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Clinical and Genetic Characteristics of Coronaviruses with Particular Emphasis on SARS-CoV-2 Virus

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Abstract

The rapidly spreading Coronavirus Disease 2019 (COVID-19) pandemic has led to a global health crisis and has left a deep mark on society, culture, and the global economy. Despite considerable efforts made to contain the disease, SARS-CoV-2 still poses a threat on a global scale. The current epidemiological situation caused an urgent need to understand the basic mechanisms of the virus transmission and COVID-19 severe course. This review summarizes current knowledge on clinical courses, diagnostics, treatment, and prevention of COVID-19. Moreover, we have included the latest research results on the genetic characterization of SARS-CoV-2 and genetic determinants of susceptibility and severity to infection.

Keywords: COVID-19, SARS-CoV-2, genetic determinants, diagnostics, vaccine

Introduction

Coronaviruses (CoVs) are unsegmented single-stranded RNA viruses, belonging to the subfamily *Coronavirinae*, family *Coronaviridae*, and order Nidovirales (Weiss and Leibowitz 2011). The structural differences of their domains became the basis for the identification of four groups: α, β, γ, and δ (Li 2016). For a long time, coronaviruses were recognized as pathogens not posing a significant threat to humans. In most cases, they caused mild infections, similar to the common cold. However, the occurrence of the etiological factor of a severe acute respiratory syndrome (SARS-CoV) in 2003 and the Middle East respiratory syndrome (MERS-CoV) in 2012, drew the world's attention to their species barrier-crossing capacity and the destructive potential of human CoVs (Song et al. 2019). It is now known that infections caused by coronaviruses can cause severe dysfunctions of the respiratory, gastrointestinal, or central nervous systems (Perlman and Netland 2009). In late December 2019, the first cases of illness caused by SARS-CoV-2 were reported in Wuhan in China's Hubei province. The rapidly evolving Coronavirus Disease 2019 (COVID-19) has led to a global healthcare crisis. Initially, the adverse effects of COVID-19 were thought to occur mainly in the respiratory tract, causing pneumonia and acute respiratory distress syndrome (ARDS). It is well known that SARS-CoV-2 infection can lead to extensive thrombotic lesions with microangiopathy, multi-organ failure, and death (Ackermann et al. 2020).

SARS-CoV-2 belongs to the group of zoonotic viruses that can infect both humans and animals. Genetic analysis showed that the new pathogen belongs to the subgenus *Sarbecovirus*. It is more similar to two bat-derived strains (SL-CoVZC45 and SL-CoVZXC21) than to known coronaviruses, including the virus from the SARS outbreak in 2003 (Lu et al. 2020). The recent publications demonstrated the importance of individual variability in response to SARS-CoV-2 infection. Individual body predisposition, modulated by genetic background, may determine the course of COVID-19 and further prognosis. Despite performing analyses, knowledge of the influence of genetic factors on the interindividual

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variability of patients with COVID-19 is insufficient to establish fully effective diagnostic and therapeutic interventions. Therefore, a better understanding of this topic is a priority for many researchers worldwide.

Risk factors of severe course of COVID-19 and death

The clinical part of the manuscript (risk factors, clinical course, diagnosis, treatment, and prevention) was written in September 2021, with an update in February 2022. Demographic risk factors for disease progression include male gender, age over 65, and smoking. Moreover, comorbidities such as diabetes, cardiovascular diseases, arterial hypertension, malignant neoplasms, respiratory diseases (mainly chronic obstructive pulmonary disease), chronic kidney disease, and liver diseases increase the risk of severe COVID-19 and death (Zheng et al. 2020; Zhou et al. 2020). Laboratory indicators of possible severe disease are thrombocytopenia, elevated IL-6 levels, Ast > 40 U/l, creatinine ≥ 133 mol/l, troponin I (hs-cTnI) > 28 pg/ml, procalcitonin (PCT) > 0.5 ng/ml, lactate dehydrogenase (LDH) > 245 U/l, and D-dimers > 0.5 mg/l. The manifestation of symptoms such as dyspnea, weakness, and sputum production has also been associated with the probable fatal course of COVID-19 (Zhou et al. 2020).

In mechanically ventilated patients and those connected to ECMO, the prognosis is poor, and high mortality is observed in these groups. Hospital mortality of patients connected to ECMO due to COVID-19 is 37% and is similar to ARDS caused by diseases other than COVID-19 (Barbaro et al. 2020; Ramanathan et al. 2021). In the USA, the 28-day mortality after the ICU (intensive care unit) admission was defined as 35%. In such conditions, the following factors were considered independent risk factors for death: age over 80, male sex, BMI over 40, ischemic heart disease, active neoplastic disease, PaO_2:FiO_2 below 100, and liver and kidney failure (Gupta et al. 2020).

Clinical course

SARS-CoV-2 is transmitted mainly by droplets during face-to-face exposure (by sneezing or coughing); however, transmission is possible through direct contact with the infected person or with contaminated surfaces, although it is a marginal transmission route (Wiersinga et al. 2020; Ravindra et al. 2022). In addition, the possibility of fecal-oral transmission has been suggested, which may be evidenced by the presence of SARS-CoV-2 RNA in rectal swabs or stools (assayed by RT-PCR) (Cheung et al. 2020; Bwire et al. 2021).

The disease can take a diverse clinical course. It is often asymptomatic, or it runs as a mild respiratory infection. However, some patients will develop severe pneumonia with cytokine release syndrome (CRS) and progression to respiratory failure (ARDS). Mortality in Poland was estimated at 2.106% on the 4th of February 2022 (The Johns Hopkins Coronavirus Resource Center 2022).

The incubation period ranges from two to 14 days. The median incubation period is 5.1 days, while 97.5% of all infections will develop within 11.5 days. The incubation period of SARS-CoV-2 is similar to that of other highly pathogenic coronaviruses: SARS (median five days, range 2–14) and MERS (median 5–7 days, range 2–14 days) (Lauer et al. 2020). The SARS-CoV-2 infection has a frequent oligosymptomatic course, including symptoms such as fever, chills, cough, shortness of breath, difficulty breathing, fatigue, headache, throat, muscle or body aches, runny nose, symptoms of conjunctivitis, anorexia, nausea, vomiting, diarrhea, abdominal pain, and loss of sense of smell (anosmia) or taste (ageusia) (Wiersinga et al. 2020). The last two symptoms are frequent in women, children, adolescents, and young adults (Lechien et al. 2020). In the elderly pulmonary manifestations may be preceded by atypical symptoms such as diarrhea with dehydration, hypotonia, cognitive dysfunction, delirium, falls, and body temperature may fluctuate daily with periods of hypothermia (Blain et al. 2020).

As the disease progresses, symptoms of pneumonia and increasing respiratory failure become crucial. Initially, the inflammation is interstitial, but it changes to a mixed form with bacterial superinfections. Dyspnea became the leading symptom, and the chest CT showed several changes: ground-glass opacity (GGO), crazy-paving pattern, and consolidation. The changes mainly affect the lower lobes of the lungs (Alsharif and Quarashi 2021).

There may also be diffuse alveolar damage, edema of the inter-alveolar spaces, protein-rich exudate into the lumen of the alveoli, inflammation, pneumocytes necrosis, formation of hyaline membranes, and fibrosis. Vascular changes may occur as microangiopathy and macroangiopathy (blood clots and hemorrhagic foci) (Englisch et al. 2020). Clinical prognosis depends mainly on the patient's age and comorbidities (Zheng et al. 2020), while radiographic prognostic criteria assess to what extent the lungs are involved. A generalized inflammatory response of the organism, the so-called cytokine storm, may develop, and respiratory failure may progress to a multi-organ failure. Septic complications may occur (Koçak Tufan et al. 2021). Also, thromboembolic complications can be found, especially in those requiring hospitalization. Venous thromboembolism (VTE) occurs in 26%, pulmonary embolism (PE) in

12%, and deep vein thrombosis (DVT) alone in 14% of the patients. Among those requiring treatment in ICUs, the risk of complications is as follows: VTE 24%, PE 19%, and DVT 7%, and of note is the significantly higher incidence of pulmonary embolism. Independently of the hospital ward, the following vessels may be involved in pulmonary embolism: main trunk and lobar arteries in 37.8%, segmental arteries in 37.9%, and subsegmental arteries in 19% of people (Porfidia et al. 2020).

The outcome of the disease is a resolution of inflammatory changes with gradual recovery or death of the patient. After a severe course of the disease, the patient may require lengthy rehabilitation and may never return to the function and respiratory capacity before the disease.

In December 2020, the Alpha variant (B.1.1.7) was identified in the United Kingdom as the first SARS-CoV-2 VOC (Variant of Concern) (Rambaut et al. 2020). Like the second, the Beta variant (B.1.351) was detected in South Africa in 2020. The Beta variant has three mutations, including K417N, E484K, and N501Y in the Spike protein receptor-binding domain (Tegally et al. 2020). In January 2021, the Gamma variant (P.1) was reported in Brazil. The Gamma variant carries three mutations: K417T, E484K, and N501Y in the Spike protein receptor-binding domain (Faria et al. 2021). In December 2020, the Delta variant (B.1.617.2) carrying mutations: 452R and 478K was first reported in India. The Omicron variant (B.1.1.529) was first described in South Africa in November 2021 (WHO 2022). All VOCs are more transmissible than the wild-type virus. Alpha, Beta, Gamma, and Delta variants cause more severe illnesses than wild-type viruses regarding hospitalization, ICU admission, and mortality. The Beta and Delta variants are at higher risk to patients than the Alpha and Gamma variants (Lin et al. 2021).

Diagnostics

To identify SARS-CoV-2, the real-time RT-PCR (real time Reverse Transcription Polymerase Chain Reaction) technique may be used and is considered a reference method. Real time RT-PCR detects regions of the SARS-CoV-2 genome encoding the following proteins: ORF1a/b (Open Reading Frame 1a/b), ORF1a, E (envelope), N (nucleocapsid), and S (Spike). Detectable RdRp (RNA-dependent RNA polymerase) is a part of ORF1a/b (Ravi et al. 2020; WHO 2020; Yüce et al. 2021). The specimens for the assay may include nasal, nasopharyngeal, pharyngeal, sputum, bronchoalveolar lavage fluid (BALF), blood, stool, and rectal swabs. Real time RT-PCR is more sensitive to virus detection when testing biological material from the lower respiratory tract than the upper respiratory tract.

The overall real time RT-PCR sensitivity is high (89.1%), as well as its specificity (98.9%) (Mustafa Hellou et al. 2021). Nasopharyngeal swabs are the most often tested. Real time-RT-PCR from bronchial lavage fluid (BALF) has the highest sensitivity (the positive detection rate of 91.8%). Any SARS-CoV-2 RNA molecules were detected in urine or genital swabs. Although real time RT-PCR of bronchial lavage fluid has the highest sensitivity, the fluid is collected by bronchoscopy. It is an invasive method, almost impossible to perform in a patient with severe dyspnea and, therefore, not applicable in daily practice (Böger et al. 2021; Bwire et al. 2021). The real time RT-PCR from rectal swabs has a high positive detection rate and detects the presence of SARS-CoV-2 RNA in stools (Cheung et al. 2020). The timing of material collection for molecular testing is vital in the diagnosis. Clinical materials should be collected while the virus is replicating in the epithelium of the upper respiratory tract. Typically, viral replication continues until ten days after the onset of symptoms. After this time, the sensitivity of molecular tests decreases significantly. The most crucial technique remains real-time signal detection. PCR assay should be repeated when a specific clinical picture (or radiological changes) occurs, and the initial test brings a negative result. Real time RT-PCR is characterized by higher sensitivity than antigen tests (89.1% vs 73,8%).

