NATURAL SCIENCES

COVID-19

COVID-19. SARS-Cov-2, pandemic, transmission pathways, distribution features, and individual susceptibility.

http://doi.org/10.33384/26587270.2020.04.02.06e

Tikhonov D.G., Vladimirtsev V.A.

Annotation. In December 2019, an outbreak of pneumonia of unknown etiology was registered in Wuhan, Hubei province of the people's Republic of China. The virus was soon isolated and its genome sequenced. It is called the severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2), and the disease caused by it is coronavirus infection – 19 (COVID-19). Who recognized the COVID-19 outbreak as a pandemic on March 11. The entire world is currently affected by the pandemic. The first focus of coronavirus infection in Russia was detected on February 27, brought from Europe. The infection reached the most remote corners of Siberia by mid-April. The purpose of this study is to analyze the characteristics of SARS-Cov-2, its pathways into the body and individual susceptibility to the virus.

Methods and materials. The review of scientific articles on the research topic was based on the analysis of scientific articles on COVID-19. Articles were searched in the Web of Sciences, Scopus, PubMed, and eLIBRARY databases, as well as by article links.

Results. The SARS-Cov-2 virus is a single-stranded positive-chain RNA virus from the Coronavirus family (Coronaviridae). According to most researchers, the SARS-Cov-2 virus evolved from bat coronaviruses, with the approximate time of divergence from the nearest bat virus species RaTG13 occurring in 1963. It uses ACE-2 receptors, which are widely present throughout the body, to enter host cells. High virus contagiousness is provided by the acquisition of an additional furin site for cleavage of the spike protein in the form of the amino acid sequence Arg-Arg-Ala-Arg (^{682}RRAR^{685}). This site of the S_1 domain of the spike protein can be cleaved by: transmembrane serine protease 2 (TMPRSS2), furin, but also many cellular and extracellular proteases, as well as plasmin(ogen)s. Many ways of cleavage of the spike protein significantly increase the ability of the virus to enter the cell and its contagiousness.

The main routes of transmission of SARS-Cov-2 are respiratory drops and close contact. The main entrance gate of the virus is the respiratory tract, may be conjunctiva, likely fecal-oral pathway. The article discusses the skin as an entrance gate. Some skin manifestations of the disease can be caused by this way. The incubation period of COVID-19 lasts on average 5-6 days, while the live infectious virus begins to be released 2-3 days before the first symptoms appear and stops on the 8th day after the symptoms appear, but only in severe patients the virus release can last up to 15 days. Asymptomatic patients may account for 40% of cases. Features of individual susceptibility to COVID-19 and the severity of clinical manifestations may be caused by: 1) the property of allelic variants of the virus and their virulence; 2) the infectious dose of the virus; 3) the use of protective equipment; 4) individual characteristics of the human body; 5) pathogenic mechanisms of infection development.

The hypothesis of the protective role of the mumps vaccine explains the phenomenon of extremely low morbidity, asymptomatic or mild infection in children more convincingly. Mass vaccination against mumps in our country began in 1981 (39 years ago), which is probably why children and people under 40 rarely get a severe form of infection in our country.

Conclusion. SARS-Cov-2 has pandemic potential and is estimated to be more severe than pandemic influenza viruses. Active isolation of the virus before the onset of symptoms, including by asymptomatic patients (including children), causes the rapid spread of infection and reduces the effectiveness of anti-epidemic measures. The presence of a significant segment of the population with cross-immunity to SARS-Cov-2, including and as a result of vaccination, it is the most likely cause of a high percentage of asymptomatic and mild forms of the disease among children and young people. Effective protection against coronavirus infection in 2019 can only be achieved by taking comprehensive measures to prevent the virus from entering the body through the respiratory tract, per os, conjunctiva and skin,

although the latter pathway is not taken into account anywhere in the world. It should be noted that COVID-19 cannot be classified as a particularly dangerous infection, but its high contagiousness, the likelihood of multiple entry gates of the virus into the human body, multi-organ lesions and a high mortality rate of risk groups make it a special infection that requires significant efforts of humanity to eliminate it.

