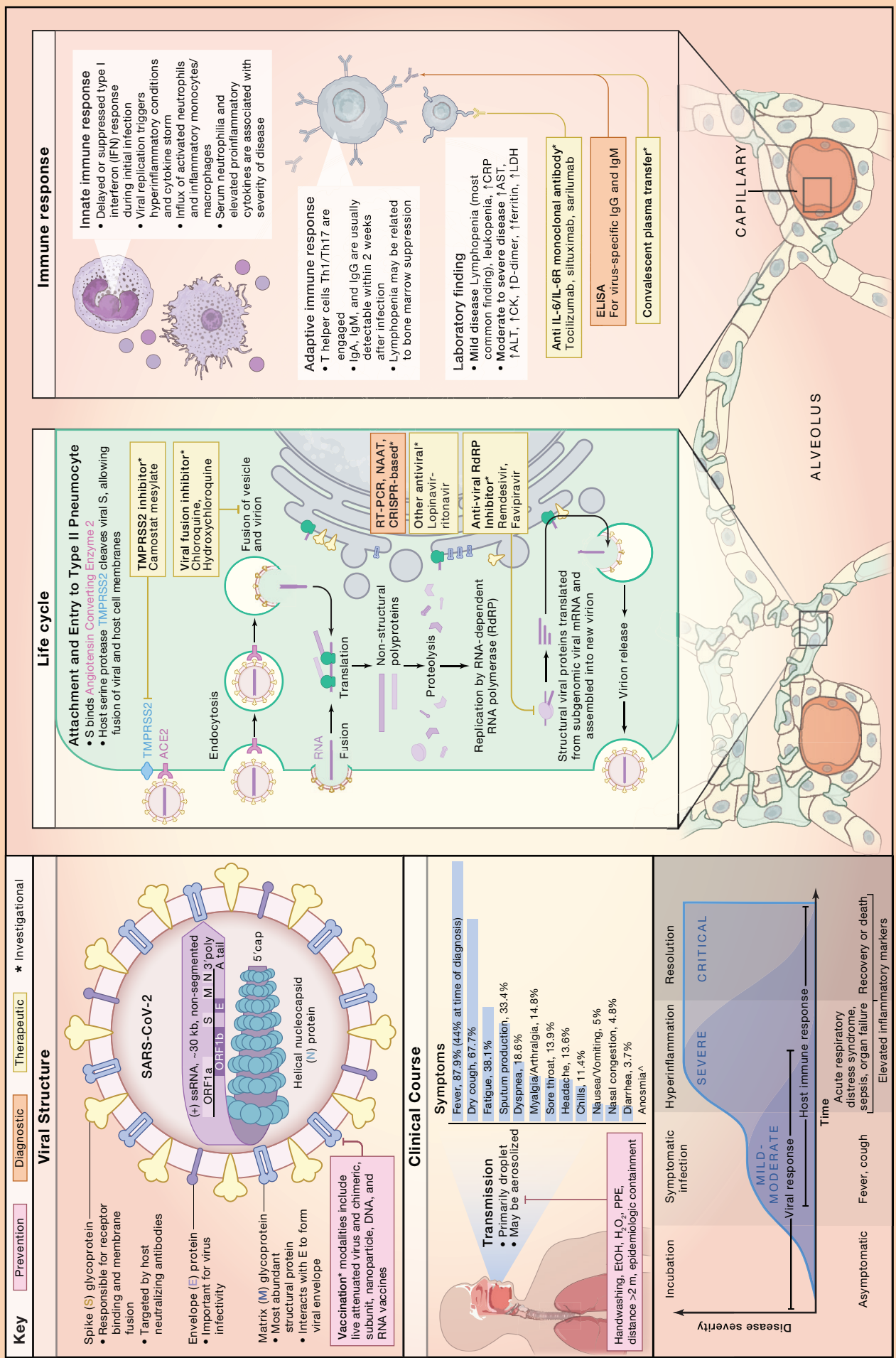




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In December 2019, several cases of pneumonia of unknown origin were reported in Wuhan, China. The causative agent was characterized as a novel coronavirus, initially referred to as 2019-nCoV and renamed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Zhou et al., 2020b). This respiratory illness, coronavirus disease 2019 (COVID-19), has spread rapidly by human-to-human transmission, caused major outbreaks worldwide, and resulted in considerable morbidity and mortality. On March 11, 2020, WHO classified COVID-19 as a pandemic. It has stressed health systems and the global economy, as governments balance prevention, clinical care, and socioeconomic challenges.

## Virology and Immunology

Classified in the Coronaviridae family and betacoronavirus genus, SARS-CoV-2 is the seventh coronavirus known to infect humans. Coronaviruses are enveloped positive-sense, single-stranded RNA viruses with mammalian and avian hosts. Human coronaviruses include 229E, NL63, OC43, and HKU1, which are associated with mild seasonal illness, as well as viruses responsible for past outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Genetic analyses implicate bats as a natural reservoir of coronaviruses and other animals as potential intermediate hosts in the emergence of SARS-CoV-2 (Andersen et al., 2020).

The SARS-CoV-2 30 kb genome encodes proteases and an RNA-dependent RNA polymerase (RdRp) as well as several structural proteins. The SARS-CoV-2 virion is composed of a helical capsid formed by nucleocapsid (N) proteins bound to the RNA genome and an envelope made up of membrane (M) and envelope (E) proteins, coated with trimeric spike (S) proteins (Zhou et al., 2020b). The S protein binds to the ACE2 enzyme on the plasma membrane of type 2 pneumocytes and intestinal epithelial cells. After binding, the S protein is cleaved by a host membrane serine protease, TMPRSS2, facilitating viral entry (Hoffmann et al., 2020).

