COVID-19, Influenza, and Other Acute Respiratory Viral Infections: Etiology, Immunopathogenesis, Diagnosis, and Treatment. Part I. COVID-19 and Influenza

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Abstract—The paper briefly reviews pathogens causing acute respiratory viral infections (ARVIs), including influenza viruses; coronaviruses, including SARS-CoV-2; parainfluenza viruses, adenoviruses, pneumoviruses, and specifically respiratory syncytial virus and metapneumoviruses, enteroviruses, rhinoviruses, and bocaviruses. This review presents modern data on the structure and replication of viruses, epidemiology, and immunopathogenesis of diseases and on diagnostics, preventive vaccination, and antiviral drugs for the treatment of ARVIs. Special attention is paid to the SARS-CoV-2 virus caused COVID-19 pandemic with analyses of similarities and differences between COVID-19 and other ARVIs, first of all, influenza virus. Topical issues regarding ARVI vaccination and the search for new broad-spectrum antiviral drugs are discussed.

Keywords: COVID-19, influenza, acute respiratory viral infection, respiratory viruses, SARS-CoV-2, viral replication, immunopathogenesis, acute respiratory viral infection prophylaxis

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The most common respiratory viruses causing acute respiratory viral infections (ARVIs) in the Russian Federation include influenza virus, respiratory syncytial virus, rhinovirus, metapneumovirus, parainfluenza virus, enterovirus, human coronavirus, adenovirus, and human bocavirus, which are responsible for about 70% of ARVI cases [1, 2]. The same situation is observed in many other countries.

An upper acute respiratory tract infection is an infection of the upper respiratory airways, including the nose, larynx, nasopharynx, oropharynx, throat, sinuses, conjunctiva, and inner ear. The common symptoms are rhinosinusitis, or a cold, acute sinusitis, acute laryngitis, conjunctivitis, and otitis media. A lower respiratory tract infection involves the airways below the larynx, including the trachea, bronchi, and the bronchoalveolar region, and manifests as bronchitis, bronchiolitis, and acute pneumonia. The identification of a pathogen hardly ever relies on the clinical symptoms. A correct diagnosis requires nucleic-acid amplification-based diagnostics, such as polymerase chain reaction (PCR).

Respiratory viruses spread via two main transmission routes: (1) transmission via droplets and aerosols and (2) contact with contaminated inanimate objects or surfaces (fomites). Airborne transmission via droplets and aerosols is the most common route of infection. Large respiratory virus-laden droplets (10–100 μm in diameter) contaminate the immediate vicinity of the infected individuals (≤0.9 m), while smaller droplets (<10 μm in diameter) produced by coughing or sneezing may convey infection beyond 1 m from the infectious person (≥1.8 m). Fomite transmission resulting from self-inoculation of the respiratory airways mucosa is the second most common route of infection. The survival time of respiratory viruses on inanimate surfaces may vary from minutes to up to days and depends on a range of factors. A metagenomic study of virome from 210 nasopharyngeal samples collected in children (70%) and adults hospitalized with flu-like symptoms was conducted by a laboratory of the Caroline Institute (Stockholm, Sweden). The study revealed 39 species and a wide variety of viral strains, with most nucleotide sequences belonging to pathogens of three families: Paramyxoviridae, Picornaviridae, or Orthomyxoviridae (in 2012, when the article was published, respiratory syncytial viruses and metapneumoviruses were classified to the family Paramyxoviridae) [3].

Reverse-transcription polymerase chain reaction (RT-PCR) is the most common and sensitive diagnostic tool. RT-PCR is used to detect viral nucleic acid in
a clinical sample, as well as to assess viral load. The high viral load is commonly correlated with an increased disease severity and hence viral load may predict whether a patient will develop a serious condition [4].

COVID-19

The Emergence of Human Pathogenic Coronaviruses

Coronaviruses were not considered as highly pathogenic for humans before the beginning of the 21st century. An outbreak of atypical pneumonia caused by SARS-CoV, i.e., severe acute respiratory syndrome coronavirus, occurred in 2003 [5]. The Middle East respiratory syndrome coronavirus (MERS-CoV) that also emerged from animal reservoirs led to an outbreak of a respiratory illness with high mortality in 2012 [6].

In early December of 2019, an outbreak of unusual viral pneumonia was first reported from Wuhan City, China. The novel coronavirus disease 2019 (COVID-19) caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread all over the world. On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic [7]. The emergence of the pandemic in China and other nations is described in detail by the reviews in [8–10]. As of April 24, 2021, a total of 145,240,343 COVID-19 laboratory-confirmed cases were recorded around the globe, of which 3,082,137 cases were fatal, and the number of COVID-19 infections continues to grow [11].

