 14 Feb 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
18. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. CCDCW. 2020 Feb 1;2(8):113–122.
19. 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.
20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.
21. Wei WE, Li Z, Chiew CJ, et al. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:411–415.
22. Kimball A, Hatfield KM, Arons M, et al. Public Health – Seattle & King County, CDC COVID-19 Investigation Team. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:377–381.
23. Ong SW, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. 2020;323:1610–1612.

24. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20:656–657.

25. Cheng P, Luo K, Xiao S, et al. Predominant airborne transmission and insignificant fomite transmission of SARS-CoV-2 in a two-bus COVID-19 outbreak originating from the same pre-symptomatic index case. J Hazard Mater. 2022;425:128051. doi: 10.1016/j.jhazmat.2021.128051.

●● An interesting paper on airborne transmission of COVID-19

26. Peeling RW, Heymann DL, Teo YY, Garcia PJ. Diagnostics for COVID-19: moving from pandemic response to control. Lancet. 2021:S0140-6736(21)02346-1. doi: 10.1016/S0140-6736(21)02346-1.

27. Ng JKC, Ngai JCL, Ng SSS, Hui DSC. Collection of lower respiratory specimen by bronchoscopy for the diagnosis of COVID-19. Int J Infect Dis. 2021;105:326-328.

28. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020;323:1843-1844.

29. Aydillo T, Gonzalez-Reiche AS, Aslam S, et al. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. N Engl J Med. 2020;383:2586–2588.

30. Pujadas E, Chaudhry F, McBride R, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. Lancet Respir Med. 2020 Sep;8(9):e70. doi: 10.1016/S2213-2600(20)30354-4.

31. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27:1205-1211.

●● An excellent paper on the protective neutralizing antibody levels

32. WHO. Therapeutics and COVID-19: living guideline.14 January 2022. Accessed 14 Feb 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

33. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383:1813-1826.

34. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al; MOVe-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386:509-520.

35. FDA NEWS RELEASE. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. 22 Dec 2021. Accessed 14 Feb 2022. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

36. WHO. COVID-19 vaccine tracker and landscape. 11 Dec 2022. Accessed 14th Feb 2022. Available at: COVID-19 vaccine tracker and landscape (who.int)
***A comprehensive COVID-19 vaccine tracker which updates regularly*

37. WHO. Advice for the public: Coronavirus disease (COVID-19). Last updated on 1 Oct 2022. Accessed 14 Feb 2022. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public

38. WHO. Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed. Interim guidance 12 July 2021. Accessed 14 Feb 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-2021.1

Table 1: Summary of phenotypic impacts* of variants of concern [8]

	Alpha	**Beta**	**Gamma**	**Delta**	**Omicron**
Transmissibility	Increased transmissibility	Increased transmissibility	Increased transmissibility	Increased transmissibility	Increased transmissibility.
Disease severity	Possible increased risk of hospitalization, possible increased risk of severe disease and death	Possible increased risk of hospitalization, possible increased in-hospital mortality	Possible increased risk of hospitalization, possible increased risk of severe disease	Possible increased risk of hospitalization	Reduced risk of hospitalization and severe disease
Risk of reinfection	Neutralizing activity retained, risk of reinfection remains similar	Reduction in neutralizing activity reported; T cell response elicited by D614G virus remains effective	Moderate reduction in neutralizing activity reported	Reduction in neutralizing activity reported	Increased risk of reinfection
Impacts on diagnostics	Limited impact – S gene target failure (SGTF), no impact on overall result from multiple target RT-PCR; No impact on Ag RDTs observed	No impact on RT-PCR or Ag RDTs observed	None reported to date	No impact on RT-PCR or Ag RDTs observed	PCR continues to detect Omicron. Impact on Ag-RDTs is under investigation: Results are mixed as to whether or not there may be decreased sensitivity to detect Omicron.

**Generalized findings as compared to previously/co-circulating variants. Based on emerging* evidence, including non-peer-reviewed preprint articles and reports, all subject to ongoing investigation and revision.

Table 2. Definitions of disease severity in COVID-19 [17]

Asymptomatic or Pre-symptomatic Infection: Patients who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms of COVID-19.

- *Mild Illness:* Individuals who have some symptoms and signs of COVID-19 (e.g., fever, cough, malaise, sore throat, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and anosmia) but without evidence of viral pneumonia or hypoxia.

- *Moderate Illness:* Individuals who have clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air.

- *Severe Illness:* Individuals who have clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air.

- *Critical Illness:* Individuals who have acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ dysfunction.

Table 3. Advantages and disadvantages of diagnostic tests for SARS-CoV-2 infection in patients with COVID-19-like symptoms, according to clinical scenario [26].

	Aim	Advantages	Disadvantages
Within 2 weeks after symptom onset			
Molecular test (ideally nasopharyngeal or nasal swabs)	To detect viral RNA (preferred test)	Provides the most sensitive and specific means of confirming a clinical diagnosis	Expensive; requires specialised skills and instruments; testing is not at point of need; results can take longer than 24–48 h
Antigen rapid detection test (ideally nasopharyngeal or nasal swabs)	To detect viral protein if molecular testing is not available or the results are delayed	Can provide results within 15–20 min; can be done outside of a laboratory setting with minimal training; cheaper and faster to manufacture than molecular tests	Not as sensitive as molecular tests; more difficult to assure quality, especially with self-tests, compared with laboratory-based tests; if a patient tests negative, it is necessary to collect another sample for molecular testing
More than 2 weeks after symptom onset			
Molecular test, antigen rapid detection test, and antibody test	To establish a late or retrospective diagnosis by using antibody tests if molecular and antigen rapid tests are both negative	Can provide results in 15–20 min if a rapid antibody test or within 24 h if a laboratory-based assay	Antibody tests can be non-specific and cause false-positive results; can be difficult to determine if seropositivity is vaccine-induced or natural