COVID-19 Pandemic and Vaccination

2

Yonatan Oster

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was first described as the causative agent of acute respiratory infection in an outbreak in Wuhan, China, in the last months of 2019 [1]; this infection was later named coronavirus disease 2019 (COVID-19). The virus rapidly spread worldwide to create a global pandemic, including more than 500 million diagnosed infections and 6.3 million deaths, as of June 2022. The SARS-CoV-2 virus is a small RNA virus belongs to the coronaviruses family, which consists many viruses, mostly infecting animals but not humans. Other human affecting coronaviruses are very common and known to cause mild upper respiratory infections. Two of the viruses in this family have caused global outbreaks in the past, SARS-CoV-1 (previously SARS) in 2003 and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) which have caused several outbreaks since 2012. Contrary to most human coronaviruses who cause a very mild disease, the SARS-CoV-1 and MERS-CoV can cause severe disease with high mortality approaching 30%. The global spreading of COVID-19 has caused an immense effect on global health, finance, and geopolitics, and some of the data we know so far will be discussed in this chapter. Since its discovery in 2019, many mutations were found in the viral RNA, and accumulation of several mutations creates different viral variants that have distinct clinical and immunologic characteristics. The WHO has decided to classify and name the variants by Greek letters. The original virus is known as the wild type, and the common variants are the alpha, beta, delta, and omicron. The gradual emergence of these variants created the wavy pattern

Y. Oster (✉)
The Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

Department of Clinical Microbiology and Infectious Diseases, Hadassah Medical Center, Jerusalem, Israel
e-mail: yonatano@hadassah.org.il

J. G. Schenker et al. (eds.), *Hot Topics in Human Reproduction*, Reproductive Medicine for Clinicians 3, https://doi.org/10.1007/978-3-031-24903-7_2

of the pandemic, where a rise in morbidity is stopped by preventive measures and a certain immunity of the population, only to rise again after several months due to the development of a new variant [2]. In general, newer variants are more infective than their preceding and tend to cause a less severe disease.

Modes of Transmission

As a respiratory pathogen, the main mode of transmission of COVID-19 is through respiratory secretions. Similar to most respiratory pathogens, the virus particles can be found in respiratory droplets causing person-to-person transmission in close contact circumstances. The duration and distance during exposure to a positive person will affect the probability of transmission, so household exposure will more likely lead to infection than a short random outdoor encounter [3]. High viral loads are found in the first few days of infection, after 2–3 days of incubation, and levels decline after several days in immunocompetent persons. Additionally, two other modes of transmission were highly studied during the pandemic. First, as in the outbreaks caused by other coronaviruses, some virus particles can be spread through aerosol, which are much smaller droplets that can be transmitted to a longer distance and stay in the airborne for longer time [4]. Studies have shown that most of the virus is not carried by aerosol; however some medical procedures do, for example, endotracheal intubation and extubation, bronchoscopy, or open suctioning of airway secretions [5]. Another suspected mode of transmission is through contact, which is common in other respiratory infections, as virus-containing droplets fall on close surfaces and fomites, including hands, which can be also directly contaminated by touching the mouth or nose. This route is related to a small part of transmissions, mainly because the virus can stay infective only for several hours on dry surfaces [6]. The infectivity of the virus, measured by the average number of people any positive person infects (also called R0), is much higher than the Influenza virus or other common respiratory viruses [7]. A major reason for this high infectivity is the pre-symptomatic [8] and even asymptomatic transmission of COVID-19 [9], which assisted in the global spread of the pandemic.