Serological assays detect and measure the titers of antibodies against S (Spike), N (Nucleocapsid), and RBD (receptor binding domain) antigens of SARS-CoV-2. Therefore, the S and N proteins are the most immunogenic and useful antigens in serological diagnostics (Makoah et al. 2021; Ong et al. 2021). The production of antibodies is a consequence of COVID-19 or vaccination against it. The are several methods used for antibody detection: enzyme-linked immunoassays (ELISAs), chemiluminescent immunoassays (CLIAs), rapid diagnostic tests (RDTs), and neutralization assays. RDTs include lateral flow tests (LFTs) (Ravi et al. 2020). CLIAs have a higher sensitivity and range compared to ELISAs. RDTs are characterized by the lowest sensitivity and the shortest assay period (the results obtained after approx. 15 minutes). In comparison, the results of ELISAs and CLIAs are provided within 30–100 minutes (Ravi et al. 2020). IgA, IgM, IgG antibodies, or a mixture of the above classes can be detected and presented as the so-called total score (Ong et al. 2021). The earliest IgA seroconversion can be found two days after the first clinical symptoms, while IgM seroconversion – in about three to five days from the first symptoms (Yu et al. 2020). The peak of antibody production is in the second and third weeks of the disease. Higher titers of IgA compared to IgM antibodies have been found (Padoan et al. 2020). IgG antibodies become detectable seven to 14 days after the first symptoms, peak in the

third and fourth weeks, and remain at a high level until the sixth week of the disease (Guo et al. 2020; Makoah et al. 2021). Seroconversion may be absent or delayed in the asymptomatic group, and specific antibody titers lower than in symptomatic patients. According to meta-analysis, the specificity of serological assays is 95–99% (Lisboa et al. 2021). Despite the ongoing SARS-CoV-2 infection, the results may be negative when congenital and acquired humoral deficiencies coexist (e.g., people with AIDS or agammaglobulinemia). Patients may be in the serological window when, despite being infected with SARS-CoV-2, they have not yet developed an immune response, and antibodies concentration is too low. Serological tests are characterized by low sensitivity in the early phase of COVID-19 (first seven to 10 days); thus, they cannot replace PCR during this infection period (Makoah et al. 2021). Serological assays may be used in epidemiological studies, evaluation of the response to a vaccine, and diagnostics of post-inflammatory syndromes. They may be helpful in the diagnosis of COVID-19 plausible in people with a typical, long-lasting clinical picture and/or radiographic image of the lungs but with negative RT-PCR results (WHO 2020; Flisiak et al. 2021).

Antigen tests detect SARS-CoV-2 proteins (most often nucleocapsid) based on the LFIAs (lateral flow immunoassays) technique. The most frequently tested material is a nasopharyngeal swab (Aguilar-Shea et al. 2021). Tests available in healthcare facilities are characterized by high sensitivity and specificity. According to the European Center for Disease Prevention and Control (ECDC), the diagnostic sensitivity of antigen tests should be ≥ 90%, and specificity ≥ 97% (ECDC 2020). Based on the meta-analysis, their sensitivity and specificity were estimated at 73.8% and 99.7%, respectively (Brümmer et al. 2021). The assay's practical application is limited to the initial stage of the disease when the number of virions in specimens is at the highest level (up to 5–7 days from the onset of clinical symptoms). These assays have several advantages as lower costs when compared to nucleic acid amplification tests (NAAT), short time of analysis (15–30 minutes); the possible use outside health care facilities, without specialized medical equipment (in workplaces, places of service or in patients' homes). They are also used in ambulances, emergency rooms, and airports (Flisiak et al. 2021). Due to a small number of SARS-CoV-2 virions in the specimens, the results of antigen tests may be negative. Therefore, positive antigen test results correlate better with the period of COVID-19 infectivity than NAAT' results (Hirotsu et al. 2020; Yamayoshi et al. 2020).

In the early stages of COVID-19 infection, chest X-rays may not be sensitive enough to detect suggestive changes (Zu et al. 2020). Therefore, computer tomography (CT) is the primary imaging measure (Alsharif and Qurashi 2021). It helps to establish the diagnosis, assesses the extent of inflammatory changes (CT Score), detect complications, and determine the outcome of the disease. Milky glass-like lesions (GGO, ground-glass opacity) predominate in the early phase of infection (up to seven days from the onset of clinical symptoms). After day 7, inflammatory consolidations, cobblestone patterns, and fibrosis predominate. CT score strongly correlates with the severity of the disease, the most strongly with CRP and D-dimer levels. CT score > 18 points is associated with significantly higher mortality (Francone et al. 2020).

Treatment

The principles of treatment and diagnosis of COVID-19 in Poland have been compiled as recommendations by the Polish Society of Epidemiologists and Infectious Disease Doctors. The disease was divided into four stages: 1) asymptomatic or oligosymptomatic, 2) fully symptomatic, 3) respiratory failure (called cytokine storm stage), and 4) full respiratory distress stage (ARDS).

The oligosymptomatic stage is characterized by normal saturation (SpO_2 > 95%). It does not routinely require hospital treatment, and the patient should self-monitor the saturation at home. In addition, the patients should rest, and take adequate oral hydration, anti-inflammatory drugs, and antipyretics if administered. There are no indications for the routine treatment with antibiotics, anti-influenza drugs, vitamin D_3, low-molecular-weight heparins, or systemically administered corticosteroids (Flisiak et al. 2021).

In October 2021, the FDA (Food and Drug Administration) conditionally approved REGEN-COV (casirivimab, imdevimab), a drug for the treatment and post-exposure prophylaxis of COVID-19. The drug may be used in the oligosymptomatic stage. It should be used to manage COVID-19 in patients at high risk of developing severe disease. The treatment reduces the risk of death and hospitalization and the duration of clinical symptoms (Weinreich et al. 2021). In addition, it may be used in post-exposure prophylaxis after home contact with a sick person to prevent the infection and the symptomatic form of the disease (O'Brien et al. 2021). The exposure is considered to be, among others, a 15-minutes contact within 24 hours, without personal protection equipment (PPE), and within 1,8 meters (CDC 2021). REGEN-COV displays activity against SARS-CoV-2 VOC (Variants of concern) (Weinreich et al. 2021).

Molnupiravir (Lagevrio) is approved to treat mild to moderate COVID-19. It should be administered up to five days after the onset of clinical symptoms. It is used orally, at a dose of 800 mg twice a day for 5 days.

It can be administered to patients with impaired liver and kidney functions but is absolutely contraindicated during pregnancy. Although it is a well-tolerated drug, some side effects may include diarrhea, nausea, dizziness, and headache. Molnupiravir is a prodrug that is metabolized to the ribonucleoside analog of N-hydroxycytidine (NHC). In cells, NHC is phosphorylated to triphosphate (NHC-TP). With the participation of RNA polymerase, it binds to viral RNA, leading to the accumulation of errors and suppression of replication (Lagevrio, Summary of Product Characteristics). The drug is considered safe and well-tolerated. It reduces the risk of death and hospitalization due to COVID-19, and lowers the time to SARS-CoV-2 RNA clearance (Singh et al. 2021). Molnupiravir is active *in vitro* against SARS-CoV-2 VOC (Variants of concern) (Vangeel et al. 2022).

In the full symptomatic stage, the saturation falls below 95%, and the patient usually requires hospitalization. In this phase, causal treatment should be implemented. The first-choice drug is remdesivir (Veklury) administered intravenously (by slow infusion) at 200 mg on the first day and 100 mg on the following four days. During the drug administration, aminotransferase activity should be monitored daily as remdesivir is hepatotoxic. Another possibility of causal treatment is the transfusion of a group-compatible plasma from the recovered patients. Low molecular weight heparins in prophylactic or therapeutic doses may also be implemented. From day two to five of remdesivir therapy, systemic dexamethasone at 4 mg is added and maintained until the end of the second week of the illness. Additionally, passive oxygen therapy could be administered.

Remdesivir is an RNA polymerase inhibitor registered for the treatment of COVID-19 in adolescents (aged 12 years and over and weighing more than 40 kg) and adults with pneumonia when the clinical condition requires oxygen administration. Treatment with remdesivir is contraindicated in renal failure with eGFR below 30 ml/min and liver damage with ALT activity exceeding five times the upper limit of the normal level. It should not be taken during pregnancy, breastfeeding, and hypersensitivity to the active substance and excipients. According to the SmPC (summary of product characteristics), the total treatment duration is five to 10 days. However, a randomized phase 3 clinical trial (Goldman et al. 2020) did not demonstrate an advantage of a 10-day treatment over a 5-day treatment (clinical improvement was obtained in 54 and 64% of subjects, respectively). According to the SmPC, the recommended dose is 200 mg on the first day and 100 mg on subsequent days. The activity of eGFR and ALT should be monitored throughout the treatment period. The most common adverse reactions include liver damage with transaminase elevations, nausea, vomiting, headache, and rash (Veklury, Summary of product characteristics). Remdesivir has in vitro activity against SARS-CoV-2 VOC (Variants of concern) (Vangeel et al. 2022).

Stage 3 disease (respiratory failure, cytokine storm) usually occurs at week 2, SpO_2 falls below 90%, and the patient requires hospitalization. Treatment with tocilizumab can be administered. It is a monoclonal antibody that binds specifically to IL6 receptors (both soluble and membrane-bound). The indication for the tocilizumab administration is IL6 concentration above 100 pg/ml. The drug is administered intravenously (8 mg/kg, max dose 800 mg) in a one-hour infusion. If there is no improvement after the first dose, a second dose may be given after 8–24 hours. Due to the risk of developing severe bacterial infections, the drug should not be given to patients with a neutrophil count below 2 K/ml. Liver damage with an ALT value above five times the upper limit of normal level is also a contraindication for therapy (RoActemra, Summary of product characteristics). Simultaneously with tocilizumab, we administer dexamethasone intravenously. The initial dose was 8 mg, and it later was reduced to 4 mg after 5 days of therapy. A group of patients with severe COVID-19-associated pneumonia treated with tocilizumab showed decreased mortality, risk of needing mechanical ventilation, and no increased risk of severe bacterial infections (Lan et al. 2020; Tleyjeh et al. 2021). Also, a study conducted on the Polish population showed a beneficial effect of tocilizumab. A decrease in the systemic inflammatory response (CRP, procalcitonin, fibrinogen concentrations) and a rapid improvement of clinical conditions for most patients were observed (Tomasiewicz et al. 2020).

In the last stage of the disease (ARDS), the patient should be admitted to the Intensive Care Unit, where ventilator therapy or ECMO can be administered.

Lopinavir/ritonavir, chloroquine, and hydroxychloroquine should not be used for the treatment due to a lack of efficacy evidence (Horby et al. 2020; Kashour et al. 2021). In addition, concomitant administration of remdesivir and chloroquine/hydroxychloroquine is not recommended since they exert antagonistic effects on intracellular metabolism and antiviral activity.

Prevention

The first cases of COVID-19 were diagnosed in Europe in January 2020 (Lescure et al. 2020), and already in December of that year, the EMA (European Medicines Agency) conditionally approved the vaccine from BioNTech and Pfizer. The trials were based on mRNA platforms (BNT162b2, Pfizer, BioNTech; mRNA-1273, Moderna), vector vaccines (chAdOx1-S, AstraZeneca; Ad26.COV2-S, Janssen) or inactivated viruses (e.g., Sinovac). Laboratory evaluation of vaccine

efficacy was performed by assessing their ability to induce the production of total IgG or neutralizing antibodies (against S protein) and their ability to induce a response from T lymphocytes (assessed, for example, by the ELISpot assay) (Ong et al. 2021). The highly immunogenic S protein plays a crucial role in infecting the host cells – it mediates the entry of virions into the host cells. Blocking it will prevent the virus from multiplying; hence, this protein has become the primary target of COVID-19 vaccines. Sequencing of SARS-CoV-2 new variants provides valuable information about mutations, especially in S protein, which may lead to the development new and better vaccines that provide long-term protection and neutralize mutated variants of SARS-CoV-2 (Harvey et al. 2021; Malik et al. 2022).