All three highly pathogenic human coronaviruses, i.e., SARS-CoV, SARS-CoV-2, and MERS-CoV, belong to the Betacoronavirus genus (subfamily Orthocoronavirinae, family Coronaviridae, order Nidovirales).

Disease Course

The clinical spectrum of coronavirus disease 2019 ranges from asymptomatic to mild infections or multiorgan failure and death. Preexisting cardiovascular conditions, renal dysfunction, liver pathology, diabetes, Parkinson’s disease, and cancer exacerbate SARS-CoV-2 infection [12]. The most common symptoms reported by COVID-19 patients include fever or chills, headache, muscle aches, dry cough, fatigue, and shortness of breath. Furthermore, the frequent complaints include sore throat, partial or complete loss of smell and/or taste, nausea or vomiting, diarrhea, and a runny nose. Some have lymphopenia, thrombocytopenia, and leukopenia [13]. Most patients had elevated levels of C-reactive protein, while elevations of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and D-dimer were less frequent [14]. The mean incubation period of SARS-CoV-2 is 5–7 days, but it may vary from 3 to 24 days. The patients usually recover in 2–4 weeks [15]. According to various reports, asymptomatic persons seem to account for approximately up to 80% of SARS-CoV-2 infections [16].

Although all age groups are susceptible to SARS-CoV-2, most children do not develop symptoms or they develop a mild form of COVID-19. For example, it was reported that children account for 1–5% of all asymptomatic global cases [17]. The mechanisms explaining milder COVID-19 and lack of pneumonia in children still remain to be elucidated. Herein, angiotensin-converting enzyme-2 (ACE2) and/or membrane-bound serine proteinase 2 (TMPRSS2) in the upper and lower respiratory system may explain viral infectivity: expression of ACE2 and TMPRSS2 utilized by the SARS-CoV-2 virus for cell entry is much lower in children than adults [18]. Patients aged 65 years and above with cardiovascular or cerebrovascular disease and hyperglycemia have an increased risk of COVID-19. Higher levels of circulating D-dimer, C-reactive protein, lactate dehydrogenase, and IL-6 also correlate with COVID-19 severity. The symptoms include breathing problems because of pneumonia and development of acute respiratory distress syndrome (ARDS). This life-threatening lung condition prevents sufficient oxygen from crossing the alveoli into the blood. In addition, hypercytokinemia, or a cytokine storm, centered in the lungs drives lung injury resulting in hypoxemia and multiorgan failure [19].

The main histopathological changes of COVID-19 disease relate to the lungs. Histopathological evaluation of severe COVID-19 highlights bilateral diffuse alveolar damage, hyaline membrane formation, desquamation of pneumocytes, and fibrin deposition. In some cases, exudative inflammation was shown. Immunohistochemistry revealed that viral antigens were present in the upper respiratory airways, bronchial epithelium, and submucosal gland epithelium and in type I and II pneumocytes, alveolar macrophages, and hyaline membranes in the lungs [20].

The cardiovascular complications of COVID-19 include heart failure, myocarditis, pericarditis, vasculitis, and arrhythmias. Elevated troponin release was reported among some COVID-19 patients that is frequently linked to poor prognosis. In addition to changes in the lungs, the SARS-CoV-2 virus can disturb the functions of the kidneys, liver, and reproductive and neural systems. The expression of ACE2 across multiple organs may explain its capacity to infect extrapulmonary organs. Different forms of pathology caused by COVID-19 infection are reviewed exhaustively in [21].

The earliest COVID-19 study reported a basic reproduction number of 2.2 [22].