Key words: SARS-Cov-2, COVID-19, routes of transmission, features of distribution, individual susceptibility.

For citations: Tikhonov D.G., Vladimirtsev V. A. COVID-19. SARS-Cov-2 pandemic, transmission pathways, distribution features, and individual susceptibility // Siberian Research. 2020. 4(4). P. 48–60. http://doi.org/10.33384/26587270.2020.04.02.06e

Received November 9, 2020; accepted for publication December 13, 2020; published 15, December, 2020.

INTRODUCTION.

In December 2019, an outbreak of unknown pneumonia was reported in Wuhan, Hubei province of the people's Republic of China [1]. The Chinese authorities informed the who office in China about this on January 31, 2020, and on January 7, the country's health authorities reported the release of a new type of coronavirus [2]. The result of sequencing the complete genome isolated in the Wuhan seafood market of the virus under the identification name Wuhan-Hu-1 was published on January 13 in the open access database GenBank under the number NC_045512. The authors published the data in the journal Nature on February 3 [3]. On February 23, the research group of the International Committee on taxonomy of viruses made a consensus decision on the name of the new coronavirus – SARS Cov-2 [4]. It was determined that this strain of the virus belongs to the family of coronaviruses, the genus of beta coronaviruses, and the type of coronaviruses associated with severe acute respiratory syndrome (SARS). The infection caused by the new coronavirus is called COVID-19 [5].

On January 22, 2020, the WHO mission to China made a statement that there was evidence of human-to-human transmission in Wuhan [6]. Soon the first article was published in the Lancet magazine about the clinical manifestations of a new coronavirus infection. The article is the first to note human-to-human transmission. The main symptoms of the disease are fever, dry cough, shortness of breath, and bilateral turbidity of the lungs in the form of ground glass on the chest CT. Unlike other previous epidemics, SARS rarely showed symptoms from the gastrointestinal tract, such as diarrhea in 3% of cases versus 20-25% [7]. On January 30, WHO declared a public health emergency of international significance, and on March 11, it described the outbreak of coronavirus infection as a pandemic [6].

The Aim of this study is to analyze the features of SARS-Cov-2, its pathways into the body, and the characteristics of individual susceptibility to the virus.

Method and materials. The review of scientific articles on the research topic was based on the analysis of scientific articles on COVID-19. Articles were searched in the Web of Sciences, Scopus, PubMed, and eLIBRARY databases, as well as by article links.

Severe acute respiratory syndrome virus (SARS Cov-2). The SARS Cov-2 virus is a single-stranded positive-chain RNA virus from the Coronavirus family (Coronaviridae). It belongs to the genus Betacoronaviruses, the subgenus Sarbecoviruses, and the type of Coronaviruses associated with severe acute respiratory syndrome [8]. To date, there are 7 strains of the coronavirus family that are pathogenic to humans: four of them (HCov-229E, HCov-NL63, HCov-OC-43, HCov-HKU-1) cause respiratory diseases of varying severity, mainly mild. In the structure of acute respiratory diseases of viral etiology, these coronaviruses occupy 8.15% [9]. Three strains: MERS-Cov, SARS-Cov, and SARS-Cov-2 (SARS-Cov-2) cause severe respiratory diseases. The virion of the latter can have a spherical or oval shape, consists of a lipid shell, inside which is placed a capsid protein n associated with a single-stranded +RNA. Structural proteins are embedded in the lipid envelope: S, M, and E (Fig. 1). The genome of the virus registered for the first time in Wuhan (China) consists of 29903 base pairs (bp) [10].