Based on our understanding of SARS and MERS, and their similarity to COVID-19, the human immune response in mild cases is likely characterized by a robust type I interferon antiviral response and CD4<sup>+</sup> Th1 and CD8<sup>+</sup> T cell response, resulting in viral clearance. In severe cases, there is likely an initial delay in the antiviral response and subsequently increased production of inflammatory cytokines with an influx of monocytes and neutrophils into the lung, leading to cytokine storm syndrome. These cytokines, including interleukin (IL)-1, IL-6, IL-12, and tumor necrosis factor- $\alpha$ , lead to increased vascular permeability and may contribute to respiratory failure (Prompetchara et al., 2020). Another hallmark of severe disease is lymphopenia, which may be due to direct infection of lymphocytes or suppression of bone marrow by the antiviral response. Neutralizing IgM and IgG antibodies to SARS-CoV-2 can be detected within 2 weeks of infection; it is still unknown whether patients are protected from reinfection (Wölfel et al., 2020; Prompetchara et al., 2020).

## Transmission and Clinical Course

SARS-CoV-2 is thought to spread primarily via respiratory droplet and fomite transmission, although the possibility of fecal-oral transmission is being investigated (Wölfel et al., 2020). It can spread over longer distances when aerosolized. Once infection is established, the clinical course of COVID-19 is variable, making both case identification and triage difficult. Notably, asymptomatic and presymptomatic transmission has been described. For those who become symptomatic, the incubation period, the time from exposure to symptom onset, is 4–5 days on average (Li et al., 2020). The most common symptoms include cough, fever, and fatigue. For a minority of patients, the disease worsens approximately 5–10 days after symptom onset, resulting in complications such as acute respiratory distress syndrome (ARDS) and other end organ failure (Zhou et al., 2020a). Patients over 60 and those with comorbid conditions, including cardiovascular disease, underlying respiratory conditions, and cancer, are at higher risk for these severe complications and death. In comparison, children have a milder clinical course (CDC, 2020).

## Diagnosis and Management

Reverse transcriptase-polymerase chain reaction of respiratory samples remains the gold standard for diagnosing COVID-19, though immunoassays, isothermal nucleic acid amplification tests, and CRISPR-based diagnostic tests are in development to facilitate rapid point-of-care testing and address global testing shortages (Pang et al., 2020). Among those diagnosed, common laboratory findings include lymphopenia, elevated markers of inflammation including C-reactive protein, and elevated markers of coagulation cascade activation including D-dimer; higher viral load and inflammatory marker levels correlate with increased disease severity. Chest computed tomography (CT) scans of symptomatic patients are sensitive for detecting disease but nonspecific (CDC, 2020).

The current management of COVID-19 is focused on infection control, supportive care including ventilatory support as needed, and treatment of sequelae and complications. Patients with suspected COVID-19 who are asymptomatic or mildly ill are recommended to self-isolate for 2 weeks from the day of exposure, use acetaminophen as needed, remain hydrated, and monitor for worsening symptoms. Patients with more severe disease are admitted to the hospital for treatment of hypoxia, respiratory failure, ARDS, and septic shock.

## Investigational Therapies and Vaccine Development

Multiple clinical trials are underway to define potential roles for antiviral agents and specific immunomodulators. Antiviral agents under investigation include inhibitors endosome maturation (hydroxychloroquine), inhibitors of viral RNA-dependent RNA polymerase (remdesivir, favipiravir) and inhibitors of viral protein synthesis and maturation (lopinavir/ritonavir); immunomodulators under investigation include interferon- $\beta$  and blockade of IL-6 receptor or IL-6 (tocilizumab, siltuximab, sarilumab) (McCreary and Pogue, 2020). Passive immunization with convalescent plasma and active immunization strategies involving live-attenuated virus, chimeric virus, subunit, nanoparticle, RNA, and DNA are in development and testing. As the field looks toward the future of COVID-19 therapy, temporality of treatment should be considered, as some therapies could show greater efficacy at different disease stages.

## DECLARATION OF INTERESTS

S.P. is on the scientific advisory board of Abpro, Inc.

## REFERENCES

- Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., and Garry, R.F. (2020). The proximal origin of SARS-CoV-2. *Nat. Med.* Published online March 17, 2020. 10.1038/s41591-020-0820-9.
- CDC (2020). Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention, <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.-H., Nitsche, A., et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. Published online March 5, 2020. 10.1016/j.cell.2020.02.052.
- Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S.M., Lau, E.H.Y., Wong, J.Y., et al. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N. Engl. J. Med.* 382, 1199–1207.
- McCreary, E.K., and Pogue, J.M. (2020). Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. *Open Forum Infect. Dis.* 7, ofaa105.
- Pang, J., Wang, M.X., Ang, I.Y.H., Tan, S.H.X., Lewis, R.F., Chen, J.I.-P., Gutierrez, R.A., Gwee, S.X.W., Chua, P.E.Y., Yang, Q., et al. (2020). Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review. *J. Clin. Med.* 9, 623.
- Prompetchara, E., Ketloy, C., and Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac. J. Allergy Immunol.* 38, 1–9.
- Wölfel, R., Corman, V.M., Guggemos, W., Seilmaier, M., Zange, S., Müller, M.A., Niemeyer, D., Jones, T.C., Vollmar, P., Rothe, C., et al. (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature*. 10.1038/s41586-020-2196-x.
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., et al. (2020a). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 395, 1054–1062.
- Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., et al. (2020b). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579, 270–273.