Infection

SARS-CoV-2 is mainly a respiratory pathogen, as the virus invades and replicates in the mucosa of the naso- and oropharynx. In some cases, however, the infection progresses to the lower respiratory tract, to create pneumonia that can be mild but also severe and life-threatening [10, 11]. The symptoms of most patients are related to the upper and lower respiratory system and include cough, sore throat, and coryza, as well as systemic symptoms such as fever, malaise, headache, and loss of appetite. Loss of taste and/or smell was frequently reported with the first few variants but had become a rare phenomenon with the omicron variant. The virus can cause some manifestation out of the respiratory system, including myocarditis,

gastrointestinal symptoms, and hyper-coagulation, mainly pulmonary emboli, stroke, and coronary disease. Risk factors of progression to severe disease are older age, immunosuppression (mainly in the humoral system), obesity, and chronic lung and cardiovascular pathologies. The main feature of severe COVID-19 is the acute respiratory distress syndrome (ARDS) complicated by multi-organ failure, mainly renal. Duration of symptoms in mild cases is usually 5 days or less in the immunocompetent, but can be much longer in immunocompromised patients. Some symptoms may persist longer, such as cough or loss of taste and/or smell. Post-COVID-19 symptoms, such as fatigue, shortness of breath, or memory loss, were described in many recovered patients. A rare inflammatory phenomenon, multisystem inflammatory syndrome, had developed in adults and children following COVID-19, resulting in high mortality [12].

Diagnosis

Clinical diagnosis of COVID-19 infection is challenging, as most patients present mild non-specific symptoms. Epidemiological data, such as rate of COVID-19 infection in a specific area, or close contact with a known case can assist in this diagnosis. The gold standard of laboratory testing is the real-time PCR, performed on nasopharyngeal and oropharyngeal swabs or on respiratory secretions. PCR tests have very high sensitivity and specificity, but are limited by high costs, long turnover times, and the need for expensive equipment and supplies. Lateral flow antigen tests provide rapid and cheap results and do not require trained laboratory technicians, but their sensitivity is 30–40% lower than for RT-PCR, depending on whether tested subjects are symptomatic [13]. This lower sensitivity has some advantages, as RT-PCR can detect residual viral RNA sometimes weeks after the infection. Serology tests are rarely used for diagnosis of acute infection, as IgM titers rise only 1–2 weeks following an infection. IgG antibody titers, however, can be useful in identifying previous infections. Anti-S antibodies can be found in previously infected and vaccinated persons, so anti-N antibodies should be measured to discriminate between these populations, as they do not rise after vaccination. Unfortunately, serologic tests cannot be used yet for assessment of protection from reinfections, as they represent only one part of a complex immune response. Additionally, antibodies against one variant might not be protecting against others.

Treatment

The majority of COVID-19 positive persons develop only a mild disease and require no therapy except bed rest and anti-pyretics. Sicker patients may need oxygen supplement and the use of noninvasive or invasive ventilation. These patients should get adequate supportive care as well. Due to the hyper-coagulation produced by the infection, all hospitalized patients are given prophylactic anticoagulation, mainly low-molecular-weight heparin, to prevent severe thrombotic complications [14].

Since the first appearance of SARS-CoV-2 in 2019, many anti-inflammatory medications were suggested to mitigate the disease progression. The most successful drug group is corticosteroids, and most of the moderate and severe patients receive them, mainly dexamethasone, which was proven in the multi-center, international, RECOVERY study [15]. Other options, such as anti-IL-6 agents, may have a role in some cases [16]. Secondary infections are described in many COVID-19 patients. Few are respiratory co-infections, which can be bacterial, viral, or fungal, others hospital-related infections [17].

Antivirals

The search for effective antiviral medications to treat COVID-19 is still in progress; however several such drugs have already been used on millions of patients. Remdesivir is an adenosine-analogue that stops viral RNA transcription. Its effectiveness was proven in shortening time to recovery in moderate and severe disease and in preventing disease progression in high-risk patients with mild disease [18]. It is administered intravenously, making its use in non-hospitalized patients difficult. Two oral antiviral agents, Paxlovid (ritonavir-boosted nirmatrelvir) and Lagevrio (Molnupiravir), are effective in preventing disease progression in high-risk patients, when given in the first 5 days of the disease [19, 20]. Several other agents were suggested as treatments; some existing medications such as ivermectin, hydroxychloroquine, or azithromycin; and some novel agents, which all failed in controlled clinical trials. Antibody transfusion, by either plasma of recovered patients [21, 22] or synthetic monoclonal antibodies [23], has been used in different clinical scenarios with mixed results, depending also on the current SARS-CoV-2 variant.