The most effective vaccines are those based on the mRNA platform (BNT162b2; mRNA-1273), with an efficacy of more than 94% (McDonald et al. 2021). A Russian-made vector vaccine (rAd26/Ad5) is also characterized by high (91.6%) efficacy and good tolerability (Logunov et al. 2021).

Vaccines (BNT162b2, mRNA-1273, ChAdOx1) are effective against VOC ((Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2)). After two doses of vaccines, their effectiveness against symptomatic infection on the seventh day and later was 89–92%, 87%, 88%, 82–89%, and 87–95% against Alpha, Beta, Gamma, Beta/Gamma, and Delta variants, respectively (Nasreen et al. 2022). T cells after vaccination recognize SARS-CoV-2 VOC, including Omicron (B.1.1.529). Receptor-binding domain (RBD) of the memory B cells' recognition of Omicron is reduced to 42% compared to other variants (Tarke et al. 2022).

By the end of January 2022, almost 10 billion doses of COVID-19 vaccines had been administered, and over 4 billion people were fully vaccinated. In Poland, 21,81 million people, i.e., 57,46% of the population, were fully vaccinated, which is the worst result compared to Western European countries. In France, 76.94% of the population was fully vaccinated; in Germany – 74.29%, Italy – 76.79%, the United Kingdom – 72.56%, Ireland – 78.75%, and Spain – 81.38% (The Johns Hopkins Coronavirus Resource Center 2022).

Comirnata's mRNA vaccine (BNT162b2) was the first to receive the EMA approval and was authorized for use in Europe. It was registered for the active immunization of adults and children above 12 years of age. Basic vaccination is administered intramuscularly in a two-dose schedule. A booster dose (third dose) is given six months after the second. The most common adverse reactions were injection site pain, fatigue, headache, myalgia, chills, fever, and swelling at the injection site (Comirnaty, Summary of product characteristics).

Moreover, there is an increased risk of myocarditis and pericarditis (more often after the second dose in young males) (Chua et al. 2021). mRNA is encapsulated in lipid nanoparticles, allowing its delivery to host cells. Then, the SARS-CoV-2 antigen (glycoprotein S) is transiently expressed. It is characterized by high efficacy, 95% for the primary endpoint of the study, and 91.3% for the secondary endpoint (Comirnaty, Summary of product characteristics). A dose of ten micrograms is approved for children 5 to 11 years of age.

Another mRNA vaccine is Spikevax, previously COVID-19 Vaccine Moderna (mRNA-1273-SARS-CoV). The vaccine contains mRNA encoding the SARS-CoV-2 S protein encapsulated in lipid nanoparticles. After intramuscular injection, cells at the administration site absorb the lipid nanoparticles, providing mRNA sequences for translation and protein biosynthesis. The delivered mRNA does not penetrate the cell nucleus, does not interact with the genome, is incapable of replication, and its expression is transient. The immune system recognizes the S protein as a foreign antigen, which triggers a response from T and B lymphocytes. The vaccine is licensed for administration to persons 12 years of age and older. The basic vaccination cycle consists of two intramuscular doses (0.5 ml each), with the second dose given 28 days after the first dose. A booster vaccination is given six months after the second dose (0.25 ml, 50 micrograms mRNA) (Spikevax, Summary of product characteristics). Vaccine efficacy has been estimated at 94% and is characterized by the strong humoral response directed against S-glycoprotein (McDonald et al. 2021). The most reported adverse reactions were mild, self-limiting, and included injection site pain, fatigue, headache, muscle pain, joint pain, chills, nausea or vomiting, armpit swelling or tenderness, fever, injection site swelling, and redness. These occurred more frequently in younger age groups (Spikevax, Summary of product characteristics). There is an increased risk of myocarditis and pericarditis following vaccination. It most often develops a few days after vaccination, mainly within 14 days. These site effects are more common in young males. Clinical course is similar as in unvaccinated person (Gargano et al. 2021).

Another vaccine is ChAdOx1-S (COVID-19 Vaccine AstraZeneca, Vaxzevria). It is a replication-deficient recombinant chimpanzee adenovirus with the S (Spike) SARS-CoV-2 glycoprotein coding sequence and is registered for persons over 18 years of age. The vaccination cycle consists of two doses, with the second given between the fourth to 12 weeks after the first. Common adverse reactions are similar to other vaccines, more pronounced after the first dose. Local synthesis of the SARS-CoV-2 glycoprotein S, production of neutralizing antibodies, and stimulation of the cellular immune response occur following the vaccine administration. ChAdOx1-S induces the most potent T cell response in the ELISpot assay (McDonald et al. 2021).

Table I
Brief characteristics of COVID-19 vaccines registered in the European Union.

Vaccine	Platform	Target population	Vaccination schedule	Side effects	Effectiveness in registration trials
Comirnaty	mRNA	above 12 years old	2 doses (second 3 weeks after first); booster dose 6 months after second	local side effects, flulike symptoms, myocarditis, pericarditis, erythema multiforme	91.3–95.0%
Spikevax	mRNA	above 12 years old old	2 doses (second 28 days after first); booster dose 6 months after second	local side effects, flulike symptoms, myocarditis, pericarditis, erythema multiforme	94.1%
COVID-19 Vaccine Janssen	vector (adenoviral)	above 18 years old old	1 dose, booster dose after 2 months	local side effects, flulike symptoms, thrombosis, thrombocytopenia, VITT, CLS, Guillain-Barre syndrome	66.1–85.4%
Vaxzevria	vector (adenoviral)	above 18 years old	2 doses, the second 4 to 12 weeks after the first	local side effects, flulike symptoms, thrombosis, thrombocytopenia, VITT, CLS, Guillain-Barre syndrome	59.5–74.0%
Nuvaxovid	Protein subunit vaccine	above 18 years old	2 doses, the second after 3 weeks.	local side effects, flulike symptoms	89.7%

Based on registration studies (COV002, COV003), vaccine efficacy in subjects vaccinated with two doses was estimated at 59.5%. In the group vaccinated with two doses of those who contracted COVID-19, none required hospitalization (COVID-19 Vaccine Astra-Zeneca, Summary of product characteristics).

COVID-19 Vaccine Janssen (Ad26.COV2-S) is a monovalent recombinant vaccine. It is based on adenovirus type 26 (with no replication capability) containing the S-glycoprotein coding sequence. It was registered for use in adults. It has the advantage of being a single-dose scheduled vaccine. Common adverse reactions were similar to other preparations. Sporadic cases of vaccine-associated immune thrombosis and thrombocytopenia (VITT) (Franchini et al. 2021) and capillary leaking syndrome (CLS) have been observed (Choi et al. 2021). Based on the registration studies, the vaccine efficacy was estimated at 66.1–85.4%. Moreover, vaccine efficacy was higher against severe/critical COVID-19 (Sadoff et al. 2021; COVID-19 Vaccine Janssen, Summary of product characteristics).

A very rare (1:150,000 vaccinations) and severe complication following the use of the vaccines based on adenoviral vectors (ChAdOx1-S; less commonly Ad26.COV2-S) is the VITT syndrome. It is characterized by a venous thrombosis of atypical localization, usually in the central nervous system (CNS), or as a sinus vein thrombosis (CVT). Coexisting thrombocytopenia indicates the immunological background of the pathology. Severe thrombocytopenia (defined as a platelet level $<25{,}000/\mu l$) was present in 52.6% of cases. The syndrome most commonly affects young women, who take oral hormonal contraception often, with a median age of 40.5 years. Mortality is high, above 40%; furthermore, mortality increases to 60% when CVT occurs. In treatment, novel oral anticoagulants (NOAC's), intravenous immunoglobulin preparations (IVIG, 1 g/kg body weight), and high-dose steroid therapy (e.g., dexamethasone 40 mg/day for 4 days) are administered to the patients (Franchini et al. 2021). Brief characteristics of all vaccines are presented in Table I.

Omicron

The Omicron variant (B.1.1.529) was first reported in South Africa and recognized as VOC by the WHO on November 26, 2021 (WHO 2021). The Omicron SARS-CoV-2 has over 30 mutations in the Spike protein sequence, 15 of which are located within the RBD (Receptor Binding Domain). Omicron has a higher affinity for ACE2 than the Delta variant due to many mutations in RBD (Kumar et al. 2022). Omicron may be associated with a higher risk of reinfection with SARS-CoV-2 (Pulliam et al. 2021). Diagnostics of this variant do not differ from other variants. Omicron does not substantially impair NAATs performance except for S gene target failure (SGTF). It is a deletion at the amino acid positions 69 and 70 of the Spike protein sequence (it was also noticed in the Alpha variant). So, detecting only one genomic region in PCR may lead to a false-negative result, but NAATs commonly detect two, three, or four genomic regions (Ferré et al. 2022; Kumar et al. 2022). Treatment of Omicron-induced COVID-19 is the same as the disease caused by other variants (Araf et al. 2022).

Genome structure of SARS-CoV-2

The coronavirus genome (SARS-CoV) size is between 26 and 32 kilobases and has a variable number of open reading frames (ORFs) (Song et al. 2019;

Kim et al. 2020). SARS-CoV-2 is an enveloped virus with a single-stranded RNA genome with positive polarity (Song et al. 2019). The genome at the 3′ end contained ORFs encoding structural and accessory proteins: surface glycoprotein (S), a small envelope protein (E), matrix protein (M), nucleocapsid (N), and eight accessory proteins: 3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14 (Wu et al. 2020). The 20 kb region at the 5′ end contains two OFRs (ORF1a/1ab) that encode 16 non-structural proteins (NSP11-NSP16) essential for virus replication (Davies et al. 2020). In addition, the genome contains non-coding sequences and sequences that regulate the transcription process (i.e., hexanucleotide sequence ACGAAC and CUAAAC) (Yoshimoto 2020).

Sequence analysis of 103 SARS-CoV-2 genomes allowed the identification of two distinct lineages (L and S), characterized by different polymorphic variants at positions 8782 (ORF1ab: T8517C) and 28144 (ORF8: C251T, S84L). The L line was more frequent than the S line in the trial studies. The T8517C mutation in ORF1ab does not affect the sequence of the encoded protein (changes the codon AGT (Ser) to AGC (Ser). However, it may be necessary in the translation of ORF1ab because the AGT codon is preferentially chosen in contrast to AGC (Tang et al. 2020). ORF8 promotes the expression of ATF6, which, being an activating transcription factor, plays an essential role in the transcription of endoplasmic reticulum chaperone proteins (Hu et al. 2017).

The genome sequence of SARS-CoV-2 from infected patients and the GenBank database showed discrepancies indicating the significant variability of the pathogen. For coronaviruses, the average rate of evolutionary change is approximately $\sim 3 \times 10^{-4}$ substitutions during each replication cycle (Pyrc et al. 2006). These mutations may affect the transmission and infectivity of SARS-CoV-2. Therefore, further studies considering the unique genomic features, epidemiological information, and medical records of the clinical course of COVID-19 are essential.

Characteristics of the selected SARS-CoV-2 proteins

After entry into host cells, viral genomic RNA is translated. Viral non-structural proteins (NSPs) provide conditions favorable for viral infection and viral mRNA synthesis (Lim et al. 2016). Among those, non-structural protein 1 (NSP1), known as a potent inhibitor of host gene expression, is crucial. NSP1 binds to ribosomes reducing the pool of those that can participate in the translation process. More efficient translation based on viral mRNA will be favored over host mRNA in such conditions. The most recent studies show that NSP1 inhibits the translation of both native and reporter mRNAs containing the 5′UTR region of the virus. SARS-CoV-2 can adjust the cellular concentration of NSP1 to values that will prevent the reduction of viral mRNA translation but will be sufficient to inhibit translation initiation from less efficiently recruited cellular mRNAs. This mechanism helps to explain how infected host cells target their protein synthesis machinery to produce foreign pathogen proteins.