SARS-CoV-2 Virions

The virions are spherical and are surrounded by a lipid bilayer. SARS-CoV-2 carries a single-stranded
positive sense RNA genome that encodes four major structural proteins, i.e., spike (S), envelope (E), membrane (M), and nucleocapsid (N) [23]. The genomic sequence of this newly emerged virus shares 79% sequence identity with SARS-CoV, 50% with MERS-CoV [24], and 80% with seasonal human β-coronaviruses [25]. The replicase/RNA polymerase genes occupy two-thirds of the viral genome lying downstream to the 5’-end and encode large polyproteins which proteolytic cleavage yields 16 nonstructural proteins involved in viral transcription and replication. Three structural proteins (M, E, N) and most of the SARS-CoV-2 nonstructural proteins have greater than 85–90% amino-acid sequence identity with SARS-CoV. The S protein of SARS-CoV-2 consists of 1273 amino acids. It is distinct from the S proteins of most β-coronaviruses. It shares the greatest amino-acid sequence similarity of 76.7–77.0% with SARS-CoV from civets and humans, 75–97.7% with bat coronaviruses in the same subgenus, and 90.7–92.6% with pangolin coronaviruses [26]. Another specific feature of SARS-CoV-2 is the insertion of four amino-acid residues (PRRA) at the junction of subunits S1 and S2 of the S protein that enhances spike-protein cleavage into two polypeptides, S1 and S2. In contrast to other coronaviruses, the S1/S2 insertion improves protease active site accessibility not only to furin proteases but other proteases as well. This expands the spectrum of target cells for efficient viral entry.

**Life Cycle**

The multiple steps involved in the virus propagation occurring inside cells are termed the “virus life cycle,” or “viral replication.” The steps include virus attachment to target cells, viral entry into a host cell, synthesis of viral proteins, genome replication, formation of new virion particles, and virus release from cells. SARS-CoV-2 spike protein binds host ACE2 for virus entry. Besides human ACE2, SARS-CoV-2 also recognizes ACE2 from pig, ferret, mink, rhesus monkey, civet, cat, pangolin, rabbit, and dog [27]. A 211-amino-acid region (residues 319–529) at the S1 C-terminal comprises a receptor-binding domain (RBD), mediating a pivotal role in viral entry and serving as a target for development of neutralizing antibodies [28]. The entry of SARS-CoV-2 into host cells is mediated by the proteolytic activation of the S protein and endocytosis. The host cellular proteases TMPRSS2, cathepsin L, and furin cleave the S protein [29]. Heparan sulfate is a necessary cofactor for SARS-CoV-2 infection; it directly interacts with RBD to enhance spike-protein binding to ACE2 [30].

After binding to a host-cell surface, coronaviruses apparently enter cells via endocytosis and ensuing fusion of viral and cellular membranes, with the ribonucleoprotein (RNP) being transported to the cytosol. The genome contains a 5’-cap structure and a 3’-poly (A) tail, allowing it to act as an mRNA for translation of the polyproteins. The genome (about two-thirds) features two large overlapping open reading frames (ORF1a and ORF1b) translated to pp1a and pp1ab polyproteins, which are processed to generate 16 nonstructural proteins (nsp1–16). The remaining portion of the genome includes ORFs for the structural proteins: spike (S), envelope (E), membrane (M), and nucleoprotein (N). In the endoplasmic reticulum and the Golgi complex, coronaviruses assemble new virions that are transported to the cell surface where they are released into the intercellular space [21].

**Diagnostics**

The early rapid and precise identification of COVID-19 patients is critical for infection prevention and control. Therefore, diverse nucleic acid detection methods (RT-PCR, isothermal amplification of nucleic acids, CRISPR/Cas technology), protein identification (detection of coronavirus envelope protein, antibody levels), and chest imaging (X-ray, computer tomography) have been developed rapidly in many countries [31]. It is noted that the quality of IgM antibody tests has been improved significantly in recent time. IgM serology helps in coronavirus diagnostics even when viral RNA is no longer detected in samples from nasopharynx. Hundreds of versions of the test systems to detect IgG, IgA, and IgM exist at present and are used in clinics. Virus neutralization assays involve incubation of live infectious virus particles in serum and plasma with subsequent infection of susceptible cells to measure neutralizing antibodies. Live virus neutralization assays are highly specific, but appear time-consuming and require a specialized laboratory setup; hence they are mostly used during development of vaccines and their clinical trials.

**Treatment and Prevention**

Today, effective specific treatment options for COVID-19 or antiviral medications to treat SARS-CoV-2 are not available despite the fact that effective measures of COVID-19 prevention and treatment are the object of an urgent search across the globe. As of April 5, 2021, a total of 506 medications to treat COVID-19 were investigated worldwide, and 419 of these were at the stage of clinical trials [32]. Active symptomatic treatment remains the main option for patients with mild and moderate illness. Critically ill patients with respiratory failure require hospitalization and respiratory support with high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) may act as a rescue supportive treatment when the above methods fail to improve the patient condition. In addition, many patients may require antibiotics and antifungals. The potential benefits of low-dose corticosteroid treatment in a subgroup of critically ill patients...
with SARS-CoV-2 infection were demonstrated in a study in [33].