The SARS-Cov-2 genome consists of genomic +RNA and 9 subgenomic RNAS (S, 3a, E, M, 6, 7a, 7b, 8, N), expression of ORF10 by data from D. Kim et al. not confirmed. The genome encodes 4 structural (S, E, M, N) and 16 non-structural (nsp1-nsp16) proteins that play an important role in virus replication and transcription. The study of the virus transcriptome reveals at least 41 viral unknown transcripts of the RNA modification site, the functions of which are to be stud. To enter the host cell, the SARS-Cov-2 virus uses an S-glycoprotein consisting of two subunits S_1 and S_2. The complex structure of S-glycoprotein was decoded by M. Gui et al. [13]. After binding the receptor binding domain (RBD) of S – glycoprotein to the angiotensin converting enzyme 2 (Angiotensin Converting Enzyme 2-ACE – 2) to the host cell, conformational changes of S_2 occur with the formation of fusion nuclei of the virus and cell membranes. The s-glycoprotein is split into two parts by the furin of the host cell at the junction of the S_1 and S_2 subunits of the virus glycoprotein [13], which contributes to the fusion and introduction of the virus into the cell. Chinese scientists led by C. Wei et al. was found that the attachment of the S_1 subunit of the spike protein to the ACE-2 receptor is enhanced by the SR-B1 receptor of high-density lipoproteins [14]. The wide distribution of ACE-2 receptors throughout the human body contributes to multiple organ damage in COVID-19.

The infectivity of a virus is determined by its ability to easily enter the host cell. So if MERS-Cov and SARS-Cov use TMPRSS2 at entry, but do not have a furin s-glycoprotein cleavage site, then SARS-Cov-2 acquired it additionally, preserving the TMPRSS2 cleavage site. In addition, it penetrates into the host cell us-

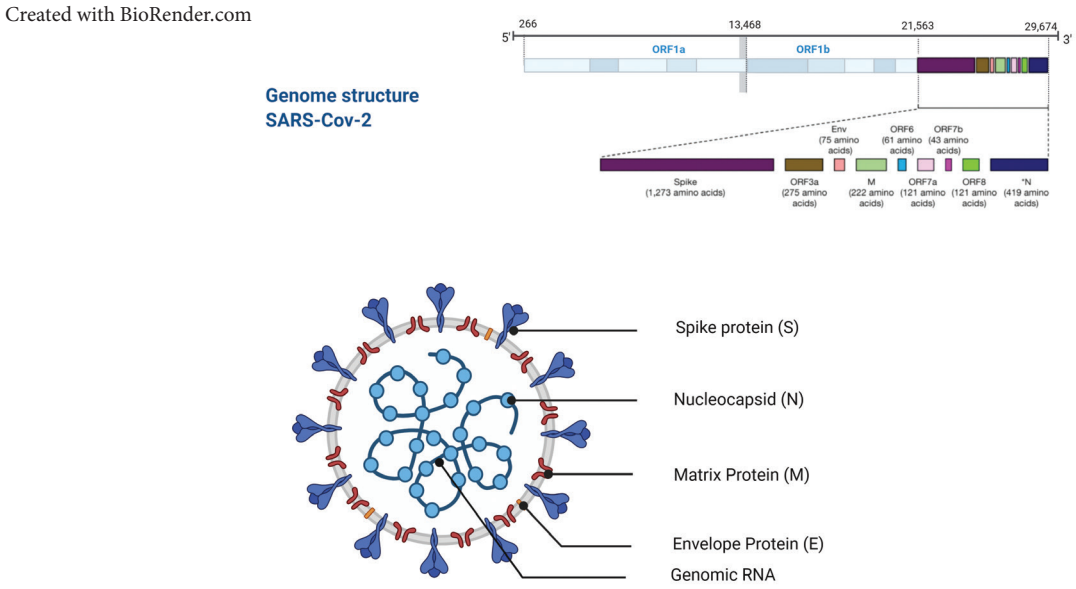

Fig. 1. Schematic structure of the Vision SARS-Cov-2 and its Genome

The S-protein located on the surface of the viral particle forms a spike, which makes the virion look like a "crown". This protein is glycosylated, which masks it from recognition. It consists of two domains S^1 and S^2. the Spike protein, due to its affinity for the apf2 receptor (ACE-2), attaches to IT, merges with the cell membrane and penetrates it, thanks to enzymes-transmembrane serine protease 2 (TMPRSS2) and furin [11];