The above mechanism ensures efficient viral gene expression (Schubert et al. 2020). NSP2 is a highly conserved protein specific to SARS-CoV viruses. It binds to two host proteins, prohibitin 1 and prohibitin 2 (PHB1, prohibitin 1; PHB2, prohibitin 2). These proteins play essential roles in regulating cell cycle progression, cell migration, cell differentiation, apoptosis, and mitochondrial biogenesis. The binding of NSP2 to PHB1 and PHB2 proteins suggests that NSP2 disrupts the host cell environment and interferes with its intracellular signaling (Cornillez-Ty et al. 2009; Yoshimoto 2020). The 200 kDa multi-domain NSP3 protein is the largest protein encoded by SARS-CoVs (not including ORF1a and ORF1ab). It has a variable structure. Individual coronaviruses can have between 10 and 16 NSP3 domains, of which eight and two transmembrane regions of the protein are highly conserved. NSP3 is an essential component of the replication and transcription complex. This protein interacts with the NSP4 in the host cell membrane rearrangement, which is necessary to initiate the replication and transcription of the viral genome (Sakai et al. 2017; Lei et al. 2018).

The nucleocapsid (N) protein is a multifunctional structural protein. Its domain structure consists of three distinct, highly conserved components: an N-terminal RNA-binding domain (NTD domain), a C-terminal dimerization domain (CTD domain), and a region rich in serine/arginine (SRD domain) (Zeng et al. 2020). The N protein allows the viral genomic RNA to be packaged into long, helical ribonucleoprotein complexes called nucleocapsids. The nucleocapsid protects the genome and ensures its replication and transmission of the pathogen. The N protein interacts with viral membrane proteins during viral assembly and assists in RNA synthesis and folding (McBride et al. 2014). Previous studies also indicate its role in regulating host-pathogen interactions by affecting the cell cycle progression and host cell apoptosis.

Furthermore, the N protein is highly immunogenic and induces host immune responses (Surjit et al. 2006; Du et al. 2008). The analyses confirmed the presence of IgA, IgM, and IgG class antibodies against the N antigen in the sera of patients with COVID-19, indicating this protein's role in modulating immunity and its important diagnostic value (Zeng, 2020). S protein is another protein of structural importance. Each protein monomer,

with a molecular mass of approximately 180 kDa, consists of two functional subunits responsible for binding to the host cell receptor (S1 subunit) and viral and cell membrane fusion (S2 subunit) (Ou et al. 2020). The S1 subunit is characterized by the presence of an N-terminal and ACE2 receptor-binding domain (RBD). The S2 subunit is composed of a fusion peptide (FP) domain, heptapeptide 1 (HR) repeat sequence, heptapeptide 2 (HR2) repeat sequence, transmembrane domain (TM), and cytoplasmic domain (CT) (Huang et al. 2020). The S protein is involved in two key events: binding to the cell receptor and inducing the fusion between the viral and cell membranes (Hussain et al. 2020).

Completion of these two processes leads to the entry of the viral RNA genome into the host cell and the subsequent start of the viral replication cycle (Belouzard et al. 2012). Replication and virions release lead to cell pyroptosis, a highly inflammatory form of cell death commonly found in many viruses. Additionally, pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) detect molecular patterns of the pathogen, which initiates an increased inflammatory response and triggers the release of pro-inflammatory cytokines from neighboring cells (McFadyen et al. 2020). It is also worth noting that SARS-CoV-2 significant transmission and infectivity may be due to the unique, compared to other CoVs, a furin cleavage site in protein S. The significant difference lies in the insertion of four amino acids (PRRA) that form a cleavage site recognized by the ubiquitous protease furin. Probably due to this additional amino acid insertion, SARS-CoV-2 gains the ability to infect organs or tissues that are not susceptible to other coronaviruses, thus providing ample opportunities for the virus to be released into the environment and significantly increasing its transmission (Wang et al. 2020). The M protein is a type III glycoprotein, the smallest among other structural proteins. According to the studies performed on SARS-CoV and MERS-CoV viruses, the M protein consists of 230 amino acids, and its molecular mass is between 25–35 kDa (Asghari et al. 2020). It has a short ectodomain at the amino end, three transmembrane domains, and a long domain at the carboxyl end of the protein.

The M protein gives the virus shape and is crucial in coordinating virus folding and forming mature viral envelopes. Homotypic interactions between M proteins are the main factor for viral envelope formation but are not sufficient by themselves for efficient viral assembly (de Haan et al. 2000). Presumably, only the interactions of the NSP3, M, and N proteins stabilize the nucleocapsid and help bind the viral genome to the replicase-transcriptase complex (RTC), which promotes the completion of viral particle assembly (Fehr and Perlman 2015).

Among all structural proteins, protein E is less understood. The E protein is hydrophobic and consists of a sequence of 74–109 amino acids with a molecular weight of 8.4–10.9 kDa. This protein plays an important role in the pathogenesis of coronaviruses. SARS-CoV with abolished E protein channel activity was significantly less infectious (Nieto-Torres et al. 2014; Asghari et al. 2020). The analyses confirmed the cation-conducting ability of the SARS-CoV-2 E-protein, which is considered a potential ion channel and an important target for the anti-COVID-19 drug development strategy (Singh Tomar and Arkin 2020). The comparative analysis of the SARS-CoV-2 genome with other coronaviruses revealed significant differences in the sequences of the multi-domain NSP3 protein and the surface protein S. The NSP3 protein contains a new large sequence insertion between two structurally and probably functionally independent domains. This newly added extended peptide sequence may act as a long inter-domain junction, extending the conformational flexibility of the protein. Furthermore, the presence of four new insertions and one highly variable surface region of the S protein has been demonstrated, which may have a structural impact on the homo-trimeric form of this protein and the functions performed by the N-terminal domain of the NTD (Srinivasan et al. 2020).

Structure and function of SARS-CoV-2 virus binding receptors in host cells

The receptor recognition is the first step of viral infection and a key determinant of host cell and tissue tropism (Walls et al. 2020). It is also an important target in a host immune surveillance and the intervention strategies (Shang et al. 2020). The SARS-CoV-2 virus uses human angiotensin-converting enzyme 2 (ACE2) as a receptor (Zou et al. 2020). ACE2 is a type I surface glycoprotein of approximately 100 kDa, consisting of 805 amino acid residues. In its structure, one can identify two functional domains: the N-terminal M2 peptidase domain and the C-terminal cofilin domain (Hussain et al. 2020). The receptor is encoded by the *ACE2* gene, which locus is on chromosome X (Xp22), spreads over 39.98 kb of genomic DNA, and contains 18 exons and 20 introns. The mechanism of S protein binding to ACE2 may depend on several factors. Upon binding, the RBD receptor-binding domain of the S1 subunit undergoes the conformational change. The dynamic structure of RBD can occur in two forms: "standing", which binds the receptor, and "lying", which responds to a state of unavailability to the host cell receptor and allows it to evade immune surveillance (Yuan et al. 2017).

Furthermore, the S protein of SARS-CoV-2 acquired mutations that enhance its affinity for the human receptor by 10–20 fold compared to the SARS-CoV, making it highly infectious (Luan et al. 2020). The analysis of

glycoprotein S structure using cryo-electron microscopy (cryo-EM) revealed that the RBD domain of SARS-CoV-2 is mainly in a "lying" position, making it unavailable to ACE2 (Wrapp et al. 2020). Therefore, it is hypothesized that despite its high affinity, the RBD domain may similarly, or to a lesser degree, interact with the ACE2 receptor compared to SARS-CoV (Shang et al. 2020).

After engaging the human receptor (ACE2), S protein is modified by the membrane-bound trans-membrane serine protease type II (TMPRSS2). The S-glycoprotein is cleaved into S1 and S2 subunits, allowing membrane fusion, the release of the virus into host cells, and its further spread (Hoffmann et al. 2020). Recent analyses of intestinal epithelial cell lines (HEK293) confirmed the importance of TMPRSS2 coexpression with ACE2 in enhancing virus infectivity. However, not only the serine protease TMPRSS2 plays an important role in S-protein cleavage and enhancement of the membrane fusion. The expression of TMPRSS4 also significantly increases viral RNA in the presence of ACE2. In addition, coexpression of TMPRSS4 and TMPRSS2 shows an additive effect favoring maximum infectivity in the cell culture (Zang et al. 2020).

On the other hand, the role of host cell proteases in SARS-CoV infection may not be limited to protein S cleaving. Previous studies suggested that ACE2 might be proteolytically modified by host cell proteases, which influenced the entry and pathogenesis of SARS-CoV. Furthermore, the arginine and lysine residues of ACE2 at positions 697 and 716 are essential for receptor modification by these proteases. In summary, TMPRSS2 and potentially related proteases promote SARS-CoV entry into the host cell through two different mechanisms: cleavage of ACE2, which may promote viral uptake, and cutting of S protein, activating it for membrane fusion process (Heurich et al. 2014).

The tissue expression and distribution of the ACE2 receptor determine the tropism of viral infection, which is crucial for understanding pathogenesis and designing therapeutic strategies. Gene expression profile analysis revealed that *ACE2* is mainly expressed in alveolar epithelial type II (AECII) cells, suggesting that these cells may serve as a reservoir for SARS-CoV-2. In addition, many other genes that positively regulate viral entry, multiplication, and transmission were found to be expressed in the ACE2-expressing cells (Zhao et al. 2020). ACE2 is expressed in the lungs and in the blood vessels, heart, kidney, and intestines. Therefore, it is now hypothesized that viral transmission via the endothelial ACE2 receptor represents a mechanism by which the virus can efficiently spread in the body, infecting different host tissues (McFadyen et al. 2020). Viral RNA has been found in urine and stool samples from COVID-19 patients, which enlarges the possibility of pathogen spread (Chen et al. 2020; Peng et al. 2020).

Genetic determinants of susceptibility to infection and severity of COVID-19

Understanding the genetic background that promotes SARS-CoV-2 transmission and infectivity is crucial for identifying the phenotype of patients predisposed to COVID-19 infection and its severity. Despite the increased efforts worldwide and the growing knowledge on the genetic determinants of COVID-19, many questions remain unanswered.

Recent autopsy analysis of the microvascular architecture of the lungs in patients who died from respiratory failure due to COVID-19 and AH1N1 influenza provided some interesting observations. More endothelial ACE2 receptors and significant changes in endothelial morphology were observed in the group with COVID-19 compared to the influenza-infected group. In addition, patients in this group were characterized by more enhanced and sprouting angiogenesis compared to post-influenza patients. The above study was supported by multiplex expression analysis of 323 angiogenesis-related genes. Among these, the expression of 69 genes was different in the COVID-19 group, while the other 26 were differentially expressed in the post-influenza group. A common expression pattern was found for 45 genes in both groups of patients (Ackermann et al. 2020). Recently, an analysis of 1,700 polymorphic variants of *ACE2* was also performed. Polymorphisms of this gene may determine changes in its expression and modulate plasma levels of the encoded protein, which increase is considered a molecular marker of bad prognosis of COVID-19 (Zipeto et al. 2020). The obtained results indicated a significant population homogeneity, which did not allow the clear selection of polymorphisms that could limit the binding of protein S to the ACE2 receptor and thus protect against viral transmission. However, it should be noted that 15 polymorphisms (rs112171234, rs12010448, rs143695310, rs1996225, rs200781818, rs2158082, rs4060, rs4646127, rs4830974, rs4830983, rs5936011, rs5936029 rs6629110, rs6632704, and rs75979613) can upregulate *ACE2* expression in various host tissues and they are more frequent in the East Asian than the European population. The differences observed between the populations indicate that there may be significant differences in susceptibility and/or response to SARS-CoV-2 infection, despite similar conditions (Cao et al. 2020). Also noteworthy is the higher mortality rate among men infected with SARS-CoV-2 compared to women. It was initially hypothesized that this might be related to the fact that *ACE2* shows an unusual heterogeneous male-female expression pattern, with higher expression in men (Tukiainen et al. 2017). However, closer examination of the expression of the mentioned gene within the lung tissue did not confirm significant differences

between patients of different sexes (Cai 2020). Looking for genetic prognostic markers for early identification of COVID-19 high-risk individuals, the rs2285666 (G8790A) polymorphism of *ACE2*, known as a potential risk factor for hypertension, type 2 diabetes, and coronary artery disease, may be important. Recent studies in the Italian population have shown that replacing the G allele by the A allele increases the strength of the splicing site, reflected by an increase in serum ACE2 protein levels in patients (Asselta et al. 2020). The analyses of the probable correlation between *ACE2* expression and the immune response of a patient infected with SARS-CoV-2 also seem interesting. It appeared that lung tissue characterized by a high level of *ACE2* expression in women or young people (aged ≤ 49 years) determines a weaker immune response to infection. The high expression of *ACE2* in the lung observed in men or older individuals (aged > 49 years) determines stronger immune signatures. It suggests that men and elderly individuals infected with SARS-CoV-2 may be particularly predisposed to an enhanced immune response manifested by a cytokine storm or immunopathological damage (Li et al. 2020a).