It has been attempted to use remdesivir, favipiravir, ribavirin, lopinavir, and ritonavir as potential inhibitors of SARS-CoV-2 replication. Lopinavir and ritonavir inhibit the 3CLpro protease, and the other three target the RNA-dependent RNA polymerase of a range of RNA viruses. Remdesivir is a drug originally developed for the treatment of Ebola virus. Remdesivir reduced the time to recovery in patients who were hospitalized with COVID-19 [34], but the reduction of mortality was not significant. Favipiravir was developed in Japan as an anti-influenza drug. It is approved for use in Russia, China, and India for the treatment of COVID-19 [35].

Upon viral infection, the interferon response is one of the main means of antiviral protection elicited by host cells. It was shown in vitro that SARS-CoV-2 is sensitive to type I interferons, which suggests that interferon medications may be effective in early treatment of COVID-19 [36]. At the same time, SARS-CoV-2 frequently provokes an excessively strong immune response known as a “cytokine storm” or “cytokine release syndrome” [37]. Hence, immunomodulatory agents that inhibit excessive inflammatory response represent an adjuvant treatment for COVID-19 patients. For example, corticosteroids, especially dexamethasone, suppress overactive immune responses and pulmonary fibrosis.

The convalescent plasma technique is another possible treatment modality. However, the technique may have side effects and mediate antibody-dependent enhancement of infection, transfusion–related acute lung injury (TRALI), and allergy. Therefore, blood-plasma transfusions from virus survivors to critically ill COVID-19 patients are generally not recommended at present. At the same time, a monoclonal antibody cocktail, regeneron, has been authorized in the United States for treatment of early COVID-19. More information on candidate drugs for the management of COVID-19 may be found in reviews [38, 39].

COVID-19 vaccination remains the most effective means to achieve prevention and control of the pandemic. The six main platforms of vaccines against COVID-19 include live attenuated virus, inactivated virus, recombinant vector vaccines, protein subunit vaccines, viruslike particles, and nucleic-acid vaccines (DNA and mRNA based) [40]. As of April 5, 2021, 216 candidate vaccines against COVID-19 were registered, and 92 of them were at different stages of clinical trials [32, 41]. The main similarities and differences between different vaccine platforms are discussed in detail by the reviews in [42, 43]. Despite the fact that mass vaccination campaigns against COVID-19 are underway in Russia, China, North America, and European and other countries, only the preliminary results of phase 3 clinical trials are available at present, which have been published for several vaccines: mRNA-1273 (Moderna, United States), BNT162b2 (Pfizer, United States), both mRNA-based; the vector vaccines GamKovidVak (Sputnik V, Gamaleya Research Center for Epidemiology and Microbiology, Russia) and AZD1222 (Oxford/AstraZeneca, United Kingdom, Sweden); vaccines based on the inactivated pathogen CoronaVac (Sinovac, China); and some others. The final results of clinical trials will be known only at the end of 2021, or even later, after evaluation of protective efficacy, duration of postvaccination immunity, delayed effects, and others.

Since the very beginning of the global pandemic, researchers have been concerned about variation of the virus. However, in February 2020, some variants of the virus were found to carry a D614G substitution in the S protein. By June 2020, the variant had spread globally, and it was suggested that this virus can be transmitted more easily and rapidly from person to person than the original strain (D614) [44]. The B.1.1.7 variant (17 amino-acid substitutions, eight of which are in protein S) was first described in the United Kingdom in December 14, 2020. The B.1.351 variant (or 501Y.V2) (nine amino-acid substitutions and one deletion in protein S) was first registered in the South Africa in December 18, 2020. The P.1 variant (or B.1.1.28.1) (17 amino-acid substitutions, ten of which in protein S) was reported in Brazil on January 12, 2021. All three variants carry the N501Y mutation, which changes the amino-acid asparagine (N) to tyrosine (Y) at position 501 in RBD of protein S. The B.1.351 and P.1 variants have two additional mutations in the receptor-binding domain, K417N/T and E484K. These mutations increase the affinity of the RBD/ACE2 interaction. It was shown that strains with the N501Y, E484K and L452R mutations evade both natural immunity (induced by prior infection) and vaccine-induced humoral immunity [45]. Serums of people vaccinated with some vaccines were studied in the neutralization reaction to compare the mutant strains with the D614 or D614G strain. The British strain (B.1.1.7) showed a modest decrease in neutralization by a factor of 1.8–2, while the serum neutralizing activity for the South African variant (B.1.351) was a factor of 6.5 and 8.6 lower for the BNT162b2 and mRNA-1273 vaccines, respectively. The AZD1222 postvaccination sera neutralized B.1.351 strain were a factor of 86 lower, including complete immune escape. The neutralizing activity for the P.1 variant among vaccinated persons was a factor of 6.7 lower for the BNT162b2 vaccine and by a factor of 4.5 for the mRNA-1273 vaccine [46].