Prevention

Governments and health organizations worldwide have made many efforts to delay the spread of COVID-19 since its first appearance in China. These efforts include restriction on international travel, indoor and outdoor gatherings, and even work places, public transportation and schools, and even curfews in some countries. Most importantly, mandatory isolation of COVID-19-positive persons and quarantine of susceptible contacts were deployed in order to interrupt the chains of infection, including active tracing of contacts [24, 25]. Additionally, the use of facemasks by the general public was promoted by many authorities. Despite these and other measures, the virus did spread worldwide in the first months of 2020; however this global effort did slow down the progression of the pandemic and allowed the health services to function amidst the worst pandemic waves. Since some virus can be transferred via aerosol, some authorities have recommended the use of N95 or similar highly effective respirators; the difficulty in wearing these correctly and consistently and the demand for these by medical organizations support the use of regular

(surgical) facemasks. Reusable cloth facemasks, while being better for the environment, were proven to be less effective [26]. Protective measures include contact and droplet protection, i.e., gown, gloves, facemask, and eye protection, with addition of N95 or similar respirators when exposure to aerosol is expected. The use of such equipment had increased the burden on the healthcare workers, but had saved many infections worldwide [27].

Vaccination

Immediately after the publication of the SARS-CoV-2 RNA sequence, the race for vaccine development began. By the end of 2020, several vaccines were available for use or at late production stages. Two vaccines, Comirnaty (BNT162b2) and Spikevax (mRNA-1273), were developed based on a novel mRNA vaccination technology and have shown very high effectiveness in preventing symptomatic disease, complications, and mortality in the first months after the first two doses [28–30]. Other vaccinations, such as the ChAdOx1, Ad26.COV2, Gam-COVID-Vac (known as Sputnik V), and others, are based on older and more studied vaccine technologies and have shown moderate-to-high effectiveness. Vaccine effectiveness and safety was proved primarily in adults, and the data had gradually expanded to younger ages. Special populations, including immunocompromised and pregnant persons, can also be vaccinated safely [31]. This protection starts to wane after several months, and a booster dose is necessary to maintain population immunity [32, 33]. Mass vaccination operations were performed in many countries, and billions of vaccine doses were given. Despite the high efficacy of the vaccines in preventing mortality and complications, their ability to prevent infection is limited, at best. Studies show that vaccinated individuals that were infected can secrete similar amounts of infective virus particles as the non-vaccinated. Additionally, vaccine efficacy is lower for newer variants, similar to the natural immunity of recovered persons. Newer and broader vaccinations are being developed. Common vaccine side effects include local pain, malaise, and even fever in mRNA vaccine recipients and regional lymph node enlargement or myocarditis in rare cases [34]. Vaccine-induced thrombotic thrombocytopenia is another rare syndrome, associated with the Ad26.COV2 and ChAdOx1 vaccines, characterized by venous or arterial thrombosis associated with thrombocytopenia and detectable anti-platelet factor 4 antibodies [35]. Another type of vaccines is passive immunizations. Evusheld, a mixture of two synthetic antibodies (Tixagevimab and Cilgavimab), can create effective protection in immunocompromised persons if given prior to their exposure to SARS-CoV-2. New vaccinations, with the ability to generate sustained protection against infection, are needed in order to eliminate this infection. It is more likely, however, that the SARS-CoV-2 will become a part of the ensemble of human respiratory infections.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33. https://doi.org/10.1056/NEJMoa2001017.
2. Chen Y, Liu Q, Zhou L, Zhou Y, Yan H, Lan K. Emerging SARS-COV-2 variants: why, how, and what's next? Cell Insight. 2022;1(3):100029. https://doi.org/10.1016/j.cellin.2022.100029.
3. Oster Y, Benenson S, Yochi Harpaz L, et al. Association between exposure characteristics and the risk for COVID-19 infection among health care workers with and without BNT162b2 vaccination. JAMA Netw Open. 2021;4(9):e2125394. https://doi.org/10.1001/jamanetworkopen.2021.25394.
4. Edwards DA, Ausiello D, Salzman J, et al. Exhaled aerosol increases with COVID-19 infection, age, and obesity. Proc Natl Acad Sci U S A. 2021;118(8):830118. https://doi.org/10.1073/pnas.2021830118.
5. Klompas M, Baker M, Rhee C. What Is an Aerosol-Generating Procedure? JAMA Surg. 2021;156(2):113–14. https://doi.org/10.1001/jamasurg.2020.6643.
6. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021;174(1):69–79. https://doi.org/10.7326/M20-5008.
7. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):taaa021. https://doi.org/10.1093/jtm/taaa021.
8. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med. 2020;382(22):2081–90. https://doi.org/10.1056/NEJMoa2008457.
9. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323(14):1406–7. https://doi.org/10.1001/jama.2020.2565.
10. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42. https://doi.org/10.1001/jama.2020.2648.
12. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334–46. https://doi.org/10.1056/NEJMoa2021680.
13. Dinnes J, Deeks JJ, Berhane S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2021;3(3):CD013705. https://doi.org/10.1002/14651858.CD013705.pub2.
14. Flumignan RLG, Civile VT, Tinôco JD, et al. Anticoagulants for people hospitalised with COVID-19. Cochrane Database Syst Rev. 2022;3:CD013739. https://doi.org/10.1002/14651858.CD013739.pub2.
15. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704. https://doi.org/10.1056/NEJMoa2021436.
16. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(5):522–32. https://doi.org/10.1016/S2213-2600(21)00099-0.
17. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266–75. https://doi.org/10.1016/j.jinf.2020.05.046.
18. Ansems K, Grundeis F, Dahms K, et al. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev. 2021;8:CD014962. https://doi.org/10.1002/14651858.CD014962.
19. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. 2022;386(15):1397–408. https://doi.org/10.1056/NEJMoa2118542.

20. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022;386(6):509–20. https://doi.org/10.1056/NEJMoa2116044.
21. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20(4):398–400. https://doi.org/10.1016/S1473-3099(20)30141-9.
22. Piechotta V, Iannizzi C, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;5:CD013600. https://doi.org/10.1002/14651858.CD013600.pub4.
23. Hirsch C, Park YS, Piechotta V, et al. SARS-CoV-2-neutralising monoclonal antibodies to prevent COVID-19. Cochrane Database Syst Rev. 2022;6:CD014945. https://doi.org/10.1002/14651858.CD014945.pub2.
24. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts [published correction appears in Lancet Glob Health. 2020 Mar 5]. Lancet Glob Health. 2020;8(4):e488–96. https://doi.org/10.1016/S2214-109X(20)30074-7.
25. Kucharski AJ, Klepac P, Conlan AJK, et al. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. Lancet Infect Dis. 2020;20(10):1151–60. https://doi.org/10.1016/S1473-3099(20)30457-6.
26. Andrejko KL, Pry JM, Myers JF, et al. Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection - California, February-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(6):212–16. Published 2022 Feb 11. https://doi.org/10.15585/mmwr.mm7106e1.
27. Su CY, Peng CY, Liu HL, Yeh IJ, Lee CW. Comparison of Effects of N95 Respirators and Surgical Masks to Physiological and Psychological Health among Healthcare Workers: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(24):13308. Published 2021 Dec 17. https://doi.org/10.3390/ijerph182413308.
28. Lindsey R, Baden Hana M, El Sahly Brandon, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.
29. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577.
30. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med. 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345.
31. Wainstock T, Yoles I, Sergienko R, Sheiner E. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. Vaccine. 2021;39(41):6037–40. https://doi.org/10.1016/j.vaccine.2021.09.012.
32. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance—VISION network, 10 states, August 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):255–63. https://doi.org/10.15585/mmwr.mm7107e2.
33. Regev-Yochay G, Gonen T, Gilboa M, et al. Efficacy of a fourth dose of Covid-19 mRNA vaccine against omicron. N Engl J Med. 2022;386(14):1377–80. https://doi.org/10.1056/NEJMc2202542.
34. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 vaccination in Israeli adolescents. N Engl J Med. 2022;386(10):998–9. https://doi.org/10.1056/NEJMc2116999.
35. Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol. 2022;9(1):e73–80. https://doi.org/10.1016/S2352-3026(21)00306-9.