The *ACE2* locus is not the only one considered therapeutic target. Genome-wide association studies (GWAS) have identified a likely genetic susceptibility locus for developing chronic heart failure (CHF) associated with COVID-19. More than eight million single nucleotide polymorphisms have been analyzed, and statistically significant correlations were shown for loci 3p21.31 and 9q34.2. Within this locus, the frequency of risk alleles of selected polymorphic variants was higher in mechanically ventilated patients than those receiving oxygen supplementation alone. Furthermore, the 3p21.31 locus is characterized by a cluster of genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*) that may shape susceptibility to COVID-19 and be also relevant to the AB0 group system. Among these, of note is the *SLC6A20* gene, which encodes sodium-imino acid transporter 1 (SIT1) and interacts with ACE2. In addition, the 3p21.31 locus also contains genes encoding chemokine receptors, including C-C motif chemokine receptor 9 (CCR9) and C-X-C motif chemokine receptor 6 (CXCR6).

The last one regulates the specific localization of tissue-resident memory T cells (TRMs) in the lung, which is the first line of defense against respiratory system pathogens (Wein et al. 2019). This meta-analysis also indicates the association of polymorphic variants: rs11385942 locus 3p21.31 and rs657152 locus 9q34.2 with SARS-CoV-2-induced respiratory failure in Italian and Spanish populations. In addition, higher susceptibility to SARS-CoV-2 infection was observed among individuals with blood group A and a protective effect of group 0 against individuals with other blood groups (Severe COVID-19 GWAS Group et al. 2020; Zhao et al. 2021).

On the other hand, individual susceptibility to SARS-CoV-2 infection and the course of COVID-19 depends on the efficiency of the natural defense mechanisms of the immune system. The ZAP protein, known as ZC3HAV1 in mammals and hZAP in humans, is crucial in the antiviral immune response. The zinc-finger of the antiviral ZAP protein binds to CpG dinucleotides in viral RNA genomes (Meagher et al. 2019). Thus, it inhibits virus replication and simultaneously mediates the degradation of the virus genome (Gao et al. 2002; Mao et al. 2013). The experimental evidence is that CpG deficiency in RNA viruses has evolved in response to specific antiviral activities of the host organism. SARS-CoV-2 is characterized by extreme CpG deficiency, allowing the virus to evolve in host tissue with high expression rates (Meagher et al. 2019). Considering the human body's defense mechanisms, the endogenous enzyme APOBEC3G, found in innate immune cells, also exhibits antiviral activity. Both ZAP and APOBEC3G show tissue-specific expression patterns in humans. The enzyme modifies viral genetic material by deaminating cytosine to uracil (Sharma et al. 2015). CpG modification on UpG in non-functional regions may reduce the virus's susceptibility to the ZAP protein activity. In contrast, deamination induced by APOBEC3G may contribute to CpG deficiency and thereby reduce the antiviral effect of ZAP protein directed against CpG sequences (Xia 2020).

Another gene involved in the regulation of the immune system is *IFITM3*, which encodes interferon-induced transmembrane protein 3. Such trans-membrane proteins are involved in the innate immune response to viral infections. It regulates the fusion of invading endocytic vesicles and directs them to lysosomes. Furthermore, IFITM3 can alter cell membrane stiffness and curvature to inhibit viral membrane fusion and further pathogen spread (Li et al. 2013; Suddala et al. 2019). Previous reports indicate that the C allele of the rs12252 *IFITM3* polymorphism is associated with an increased probability of influenza virus infection as well as an increased risk of severe influenza and death (Xuan et al. 2015). Therefore, it should be investigated within the Chinese population, where the prevalence of the CC genotype is 26.5%. Analyses in Chinese patients have shown an association of the mentioned genotypic variant with an increased predisposition to severe SARS-CoV-2 infection (Thevarajan et al. 2020; Zhang et al. 2020). Presumably, the severe and complicated course of COVID-19 may be conditioned by selected polymorphic variants of *IFITM3* affecting gene expression or the lack of functionality of the encoded IFITM3 protein, which favors SARS-CoV-2 tropism (Hachim et al. 2020).

Another hypothesis for human susceptibility to COVID-19 is based on the human leukocyte antigen (HLA) system, responsible for presenting viral antigens

to T lymphocytes. Different HLA alleles may determine individual susceptibility to COVID-19 infection and spread, as confirmed for SARS and MERS virus (Li et al. 2020b). Analysis of HLA variation and effects on cellular immune response in patients with confirmed COVID-19 revealed that HLA-B*46:01 contains the lowest number of SARS-CoV-2 binding sites, suggesting that individuals with this allele may be particularly predisposed to SARS-CoV-2 infection. In contrast, HLA-B*15:03 shows the most remarkable ability to present highly conserved SARS-CoV-2 peptides, which may enable T-cell-based defensive immunity (Nguyen et al. 2020). Studies performed within the Italian population have revealed that healthy individuals carrying the HLA-B*44 and/or C*01 alleles, and the HLA-A*25, HLA-B*08 alleles may be more susceptible to SARS-CoV-2 infection. It may be caused by the limited ability to present viral epitopes and, consequently, the inability to initiate a rapid and effective antiviral immune response. Based on these data, it can be hypothesized that the virus will efficiently replicate and spread from these patients' oral and pharyngeal mucosal areas. In addition, previous studies indicate the role of the HLA-B*44 alleles in question, as well as C*01, in the progression of inflammatory autoimmune diseases (Grams et al. 2002; Jung et al. 2016), highlighting their involvement in the process of inducing imperfect and often undesirable immune responses (Correale et al. 2020). Noteworthy, the HLA-C*01 allele represents a specific ligand for killer cell immunoglobulin-like receptors (KIRs). These receptors can inhibit the activity of cells that represent the first line of host defense against the onset of a specific T cell response. In the Chinese population, the alleles particularly predisposing to COVID-19 infection may be HLA-C*07:29 and B*15:27, but further analyses are needed due to the small size of the study group (Wang et al. 2020).

The severe and complicated course of COVID-19 may also be conditioned by activating the transmembrane serine protease TMPRSS2. TMPRSS2 promotes SARS-CoV-2 entry into the host cell via two distinct mechanisms: by cutting SARS-S, which activates the S protein to fuse with the membrane, or cleaving ACE2, which may promote viral uptake via a cathepsin L-dependent pathway (Heurich et al. 2014). Furthermore, among the hypotheses explored regarding gender-dependent differences in susceptibility to infection, the analysis of the expression and genetic variability of TMPRSS2 seems interesting. Data extracted from a large Italian cohort compared the frequency of the selected polymorphisms between Italian, European, and East Asian populations. The study identified four polymorphic variants (rs2298659, rs17854725, rs12329760, and rs3787950) with a significantly different frequency between the mentioned populations. Moreover, a haplotype consisting of polymorphisms: rs2070788, rs9974589, rs7364083 and rs463727, rs34624090, rs55964536, rs734056, rs4290734, rs34783969, rs11702475, rs35899679, and rs35041537, typical of the European population and not found in the Asian population, may regulate androgen-dependent *TMPRSS2* expression. It could explain why men are more susceptible to severe COVID-19 and die more often (Asselta et al. 2020). Also noteworthy is the haplotype of the variants: rs2070788, rs9974589, and rs7364083, whose minor allele frequency (MAF) is significantly more frequent in European than in East Asian populations. Previous studies indicate a role for the rs2070788 polymorphism in the severity of influenza A(H7N9) and A(H1N1) (Cheng et al. 2015).

Further data concerned the expression profiles of the *TMPRSS2* gene. Polymorphisms rs464397, rs469390, rs2070788, and rs383510 were found to determine *TMPRSS2* expression in lung tissue. The allele frequency of each polymorphism was then estimated in African, American, European, and three Asian populations (Chinese, Japanese and Taiwanese).

Interestingly, variants that increase *TMPRSS2* expression occur much more frequently in European and American populations than in Asian populations, which may indicate an increased susceptibility of these populations to SARS-CoV-2 infection. Recent genome-wide association studies (GWAS) involving patients from intensive care units in the U.K. identified new loci predisposing to severe and complicated COVID-19. At least two biological mechanisms determine the severe course of the disease. The first one is the innate antiviral defense mechanism, which is particularly important in the early stages of the disease (*IFNAR2* and *OAS* genes) and the life-threatening inflammatory lung damage, which is a consequence of the later pathomechanism (*DPP9*, *TYK2*, and *CCR2* genes). A new significant genome-wide association rs10735079 (chr12q24.13), located in the oligoadenylate interferon synthetase gene cluster (*OAS1*, *OAS2*, and *OAS3*) and encoding antiviral restriction enzyme activators were identified, and replicated. The mentioned associations were described for the rs2109069 (chr19p13.2) polymorphism in the gene encoding tyrosine kinase 2 (*TYK2*), the rs2109069 (ch19p13.3) polymorphism in the gene encoding dipeptidyl peptidase 9 (*DPP9*), and the rs2236757 (chr21q22.1) polymorphism in the *IFNAR2* gene, which encodes the receptor for interferons Alpha and Beta variants.

Characteristics of SARS-CoV-2 virus variants

The rapid spread of the SARS-CoV-2 virus favors its molecular evolution. In September 2020, Alpha (B.1.1.7), also known as VUI 202012/01 (Variant Under Investigation, the year 2020, month 12, variant 01), the first new

variant of the SARS-CoV-2 virus was discovered. Phylogenetic analyses have shown that SARS-CoV-2 variants accumulate nucleotide mutations at approximately 1–2 mutations per month (Duchene et al. 2020). The VUI 202012/01 has a higher number of genetic changes acquired during global transmission. The genetic structure of the Alpha variant contains eight mutations within the S protein (deletions 69-70HV, 144Y, substitutions N501Y, A570D, P681H, T716I, S982A, D1118H). Attention was paid to three of these, including N501Y within the S protein RBD domain, which the virus uses to bind to the human ACE2 receptor. The mutation involves one of the six key amino acid residues of the domain and can affect the increased affinity of the virus for host cell receptors, increasing its infectivity and virulence (Starr et al. 2020; Santos and Passos 2021). The 69-70del mutation plays a vital role in the viral mechanism of human immune response evasion. The P681H mutation is directly adjacent to the furin S1/S2 cleavage site and may be biologically relevant (Rambaut et al. 2020). Additionally, newly detected mutations affect ORF8. This small protein contains 121 amino acids. A stop codon at position 27 due to the mutation Q27stop, results in the mentioned protein loss of function. In variant B.1.1.7, there were also six synonymous mutations in ORF1ab (C913T, C5986T, C14676T, C15279T, C16176T) and one in the M gene (T26801C). The new VUI 202012/01 strain has many genetic alterations and has rapidly led to a significant increase in COVID-19 cases in the U.K. So far, other variants of SARS-CoV-2 have also been identified, such as Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and the latest Omicron (B 1.1.529). Of concern is the rapid spread of the Omicron SARS-CoV-2 variant, which was first recorded in South Africa. This variant was characterized by approximately 50 different mutations, including more than 30 in the spike protein. Some identified mutations, e.g., 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H, overlap with those in the Alpha, Beta, Gamma, or Delta variants. Omicron may be associated with increased infectivity and the ability to avoid the host's antibodies blocking the infection, primarily due to mutations in the furin cleavage site (Karim and Karim 2021; Callaway 2021; Torjesen 2021).