Thus, some features of SARS-CoV-2 and COVID-19 need more study, including an increase in virus-transmission potential and antigenic drift, causes of asymptomatic infection, association of the disease with chronic diseases, and causes of persistent and long-term postinfection effects. Knowledge of these issues will be crucial for the development of second-genera-
tion vaccines with a broad neutralizing activity against the existing and future variants of the pathogen.

INFLUENZA

The mammalian influenza A virus was first isolated in 1931 from swine by Richard Shope. In 1933, scientists from the National Institute for Medical Research in London, W. Smith, Ch. Andrews, and P. Laidlaw, isolated the virus, which caused human flu. In the Soviet Union, influenza virus A strains were first isolated from sick people in 1936 in Leningrad by A.A. Smorodintsev and in 1937 in Moscow by L.A. Zilber [47].

Taxonomy and Classification of Influenza Viruses

Influenza viruses belong to the family Orthomyxoviridae and four genera, i.e., Alphainfluenzavirus, Betainfluenzavirus, Gammainfluenzavirus, and Deltainfluenzavirus [48]. The genome is segmented and organized into eight (seven in influenza C and D virus) single-stranded negative-polarity RNAs; i.e., these RNAs do not serve as templates for protein synthesis. Human influenza A and B viruses cause seasonal epidemics almost every year. The emergence of influenza A virus with new antigenic properties may cause flu pandemics. Influenza C virus infections generally cause mild illness and do not cause epidemics among human beings. Influenza D viruses infect cattle, and no human infections from this virus have been observed.

Influenza A viruses (the Alphainfluenzavirus genus) are further characterized by the subtype of their two surface glycoproteins, the hemagglutinin (HA) and the neuraminidase (NA). There are 18 different HA subtypes and 11 different NA subtypes (H1–H18 and N1–N11, respectively). Influenza B viruses (the Betainfluenzavirus genus) are not classified by subtype but they are separated into genetic lineages. Currently, two lineages of influenza B viruses (B/Yamagata and B/Victoria) circulate globally.

Influenza Virions

The genomes of influenza A and B viruses contain eight RNA segments. Most segments encode one protein. The nucleocapsid protein encapsidates RNA to form an internal nucleocapsid, which consists of genomic RNA, a nucleoprotein, a polymerase complex, and a nuclear export protein and is surrounded by a coat of M1 protein. An internal RNA-containing nucleocapsid is surrounded by an outer lipid envelope. Transmembrane HA and NA viral glycoproteins are embedded in the envelope, and M2 protein tetramers span the viral lipid envelope to form ion channels. Influenza virus has a rounded shape, although it can be elongated. Polymerase complex (PB1, PB2, and PA) and NP-protein bind each viral RNA segment to form a ribonucleoprotein (RNP). Originally named NS2, the nuclear export protein (NEP) mediates the nuclear export of viral ribonucleoproteins and regulates viral RNA transcription (replication). The non-structural protein-1 (NS1) is synthesized in the virus-infected cells to inhibit host antiviral responses.

Life Cycle

HA is responsible for binding influenza virus to sialic acid on the surface of target epithelial cells, leading to endocytosis of the virus. M2 ion channels in the viral membrane pump protons into the endosome to acidify the virus interior. The low pH of the endosome triggers conformational changes of HA, which then drives fusion of the viral and endosomal membranes, allowing release of the ribonucleoprotein complexes into the cytosol. Once in the infected cells, the RNPs are transported to the nucleus by the NEP, where they undergo transcription and replication. New virions assemble at the inner cell surface and are released from the cell by budding. The life cycle of the influenza virus is described well in review [49].

Influenza viruses display a remarkable genetic and antigenic diversity that results from the plasticity of the viral RNA-dependent RNA polymerase and genome structure. During replication, RNA polymerase makes an average of one mistake per 10 thousand nucleotides, i.e., one mistake per replicated genome. Upon population immune pressure, mutations in antigenic sites confer an advantage. Hence, human influenza viruses display a high rate of antigenic drift, which necessitates updating vaccine strains every 2–3 years [50].

The segmented nature of the viral genome also contributes to the high variation of the influenza virus. With such a genetic structure, two different influenza strains that simultaneously infect a single host cell can undergo a rearrangement of gene segments. Such exchange of segments enables the emergence of viral particles that carry genes (and, hence, proteins) of both ancestor strains (antigenic shift, or antigenic drift). The emergence of virions that acquire genes of internal proteins from a human influenza-virus strain (well adapted to replication in human cells) and the surface glycoprotein genes from the animal flu virus may provoke an outbreak of illness or a pandemic, since people do not have immunity to such reassortant viruses [51].

Epidemiology

There may have been many pandemics in human history triggered by influenza A viruses, but only the worldwide outbreaks of influenza that occurred in the 20th and 21st centuries are documented. They include the Spanish influenza pandemic of 1918–1920 (A/H1N1), the 1957–1959 Asian flu pandemic (A/H2N2), the 1968–1970 Hong Kong flu pandemic (A/H3N2), and the 2009–2010 swine flu pandemic.
or complicated by secondary bacterial pneumonia, similar to COVID-19. Influenza infections may also pathogen [19]; in this case, the influenza disease is and multiple-organ failure, i.e., a systemic disease occurs, which is characterized by hypoxemia, shock, and weakness can persist longer; in some adults and malaise, which resolve after 3–5 days, although cough and respiratory signs rapidly, and 4–5 days after symptom onset, ARDS may also be observed [53]. The symptoms progress rapidly, and 4–5 days after symptom onset, ARDS occurs, which is characterized by hypoxemia, shock, and multiple-organ failure, i.e., a systemic disease resulting from robust inflammatory response to the pathogen [19]; in this case, the influenza disease is similar to COVID-19. Influenza infections may also be complicated by secondary bacterial pneumonia, often caused by Staphylococcus aureus, S. pneumoniae, or Streptococcus pyogenes.

Treatment and Prevention

The NA inhibitors are the most widely used antivirals for influenza. Four NA inhibitors have been approved in different countries for treatment and prevention of influenza A and B: zanamivir, oseltamivir, peramivir, and laninamivir [54]. Viruses that are resistant to NA inhibitors have remained to date at low levels, at less than 1% of circulating seasonal flu viruses globally.

To expand the treatment options, researchers are developing new classes of anti-influenza drugs. To illustrate, baloxavir, an inhibitor of a cap-dependent endonuclease (the enzyme that enables viral mRNA synthesis) suppresses influenza virus replication. It is a single-dose oral antiviral drug for treatment of influenza A and B (data on its prophylactic efficacy are not available). It was licensed in Japan and the United States in 2018 [55].

Favipiravir is an RNA-dependent RNA polymerase inhibitor for peroral and intravenous use [56]. Favipiravir was approved in Japan to treat influenza A and B with strict regulations for its clinical use. It is intended to be used against newly discovered emerging viruses that are resistant to other classes of antivirals.

In 2005, the Russian Federation introduced seasonal influenza vaccine into the National Calendar Immunizations. Nevertheless, even under the most favorable circumstances, vaccine efficacy among healthy adults is no more than 60–80% for inactivated vaccines or lower for live attenuated vaccines [57]. At the same time, even when the antigenic characteristics of vaccine strains differ substantially from the circulating variants, vaccination decreases the probability of severe disease and fatal outcomes [58, 59]. Hence, vaccines against influenza on the eve of the seasonal epidemic and the early administration of relevant etiologic antiviral agents are the most effective options to prevent seasonal influenza infection.

CONCLUSIONS

In conclusion, COVID-19 and influenza are two acute respiratory viral infections that caused pandemics in the 21st century. The influenza virus has been investigated for almost 90 years, and SARS-CoV-2 for more than two years. One hundred years ago, in 1918–1920, influenza A virus caused the most exceptionally deadly global influenza pandemic in modern human history. SARS-CoV-2 caused the most devastating epidemic to date in the 21st century. The examples of these two pandemics serve as a perfect demonstration of how scientific knowledge has advanced: medicine, molecular biology, immunology, vaccination, epidemiology, pharmacology, biotechnology, etc. The current COVID-19 pandemic has defined profoundly the most daunting challenges facing the globe. Globalization and human intrusion into wilderness areas will undoubtedly drive zoonotic spillovers, and human beings need to be prepared for such emergence of new diseases linked to zoonoses originating from wildlife. We may base our optimism on recent improvements in mRNA vaccines that favor its fast development, i.e., within 2–3 weeks, and, hence, its rapid mass production. However, this strategy does not provide a universal broad-spectrum vaccine that would provide effective immunity against many related strains of the virus. Such a universal vaccine could be used to prevent diseases caused by both seasonal viruses and pathogens that may emerge in the near future. For this reason, it will also be beneficial for researchers working toward the creation of a universal vaccine.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals or human participants performed by any of the authors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Larina, V.N., Zaharova, M.I., Benevskaya, V.F., Golovko, M.G., and Solov'ev, S.S., Acute respiratory viral infections and influenza: etiology, diagnosis and treatment algorithm, Russ. Med. Zh., Med. Obozr., 2019, vol. 3, no. 9–1, pp. 18–23.