Phenotypic consequences of the SARS-CoV-2 mutations and the unknown effects of their co-occurrence indicate that further research and enhanced genomic surveillance worldwide are needed.

Conclusions

Coronaviruses are commonly found in our surroundings, constantly pressured by anthropogenic influences. It is also worth noting that, in recent years, there have been re-peated warning signals indicating the possibility of the emergence of a virus with pandemic potential. However, scientists' suggestion on the risk of such a crisis has been largely downplayed. Therefore, it is so essential to draw the correct conclusions from the recent experience, especially as COVID-19 is probably not the last threat of viral and etiology that will confront us.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Literature

Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020 Jul 09;383(2):120–128. https://doi.org/10.1056/NEJMoa2015432

Aguilar-Shea AL, Vera-García M, Güerri-Fernández R. Rapid antigen tests for the detection of SARS-CoV-2: A narrative review. Aten Primaria. 2021 Nov;53(9):102127. https://doi.org/10.1016/j.aprim.2021.102127

Alsharif W, Qurashi A. Effectiveness of COVID-19 diagnosis and management tools: A review. Radiography. 2021 May;27(2):682–687. https://doi.org/10.1016/j.radi.2020.09.010

Araf Y, Akter F, Tang Y, Fatemi R, Parvez MSA, Zheng C, Hossain MG. Omicron variant of SARS-CoV-2: Genomics, transmissibility, and responses to current COVID-19 vaccines. J Med Virol. 2022 May;94(5):1825–1832. https://doi.org/10.1002/jmv.27588

Asghari A, Naseri M, Safari H, Saboory E, Parsamanesh N. The novel insight of SARS-CoV-2 molecular biology and pathogenesis and therapeutic options. DNA Cell Biol. 2020 Oct 01;39(10):1741–1753. https://doi.org/10.1089/dna.2020.5703

Asselta R, Paraboschi EM, Mantovani A, Duga S. *ACE2* and *TMPRSS2* variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY). 2020 Jun 05;12(11):10087–10098. https://doi.org/10.18632/aging.103415

Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, Bartlett RH, Tonna JE, Hyslop R, Fanning JJ, et al.; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet. 2020 Oct;396(10257):1071–1078. https://doi.org/10.1016/S0140-6736(20)32008-0

Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012 Jun 20;4(6):1011–1033. https://doi.org/10.3390/v4061011

Blain H, Rolland Y, Benetos A, Giacosa N, Albrand M, Miot S, Bousquet J. Atypical clinical presentation of COVID-19 infection in residents of a long-term care facility. Eur Geriatr Med. 2020 Dec;11(6):1085–1088. https://doi.org/10.1007/s41999-020-00352-9

Böger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. Am J Infect Control. 2021 Jan;49(1):21–29. https://doi.org/10.1016/j.ajic.2020.07.011

Brümmer LE, Katzenschlager S, Gaeddert M, Erdmann C, Schmitz S, Bota M, Grilli M, Larmann J, Weigand MA, Pollock NR, et al. Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: A living systematic review and meta-analysis. PLoS Med. 2021 Aug 12;18(8):e1003735. https://doi.org/10.1371/journal.pmed.1003735

Bwire GM, Majigo MV, Njiro BJ, Mawazo A. Detection profile of SARS-CoV-2 using RT-PCR in different types of clinical specimens: A systematic review and meta-analysis. J Med Virol. 2021 Feb; 93(2):719–725. https://doi.org/10.1002/jmv.26349

Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. medRxiv. 2020;2020.02.05.20020107. https://doi.org/10.1101/2020.02.05.20020107

Callaway E. Heavily mutated Omicron variant puts scientists on alert. Nature. 2021 Dec 02;600(7887):21. https://doi.org/10.1038/d41586-021-03552-w

Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 2020 Dec;6(1):11. https://doi.org/10.1038/s41421-020-0147-1

CDC. How to Protect Yourself & Others [Internet]. Atlanta (USA): Centers for Disease Control and Prevention; 2021 [cited 2022 Feb 20]. Available from https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, Yang Y, Liu B, Wang W, Wei C, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020 Jul;92(7):833–840. https://doi.org/10.1002/jmv.25825

Cheng Z, Zhou J, To KKW, Chu H, Li C, Wang D, Yang D, Zheng S, Hao K, Bossé Y, et al. Identification of *TMPRSS2* as a susceptibility gene for severe 2009 pandemic A(H1N1) influenza and A(H7N9) influenza. J Infect Dis. 2015 Oct 15;212(8):1214–1221. https://doi.org/10.1093/infdis/jiv246

Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020 Jul;159(1):81–95. https://doi.org/10.1053/j.gastro.2020.03.065

Choi GJ, Baek SH, Kim J, Kim JH, Kwon GY, Kim DK, Jung YH, Kim S. Fatal systemic capillary leak syndrome after SARS-CoV-2 vaccination in patient with multiple myeloma. Emerg Infect Dis. 2021 Nov;27(11):2973–2975. https://doi.org/10.3201/eid2711.211723

Chua GT, Kwan MYW, Chui CSL, Smith RD, Cheung EC, Tian T, Leung MTY, Tsao SSL, Kan E, Ng WKC, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following Comirnaty vaccination. Clin Infect Dis. 2021 Nov 28:ciab989. https://doi.org/10.1093/cid/ciab989

Comirnaty, Summary of product characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 9]. Available from https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

Cornillez-Ty CT, Liao L, Yates JR 3rd, Kuhn P, Buchmeier MJ. Severe acute respiratory syndrome coronavirus nonstructural protein 2 interacts with a host protein complex involved in mitochondrial biogenesis and intracellular signaling. J Virol. 2009 Oct; 83(19):10314–10318. https://doi.org/10.1128/JVI.00842-09

Correale P, Mutti L, Pentimalli F, Baglio G, Saladino RE, Sileri P, Giordano A. HLA-B*44 and C*01 prevalence correlates with covid19 spreading across Italy. Int J Mol Sci. 2020 Jul 23;21(15):5205. https://doi.org/10.3390/ijms21155205

COVID-19 Vaccine AstraZeneca, Summary of product characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 20]. Available from https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-astrazeneca-product-information-approved-chmp-29-january-2021-pending-endorsement_en.pdf

COVID-19 Vaccine AstraZeneca, Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf

COVID-19 Vaccine Janssen, Summary of product characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 20]. Available from https://www.ema.europa.eu/en/documents/product-information/jcovden-previously-covid-19-vaccine-janssen-epar-product-information_en.pdf

Davies JP, Almasy KM, McDonald EF, Plate L. Comparative multiplexed interactomics of SARS-CoV-2 and homologous coronavirus nonstructural proteins identifies unique and shared host-cell dependencies. ACS Infect Dis. 2020 Dec 11;6(12):3174–3189. https://doi.org/10.1021/acsinfecdis.0c00500

de Haan CAM, Vennema H, Rottier PJM. Assembly of the coronavirus envelope: homotypic interactions between the M proteins. J Virol. 2000 Jun;74(11):4967–4978. https://doi.org/10.1128/jvi.74.11.4967-4978.2000

Du L, Zhao G, Lin Y, Chan C, He Y, Jiang S, Wu C, Jin DY, Yuen KY, Zhou Y, et al. Priming with rAAV encoding RBD of SARS-CoV S protein and boosting with RBD-specific peptides for T cell epitopes elevated humoral and cellular immune responses against SARS-CoV infection. Vaccine. 2008 Mar;26(13):1644–1651. https://doi.org/10.1016/j.vaccine.2008.01.025

Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. Virus Evol. 2020 Aug 19;6(2):veaa061. https://doi.org/10.1093/ve/veaa061

ECDC. Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK [Internet]. Stockholm (Sweden): European Centre for Disease Prevention and Control; 2020 [cited 2021 Apr 02]. Available from https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID-19_0.pdf

Englisch CN, Tschernig T, Flockerzi F, Meier C, Bohle RM. Lesions in the lungs of fatal corona virus disease Covid-19. Ann Anat. 2021 Mar;234:151657. https://doi.org/10.1016/j.aanat.2020.151657

Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DS, Mishra S, Crispim MAE, Sales FCS, Hawryluk I, McCrone JT, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 2021 May 21;372(6544):815–821. https://doi.org/10.1126/science.abh2644

Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23. https://doi.org/10.1007/978-1-4939-2438-7_1

Ferré VM, Peiffer-Smadja N, Visseaux B, Descamps D, Ghosn J, Charpentier C. Omicron SARS-CoV-2 variant: what we know and what we don't. Anaesth Crit Care Pain Med. 2022 Feb;41(1):100998. https://doi.org/10.1016/j.accpm.2021.100998

Flisiak R, Horban A, Jaroszewicz J, Kozielewicz D, Pawłowska M, Parczewski M, Piekarska A, Simon K, Tomasiewicz K, Zarębska-Michaluk D. [Zalecenia postępowania w zakażeniach SARS-CoV-2 Polskiego Towarzystwa Epidemiologów i Lekarzy Chorób Zakaźnych, na dzień 26 kwietnia 2021] (in Polish) [Internet]. PTEiLChZ 30.04.2021 [cited 2022 Feb 04]. Available from https://www.mp.pl/covid19/zalecenia/265853,zalecenia-postepowania-w-zakazeniach-sars-cov-2-polskiego-towarzystwa-epidemiologow-i-lekarzy-chorob-zakaznych-26042021

Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT):

diagnostic and therapeutic recommendations for a new syndrome. Eur J Haematol. 2021 Aug;107(2):173–180. https://doi.org/10.1111/ejh.13665

Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, Panebianco V, Andreoli C, Colaiacomo MC, Zingaropoli MA, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020 Dec;30(12): 6808–6817. https://doi.org/10.1007/s00330-020-07033-y

Gao G, Guo X, Goff SP. Inhibition of retroviral RNA production by ZAP, a CCCH-type zinc finger protein. Science. 2002 Sep 06; 297(5587):1703–1706. https://doi.org/10.1126/science.1074276

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, Broder KR, Gee J, Weintraub E, Shimabukuro T, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021 Jul 09;70(27):977–982. https://doi.org/10.15585/mmwr.mm7027e2

Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, et al.; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020 Nov 05;383(19):1827–1837. https://doi.org/10.1056/nejmoa2015301

Grams SE, Moonsamy PV, Mano C, Oksenberg JR, Begovich AB. Two new HLA-B alleles, B*4422 and B*4704, identified in a study of families with autoimmunity. Tissue Antigens. 2002 Apr;59(4):338–340. https://doi.org/10.1034/j.1399-0039.2002.590417.x

Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis. 2020 Jul 28;71(15):778–785. https://doi.org/10.1093/cid/ciaa310

Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, et al.; STOP-COVID Investigators. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med. 2020 Nov 01;180(11):1436–1447. https://doi.org/10.1001/jamainternmed.2020.3596

Hachim MY, Al Heialy S, Hachim IY, Halwani R, Senok AC, Maghazachi AA, Hamid Q. Interferon-induced transmembrane protein (IFITM3) is upregulated explicitly in SARS-CoV-2 infected lung epithelial cells. Front Immunol. 2020 Jun 10;11:1372. https://doi.org/10.3389/fimmu.2020.01372

Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, Ludden C, Reeve R, Rambaut A, Peacock SJ, et al.; COVID-19 Genomics UK (COG-UK) Consortium. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 2021 Jul;19(7):409–424. https://doi.org/10.1038/s41579-021-00573-0

Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O, Pöhlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virol. 2014 Jan 15;88(2):1293–1307. https://doi.org/10.1128/JVI.02202-13

Hirotsu Y, Maejima M, Shibusawa M, Nagakubo Y, Hosaka K, Amemiya K, Sueki H, Hayakawa M, Mochizuki H, Tsutsui T, et al. Comparison of automated SARS-CoV-2 antigen test for COVID-19 infection with quantitative RT-PCR using 313 nasopharyngeal swabs, including from seven serially followed patients. Int J Infect Dis. 2020 Oct;99:397–402. https://doi.org/10.1016/j.ijid.2020.08.029

Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020 May21;78(4):779–784.e5. https://doi.org/10.1016/j.molcel.2020.04.022

Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, et al.; RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19; 383(21): 2030–2040. https://doi.org/10.1056/NEJMoa2022926

Hu B, Zeng LP, Yang XL, Ge XY, Zhang W, Li B, Xie JZ, Shen XR, Zhang YZ, Wang N, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog. 2017 Nov 30;13(11):e1006698. https://doi.org/10.1371/journal.ppat.1006698

Huang Y, Yang C, Xu Xf, Xu W, Liu Sw. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020 Sep; 41(9): 1141–1149. https://doi.org/10.1038/s41401-020-0485-4

Hussain M, Jabeen N, Raza F, Shabbir S, Baig AA, Amanullah A, Aziz B. Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein. J Med Virol. 2020 Sep; 92(9):1580–1586. https://doi.org/10.1002/jmv.25832

Jung ES, Cheon JH, Lee JH, Park SJ, Jang HW, Chung SH, Park MH, Kim TG, Oh HB, Yang SK, et al. HLA-C*01 is a risk factor for Crohn's disease. Inflamm Bowel Dis. 2016 Apr;22(4):796–806. https://doi.org/10.1097/MIB.0000000000000693

Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet. 2021 Dec 11;398(10317): 2126–2128. https://doi.org/10.1016/S0140-6736(21)02758-6

Kashour Z, Riaz M, Garbati MA, AlDosary O, Tlayjeh H, Gerberi D, Murad MH, Sohail MR, Kashour T, Tleyjeh IM. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chemother. 2021 Jan 01;76(1):30–42. https://doi.org/10.1093/jac/dkaa403

Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The architecture of SARS-CoV-2 transcriptome. Cell. 2020 May;181(4):914–921.e10. https://doi.org/10.1016/j.cell.2020.04.011

Koçak Tufan Z, Kayaaslan B, Mer M. COVID-19 and sepsis. Turk J Med Sci. 2021 Dec 17;51 SI-1:3301–3311. https://doi.org/10.3906/sag-2108-239

Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G. Omicron and Delta variant of SARS-CoV-2: A comparative computational study of spike protein. J Med Virol. 2022 Apr;94(4):1641–1649. https://doi.org/10.1002/jmv.27526

Lagevrio, Summary of Product Characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 15]. Available from https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-conditions-use-conditions_en.pdf

Lan SH, Lai CC, Huang HT, Chang SP, Lu LC, Hsueh PR. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents. 2020 Sep;56(3):106103. https://doi.org/10.1016/j.ijantimicag.2020.106103

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020 May 05; 172(9):577–582. https://doi.org/10.7326/M20-0504

Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020 Aug;277(8):2251–2261. https://doi.org/10.1007/s00405-020-05965-1

Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. Antiviral Res. 2018 Jan; 149:58–74. https://doi.org/10.1016/j.antiviral.2017.11.001

Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis. 2020 Jun; 20(6):697–706. https://doi.org/10.1016/S1473-3099(20)30200-0

Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016 Sep 29;3(1):237–261. https://doi.org/10.1146/annurev-virology-110615-042301

Li K, Markosyan RM, Zheng YM, Golfetto O, Bungart B, Li M, Ding S, He Y, Liang C, Lee JC, et al. IFITM proteins restrict viral membrane hemifusion. PLoS Pathog. 2013 Jan;9(1):e1003124. https://doi.org/10.1371/journal.ppat.1003124

Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020a Dec;9(1):45. https://doi.org/10.1186/s40249-020-00662-x

Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020b Apr;10(2): 102–108. https://doi.org/10.1016/j.jpha.2020.03.001

Lim Y, Ng Y, Tam J, Liu D. Human Coronaviruses: A Review of Virus-Host Interactions. Diseases. 2016 Jul 25;4(4):26. https://doi.org/10.3390/diseases4030026

Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. Front Public Health. 2021 Nov 30;9:775224. https://doi.org/10.3389/fpubh.2021.775224

Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, Lan Z, Law S, MacLean E, Trajman A, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. BMJ. 2020 Jul 01;370:m2516. https://doi.org/10.1136/bmj.m2516

Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, Kovyrshina AV, Lubenets NL, Grousova DM, Erokhova AS, et al.; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021 Feb; 397(10275):671–681. https://doi.org/10.1016/S0140-6736(21)00234-8

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb;395(10224):565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Luan J, Lu Y, Jin X, Zhang L. Spike protein recognition of mammalian ACE2 predicts the host range and an optimized ACE2 for SARS-CoV-2 infection. Biochem Biophys Res Commun. 2020 May; 526(1):165–169. https://doi.org/10.1016/j.bbrc.2020.03.047

Makoah NA, Tipih T, Litabe MM, Brink M, Sempa JB, Goedhals D, Burt FJ. A systematic review and meta-analysis of the sensitivity of antibody tests for the laboratory confirmation of COVID-19. Future Virol. 2021 Nov:10.2217/fvl-2021-0211. https://doi.org/10.2217/fvl-2021-0211

Malik JA, Ahmed S, Mir A, Shinde M, Bender O, Alshammari F, Ansari M, Anwar S. The SARS-CoV-2 mutations versus vaccine effectiveness: new opportunities to new challenges. J Infect Public Health. 2022 Feb;15(2):228–240. https://doi.org/10.1016/j.jiph.2021.12.014

Mao R, Nie H, Cai D, Zhang J, Liu H, Yan R, Cuconati A, Block TM, Guo JT, Guo H. Inhibition of hepatitis B virus replication by the host zinc finger antiviral protein. PLoS Pathog. 2013 Jul 11;9(7):e1003494. https://doi.org/10.1371/journal.ppat.1003494

McBride R, van Zyl M, Fielding B. The coronavirus nucleocapsid is a multifunctional protein. Viruses. 2014 Aug 07;6(8):2991–3018. https://doi.org/10.3390/v6082991

McDonald I, Murray SM, Reynolds CJ, Altmann DM, Boyton RJ. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. npj Vaccines. 2021 Dec;6(1):74. https://doi.org/10.1038/s41541-021-00336-1

McFadyen JD, Stevens H, Peter K. The emerging threat of (micro) thrombosis in COVID-19 and its therapeutic implications. Circ Res. 2020 Jul 31;127(4):571–587. https://doi.org/10.1161/CIRCRESAHA.120.317447

Meagher JL, Takata M, Gonçalves-Carneiro D, Keane SC, Rebendenne A, Ong H, Orr VK, MacDonald MR, Stuckey JA, Bieniasz PD, et al. Structure of the zinc-finger antiviral protein in complex with RNA reveals a mechanism for selective targeting of CG-rich viral sequences. Proc Natl Acad Sci USA. 2019 Nov 26; 116(48):24303–24309. https://doi.org/10.1073/pnas.1913232116

Mustafa Hellou M, Górska A, Mazzaferri F, Cremonini E, Gentilotti E, De Nardo P, Poran I, Leeflang MM, Tacconelli E, Paul M. Nucleic acid amplification tests on respiratory samples for the diagnosis of coronavirus infections: a systematic review and meta-analysis. Clin Microbiol Infect. 2021 Mar;27(3):341–351. https://doi.org/10.1016/j.cmi.2020.11.002

Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, Fell DB, Austin PC, Schwartz KL, Sundaram ME, et al.; Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Investigators. Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. Nat Microbiol. 2022 Mar;7(3):379–385. https://doi.org/10.1038/s41564-021-01053-0

Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, Thompson RF. Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2. J Virol. 2020 Jun 16;94(13):e00510-20. https://doi.org/10.1128/JVI.00510-20

Nieto-Torres JL, DeDiego ML, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Fernandez-Delgado R, Castaño-Rodriguez C, Alcaraz A, Torres J, Aguilella VM, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Pathog. 2014 May 1;10(5):e1004077. https://doi.org/10.1371/journal.ppat.1004077

O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, Bar KJ, Barnabas RV, Barouch DH, Cohen MS, et al; Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med. 2021 Sep 23;385(13):1184–1195. https://doi.org10.1056/NEJMoa2109682

Ong DSY, Fragkou PC, Schweitzer VA, Chemaly RF, Moschopoulos CD, Skevaki C; European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Respiratory Viruses (ESGREV). How to interpret and use COVID-19 serology and immunology tests. Clin Microbiol Infect. 2021 Jul;27(7):981–986. https://doi.org/10.1016/j.cmi.2021.05.001

Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020 Mar 27;11(1):1620. https://doi.org/10.1038/s41467-020-15562-9

Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, Cosma C, Faggian D, Matricardi P, Plebani M. IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: A longitudinal study. Clin Chim Acta. 2020 Aug;507:164–166. https://doi.org/10.1016/j.cca.2020.04.026

Peng L, Liu J, Xu W, Luo Q, Chen D, Lei Z, Huang Z, Li X, Deng K, Lin B, et al. SARS-CoV-2 can be detected in urine, blood, anal swabs, and oropharyngeal swabs specimens. J Med Virol. 2020 Sep; 92(9):1676–1680. https://doi.org/10.1002/jmv.25936

Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009 Jun;7(6):439–450. https://doi.org/10.1038/nrmicro2147

Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. Thromb Res. 2020 Dec;196:67–74. https://doi.org/10.1016/j.thromres.2020.08.020

Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, Dushoff J, Mlisana K, Moultrie H. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. medRxiv. 2021; 2021.11.11.21266068. https://doi.org/10.1101/2021.11.11.21266068

Pyrc K, Dijkman R, Deng L, Jebbink MF, Ross HA, Berkhout B, van der Hoek L. Mosaic structure of human coronavirus NL63, one thousand years of evolution. J Mol Biol. 2006 Dec;364(5):964–973. https://doi.org/10.1016/j.jmb.2006.09.074

Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, Rochwerg B, Fernando SM, Takeda S, MacLaren G, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care. 2021 Dec;25(1):211. https://doi.org/10.1186/s13054-021-03634-1

Rambaut A, Loman N, Pybus O, Barclay W, Barrett J, Carabelli A, Connor T, Peacock T, Robertson D, Volz E. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations [Internet]. 2020 [cited 2022 Feb 04]. Available from https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

Ravi N, Cortade DL, Ng E, Wang SX. Diagnostics for SARS-CoV-2 detection: A comprehensive review of the FDA-EUA COVID-19 testing landscape. Biosens Bioelectron. 2020 Oct;165:112454. https://doi.org/10.1016/j.bios.2020.112454

Ravindra K, Malik VS, Padhi BK, Goel S, Gupta M. Asymptomatic infection and transmission of COVID-19 among clusters: systematic review and meta-analysis. Public Health. 2022 Feb;203:100–109. https://doi.org/10.1016/j.puhe.2021.12.003

RoActemra, Summary of product characteristics[Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 15]. Available from https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf

Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, Goepfert PA, Truyers C, Fennema H, Spiessens B, et al.; ENSEMBLE Study Group. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021 Jun 10;384(23):2187–2201. https://doi.org/10.1056/NEJMoa2101544