2. Kurskaya, O., Ryabichenko, T., Leonova, N., Shi, W., Bi, H., Sharshov, K., et al., Viral etiology of acute respiratory infections in hospitalized children in Novosibirsk City, Russia (2013–2017), PLoS One, 2018, vol. 13, no. 9, article no. e0200117. https://doi.org/10.1371/journal.pone.0200117

3. Lysholm, F., Wetterbom, A., Lindau, C., Darban, H., Bjerkner, A., Fahlander, K., et al., Characterization of the viral microbiome in patients with severe lower respiratory tract infections, using metagenomic sequencing, PLoS One, 2012, vol. 7, no. 2, article no. e30875. https://doi.org/10.1371/journal.pone.0030875

4. Weston, S. and Frieman, M.B., Respiratory viruses, in Encyclopedia of Microbiology, Elsevier, 2019, pp. 85–101.

5. Drosten, C., Gunther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., et al., Identification of a novel coronavirus in patients with severe acute respiratory syndrome, N. Engl. J. Med., 2003, vol. 348, no. 20, pp. 1967–1976. https://doi.org/10.1056/NEJMoa030747

6. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A., and Fouchier, R.A.M., Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med., 2012, vol. 367, no. 19, pp. 1814–1820. https://doi.org/10.1056/NEJMoa1211721

7. WHO Director-General’s Opening Remarks at the Media Briefing on COVID-19, March 11, 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19–11-march-2020. Accessed April 20, 2021.

8. Hu, B., Guo, H., Zhou, P., and Shi, Z.L., Characteristics of SARS-CoV-2 and COVID-19, Nat. Rev. Microbiol., 2021, vol. 19, pp. 141–154. https://doi.org/10.1038/s41579-020-00459-7

9. Ili'icheva, T.N., Two pandemics of the 21st century: COVID-19 and “swine flu” of 2009, Med. Immunol., 2020, vol. 22, no. 6, pp. 1035–1044. https://doi.org/10.15789/1563-0625-TPO-2048

10. Shchelkanov, M.Yu., Kolobuhina, L.V., Burgasova, O.A., Kruzhkova, I.S., and Maleev, V.V., COVID-19: etiology, clinical picture, treatment, Infekts. Immun., 2020, vol. 10, no. 3, pp. 421–445.

11. WHO Coronavirus Disease (COVID-19) Dashboard, 2021. https://covid19.WHO.int/?gclid=Cj0KCQiAk537BRD0ARIsAJuNhps3wCnIHNCnDRXQkz4UQ0qLXXLcF6qbbqUcrWwVL4Evgr3sn1AhtF7EALw_wCB. Accessed April 20, 2021.

12. Wang, W.E., Tang, J.M., and Wei, F.Q., Updated understanding of the outbreak of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol., 2020, vol. 92, no. 4, pp. 441–447. https://doi.org/10.1002/jmv.25689

13. Chen, N.S., Zhou, M., Dong, X., Qu, J.M., Gong, F.Y., Han, Y., et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet, 2020, vol. 395, no. 10223, pp. 507–513. https://doi.org/10.1016/s0140-6736(20)30211-7

14. Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med., 2020, vol. 382, no. 18, pp. 1708–1720. https://doi.org/10.1056/NEJMoa2002032

15. Symptoms of Coronavirus, 2021. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed April 20, 2021.

16. Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., and Shaman, J., Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2), Science, 2020, vol. 368, no. 6490, pp. 489–493. https://doi.org/10.1126/science.abb3221

17. Ludvigsson, J.F., Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults, Acta Paediatr., 2020, vol. 109, no. 6, pp. 1088–1095. https://doi.org/10.1111/apa.15270

18. Sharif-Askari, N.S., Sharif-Askari, F.S., Alabed, M., Temsah, M.H., Al Healy, S., Hamid, Q., and Halwani, R., Airways expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 is lower in children than adults and increases with smoking and COPD, Mol. Ther. Methods Clin. Dev., 2020, vol. 18, pp. 1–6. https://doi.org/10.1016/j.omtm.2020.05.013

19. Faigenbaum, D.C. and June, C.H., Cytokine storm, N. Engl. J. Med., 2020, vol. 383, no. 23, pp. 2255–2273. https://doi.org/10.1056/NEJMra2026131

20. Martines, R.B., Ritter, J.M., Matkovic, E., Gary, J., Bollweg, B.C., Bullock, H., et al., Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States, Emerging Infect. Dis., 2020, vol. 26, no. 9, pp. 2005–2015. https://doi.org/10.3201/eid2609.20095

21. Singh, R., Kang, A., Luo, X., Jeyanathan, M., Gillgrass, A., Afkhami, S., and Xing, Z., COVID-19: Current knowledge in clinical features, immunological responses, and vaccine development, FASEB J., 2021, vol. 35, no. 3, article no. e21409. https://doi.org/10.1096/fj.202002662R

22. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med., 2020, vol. 382, no. 13, pp. 1199–1207. https://doi.org/10.1056/NEJMoa2001316
48. Krammer, F., Smith, G.J.D., Foucheir, R.A.M., Peiris, M., Kedzierska, K., Doherty, P.C., et al., Influenza, Nat. Rev. Dis. Primers, 2018, vol. 4, no. 1, pp. 1–21. https://doi.org/10.1038/s41572-018-0002-y
49. Te Velthuis, A.J.W. and Fodor, E., Influenza virus RNA polymerase: Insights into the mechanisms of viral RNA synthesis, Nat. Rev. Microbiol., 2016, vol. 14, no. 8, pp. 479–493. https://doi.org/10.1038/nrmicro.2016.87
50. Carrat, F. and Flahault, A., Influenza vaccine: The challenge of antigenic drift, Vaccine, 2007, vol. 25, nos. 39–40, pp. 6852–6862. https://doi.org/10.1016/j.vaccine.2007.07.027
51. Hay, A.J., Gregory, V., Douglas, A.R., and Yi, P.L., The evolution of human influenza viruses, Philos. Trans. R. Soc., B, 2001, vol. 356, no. 1416, pp. 1861–1870. https://doi.org/10.1098/rstb.2001.0999
52. Short, K.R., Kedzierska, K., and van de Sandt, C.E., Back to the future: Lessons learned from the 1918 influenza pandemic, Front. Cell. Infect. Microbiol., 2018, vol. 8, article no. 343. https://doi.org/10.3389/fcimb.2018.00343
53. Uyeki, T.M., Preventing and controlling influenza with available interventions, N. Engl. J. Med., 2014, vol. 370, no. 9, pp. 789–791. https://doi.org/10.1056/NEJMp1400034
54. Gubareva, L. and Mohan, T., Antivirals targeting the neuraminidase, Cold Spring Harbor Perspect. Med., 2020. https://doi.org/10.1101/cshperspect.a038455
55. Mishin, V.P., Patel, M.C., Chesnokov, A., De La Cruz, J., Nguyen, H.T., Lollis, L., et al., Susceptibility of influenza A, B, C, and D viruses to baloxavir, Emerging Infect. Dis., 2019, vol. 25, no. 10, pp. 1969–1972. https://doi.org/10.3201/eid2510.190607
56. Furuta, Y., Gowen, B.B., Takahashi, K., Shiraki, K., Smee, D.F., and Barnard, D.L., Favipiravir (T-705), a novel viral RNA polymerase inhibitor, Antiviral Res., 2013, vol. 100, no. 2, pp. 446–454. https://doi.org/10.1016/j.antiviral.2013.09.015
57. Ainslie, K.E.C., Haber, M., and Orenstein, W.A., Challenges in estimating influenza vaccine effectiveness, Expert Rev. Vaccines, 2019, vol. 18, no. 6, pp. 615–628. https://doi.org/10.1080/14760584.2019.1622419
58. Ilyicheva, T., Durymanov, A., Susloparov, I., Kolosova, N., Goncharova, N., Svyatchenko, S., et al., Fatal cases of seasonal influenza in Russia in 2015–2016, PLoS One, 2016, vol. 11, no. 10, article no. e0165332. https://doi.org/10.1371/journal.pone.0165332
59. Kolosova, N.P., Ilyicheva, T.N., Danilenko, A.V., Bulanovich, J.A., Svyatchenko, S.V., Durymanov, A.G., et al., Severe cases of seasonal influenza in Russia in 2017–2018, PLoS One, 2019, vol. 14, no. 7, article no. e0220401. https://doi.org/10.1371/journal.pone.0220401

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