Sakai Y, Kawachi K, Terada Y, Omori H, Matsuura Y, Kamitani W. Two-amino acids change in the nsp4 of SARS coronavirus abolishes viral replication. Virology. 2017 Oct;510:165–174. https://doi.org/10.1016/j.virol.2017.07.019

Santos JC, Passos GA. The high infectivity of SARS-CoV-2 B.1.1.7 is associated with increased interaction force between Spike-ACE2 caused by the viral N501Y mutation. bioRxiv. 2020; 2020.12.29.424708. https://doi.org/10.1101/2020.12.29.424708

Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, Leibundgut M, Thiel V, Mühlemann O, Ban N. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. 2020 Oct;27(10):959–966. https://doi.org/10.1038/s41594-020-0511-8

Severe Covid-19 GWAS Group; Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, et al. Genomewide association study of severe COVID-19 with respiratory failure. N Engl J Med. 2020 Oct 15; 383(16):1522–1534. https://doi.org/10.1056/NEJMoa2020283

Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci USA. 2020 May 26;117(21):11727–11734. https://doi.org/10.1073/pnas.2003138117

Sharma S, Patnaik SK, Thomas Taggart R, Kannisto ED, Enriquez SM, Gollnick P, Baysal BE. APOBEC3A cytidine deaminase induces RNA editing in monocytes and macrophages. Nat Commun. 2015 Nov;6(1):6881. https://doi.org/10.1038/ncomms7881

Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab Syndr. 2021 Nov; 15(6):102329. https://doi.org/10.1016/j.dsx.2021.102329

Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. Biochem Biophys Res Commun. 2020 Sep;530(1):10–14. https://doi.org/10.1016/j.bbrc.2020.05.206

Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses. 2019 Jan 14;11(1):59. https://doi.org/10.3390/v11010059

Spikevax, Summary of product characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Feb 20]. Available from https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

Srinivasan S, Cui H, Gao Z, Liu M, Lu S, Mkandawire W, Narykov O, Sun M, Korkin D. Structural genomics of SARS-COV-2 indicates evolutionary conserved functional regions of viral proteins. Viruses. 2020 Mar 25;12(4):360. https://doi.org/10.3390/v12040360

Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, Navarro MJ, Bowen JE, Tortorici MA, Walls AC, et al. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. Cell. 2020 Sep;182(5):1295–1310.e20. https://doi.org/10.1016/j.cell.2020.08.012

Suddala KC, Lee CC, Meraner P, Marin M, Markosyan RM, Desai TM, Cohen FS, Brass AL, Melikyan GB. Interferon-induced transmembrane protein 3 blocks fusion of sensitive but not resistant viruses by partitioning into virus-carrying endosomes. PLoS Pathog. 2019 Jan 14;15(1):e1007532. https://doi.org/10.1371/journal.ppat.1007532

Surjit M, Liu B, Chow VTK, Lal SK. The nucleocapsid protein of severe acute respiratory syndrome-coronavirus inhibits the activity of cyclin-cyclin-dependent kinase complex and blocks S phase progression in mammalian cells. J Biol Chem. 2006 Apr;281(16): 10669–10681. https://doi.org/10.1074/jbc.M509233200

Tang X, Wu C, Li X, Song Y, Yao X, Wu X, Duan Y, Zhang H, Wang Y, Qian Z, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. 2020 Jun 01;7(6):1012–1023. https://doi.org/10.1093/nsr/nwaa036

Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, Bloom NI, Goodwin B, Phillips E, Mallal S, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. Cell. 2022 Mar 3;185(5): 847–859.e11. https://doi.org/10.1016/j.cell.2022.01.015

Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N, et al. Emergence and rapid spread of a new severe acute respiratory syndrome related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv. 2020;2020.12.21.20248640. https://doi.org/10.1101/2020.12.21.20248640

The Johns Hopkins Coronavirus Resource Center [Internet]. Baltimore (USA): Johns Hopkins University and Medicine; 2022 [cited 2022 Feb 4]. Available from https://coronavirus.jhu.edu

Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, Jia X, Nicholson S, Catton M, Cowie B, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020 Apr;26(4):453–455. https://doi.org/10.1038/s41591-020-0819-2

Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, Altannir M, Altannir Y, Al-Tannir M, Tleyjeh R, Hassett L, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect. 2021 Feb; 27(2): 215–227. https://doi.org/10.1016/j.cmi.2020.10.036

Tomasiewicz K, Piekarska A, Stempkowska-Rejek J, Serafińska S, Gawkowska A, Parczewski M, Ništcigorska-Olsen J, Łapiński TW, Zarębska-Michaluk D, Kowalska JD, et al. Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study. Expert Rev Anti Infect Ther. 2021 Jan 02;19(1):93–100. https://doi.org/10.1080/14787210.2020.1800453

Torjesen I. COVID-19: omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. BMJ. 2021 Nov 29;375(2943):n2943. https://doi.org/10.1136/bmj.n2943

Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, Aguirre M, Gauthier L, Fleharty M, Kirby A, et al.; GTEx Consortium; Laboratory, Data Analysis &Coordinating Center (LDACC) – Analysis Working Group; Statistical Methods groups – Analysis Working Group; Enhancing GTEx (eGTEx) groups; NIH Common Fund; NIH/NCI; NIH/NHGRI; NIH/NIMH; NIH/NIDA; Biospecimen Collection Source Site – NDRI; et al. Landscape of X chromosome inactivation across human tissues. Nature. 2017 Oct 12;550(7675):244–248. https://doi.org/10.1038/nature24265

Vangeel L, Chiu W, De Jonghe S, Maes P, Slechten B, Raymenants J, André E, Leyssen P, Neyts J, Jochmans D. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. Antiviral Res. 2022 Feb; 198:105252. https://doi.org/10.1016/j.antiviral.2022.105252

Veklury, Summary of product characteristics [Internet]. Amsterdam (The Netherlands): European Medicines Agency; 2022 [cited 2022 Jan 5]. Available from https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020 Apr;181(2):281–292.e6. https://doi.org/10.1016/j.cell.2020.02.058

Wang W, Zhang W, Zhang J, He J, Zhu F. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). HLA. 2020 Aug;96(2):194–196. https://doi.org/10.1111/tan.13941

Wein AN, McMaster SR, Takamura S, Dunbar PR, Cartwright EK, Hayward SL, McManus DT, Shimaoka T, Ueha S, Tsukui T, et al. CXCR6 regulates localization of tissue-resident memory CD8 T cells to the airways. J Exp Med. 2019 Dec 02;216(12):2748–2762. https://doi.org/10.1084/jem.20181308

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Xiao J, Hooper AT, Hamilton JD, Musser BJ, et al.; Trial Investigators. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med. 2021 Dec 02;385(23):e81. https://doi.org/10.1056/NEJMoa2108163

Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res. 2011;81:85–164. https://doi.org/10.1016/B978-0-12-385885-6.00009-2

WHO. Classification of Omicron (B.1.1.529): SARS-CoV-2 variant of concern [Internet]. Geneva (Switzerland): World Health Organization; 2021 [cited 2022 Feb 04]. Available from https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern

WHO. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance, 19 March 2020 [Internet]. Geneva (Switzerland): World Health Organization; 2020 [cited 2022 Feb 04]. Available from https://apps.who.int/iris/handle/10665/331501

WHO. Tracking SARS-CoV-2 variants [Internet]. Geneva (Switzerland): World Health Organization; 2022 [cited 2022 Feb 15]. Available from https://www.who.int/activities/tracking-SARS-CoV-2-variants

Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). JAMA. 2020 Aug 25;324(8):782–793. https://doi.org/10.1001/jama.2020.12839

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Mar13; 367(6483):1260–1263. https://doi.org/10.1126/science.abb2507

Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z, Zhang Z, Wang J, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. 2020 Mar;27(3):325–328. https://doi.org/10.1016/j.chom.2020.02.001

Xia X. Extreme genomic CpG deficiency in SARS-CoV-2 and evasion of host antiviral defense. Mol Biol Evol. 2020 Sep 01;37(9): 2699–2705. https://doi.org/10.1093/molbev/msaa094

Xuan Y, Wang LN, Li W, Zi HR, Guo Y, Yan WJ, Chen XB, Wei PM. *IFITM3* rs12252 T>C polymorphism is associated with the risk of severe influenza: a meta-analysis. Epidemiol Infect. 2015 Oct; 143(14):2975–2984. https://doi.org/10.1017/S0950268815000278

Yamayoshi S, Sakai-Tagawa Y, Koga M, Akasaka O, Nakachi I, Koh H, Maeda K, Adachi E, Saito M, Nagai H, et al. Comparison of rapid antigen tests for COVID-19. Viruses. 2020 Dec 10;12(12):1420. https://doi.org/10.3390/v12121420

Yoshimoto FK. The proteins of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2 or n-COV19), the cause of COVID-19. Protein J. 2020 Jun;39(3):198–216. https://doi.org/10.1007/s10930-020-09901-4

Yu H, Sun B, Fang Z, Zhao J, Liu X, Li Y, Sun X, Liang H, Zhong B, Huang Z, et al. Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients. Eur Respir J. 2020 Aug;56(2): 2001526. https://doi.org/10.1183/13993003.01526-2020

Yuan Y, Cao D, Zhang Y, Ma J, Qi J, Wang Q, Lu G, Wu Y, Yan J, Shi Y, et al. Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. Nat Commun. 2017 Apr;8(1):15092. https://doi.org/10.1038/ncomms15092

Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis – A review of current methods. Biosens Bioelectron. 2021 Jan;172:112752. https://doi.org/10.1016/j.bios.2020.112752

Zang R, Castro MFG, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, Liu Z, Brulois KF, Wang X, Greenberg HB, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020 May 19;5(47): eabc3582. https://doi.org/10.1126/sciimmunol.abc3582

Zeng W, Liu G, Ma H, Zhao D, Yang Y, Liu M, Mohammed A, Zhao C, Yang Y, Xie J, et al. Biochemical characterization of SARS-CoV-2 nucleocapsid protein. Biochem Biophys Res Commun. 2020 Jun;527(3):618–623. https://doi.org/10.1016/j.bbrc.2020.04.136

Zhang Y, Qin L, Zhao Y, Zhang P, Xu B, Li K, Liang L, Zhang C, Dai Y, Feng Y, et al. Interferon-induced transmembrane protein 3 genetic variant rs12252-C associated with disease severity in coronavirus disease 2019. J Infect Dis. 2020 Jun 16;222(1):34–37. https://doi.org/10.1093/infdis/jiaa224

Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, Zhang Z, Liu L, Liu T, Liu Y, et al. Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility. Clin Infect Dis. 2021 Jul 15;73(2):328–331. https://doi.org/10.1093/cid/ciaa1150

Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med. 2020 Sep 01;202(5):756–759. https://doi.org/10.1164/rccm.202001-0179LE

Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, et al. Risk factors of critical and mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020 Aug;81(2):e16–e25. https://doi.org/10.1016/j.jinf.2020.04.021

Zhou X, Cheng Z, Shu D, Lin W, Ming Z, Chen W, Hu Y. Characteristics of mortal COVID-19 cases compared to the survivors. Aging (Albany NY). 2020 Dec 31;12(24):24579–24595. https://doi.org/10.18632/aging.202216

Zipeto D, Palmeira JF, Argañaraz GA, Argañaraz ER. ACE2/ADAM17/TMPRSS2 Interplay may be the main risk factor for COVID-19. Front Immunol. 2020 Oct 7;11:576745. https://doi.org/10.3389/fimmu.2020.576745

Zou J, Yin J, Fang L, Yang M, Wang T, Wu W, Bellucci MA, Zhang P. Computational prediction of mutational effects on SARS-CoV-2 binding by relative free energy calculations. J Chem Inf Model. 2020 Dec 28;60(12):5794–5802. https://doi.org/10.1021/acs.jcim.0c00679

Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19): A perspective from China. Radiology. 2020 Aug;296(2):E15–E25. https://doi.org/10.1148/radiol.2020200490