E-envelope proteins form ion channels that promote virus budding after Assembly;

M-matrix protein, or membrane protein, plays a key role in virus Assembly and envelope formation by capturing the substrates of an infected cell;

The N-nucleocapsid protein packs viral RNA and plays an important role in virion Assembly;

RNA – genomic RNA.

ing pyrrolidinone receptors of cell membrane [15]. It is known that the spiked protein of the virus at the site of S_1/S_2 cleavage has amino acid sequences recognized by a furin-like protease in the form of Arg-Arg-Ala-Arg (^{682}RRAR^{685}). In accordance with the C-end rule (CendR) concept, peptides in the R/KXXR/K consensus motif bind to neuropilin-1 (NRP – 1) and are transported inside the cell [16]. It is now known that the ability of the virus to merge with the host cell does not depend on the presence of the amino acid sequence ^{682}RRAR^{685} in the spike protein. This ability is significantly increased by the concentration of exogenous trypsin and trypsin-like protease of the human respiratory tract (human airway trypsin-like protease – HAT) [17].

The furin cleavage site of the spiked virus protein is available not only for furin, but also for other classes of proteases, including, probably, for plasmin. High level of plasmin(ogen) and in patients with arterial hypertension, diabetes, coronary heart disease, cerebrovascular diseases, chronic obstructive pulmonary disease and renal dysfunction, it determines the increased risk of susceptibility to the virus and the severity of COVID-19 in these patients, and the extreme level of D-dimer is the result of plasmin-associated hyperactive fibrinolysis [18].

The S_1 subunit of the spiny glycoprotein of the virus has a positive polarity, which allowed E. Kharchenko to recommend acidification of the virus environment for the prevention of infection by taking lemon, berries, organic acids and tea. According to the author: "Acidification of the virion environment, neutralizing positively charged amino acids exposed to the aqueous phase, will change the conformation of S-proteins in their trimers, which will block their interaction with the cellular receptor." S-glycoprotein has many homologous sections of the amino acid sequence with viral and human proteins, which may explain various immune collisions in COVID-19 [19].

The SARS-Cov-2 virus was found to have evolved from bat coronaviruses, with an approximate divergence time of 1963 (95% HPD: 1930-2000) from the nearest bat virus species RaTG13. Pangolin coronaviruses from the ancestral line diverged much earlier and the virus could not jump from them to humans [20]. Thus, for

decades, the virus has been circulating in the bat reservoir and over these long years has acquired the ability to transfer to the human body. The first COVID-19 outbreak occurred in Wuhan (China) in December 2019, in January, the possibility of human-to-human transmission was established. This ability of the virus was probably acquired as a result of a fairly long circulation of the pathogen between bats, pangolins, and possibly sporadically humans. So, in June 2012, in the Mojiang Hani Autonomous County, Yunnan province, China, three workers who worked in an abandoned mine died of severe pneumonia of unknown etiology [21]. These cases were later described in Li Xu's master's thesis in 2013. There were 6 cases of the disease, three of them died. In the process of searching for the pathogen, Chinese scientists extracted coronaviruses like SARS (SARS-like-Cov) from the bats of the mine where the workers were infected [22]. In addition, it should be noted that bats and pangolins were eaten and sold in Southeast Asian markets.

Main indicators of the infectious process. As of 08.12.2020, COVID-19 affected 67,938,995 people worldwide, of which 1,550,263 died [23]. The first cases of COVID-19 were imported to Russia from China on January 31, 2020 in the Siberian cities of Chita and Tyumen. As a result of timely isolation of patients, further spread of infection did not occur. The first case of a Russian citizen was registered on February 27, 2020 in Moscow. A young man came from Milan and infected his elderly parents. Many cases of the disease were probably imported from Europe, which quickly began to spread across Russia. In Siberia, the first outbreak of coronavirus infection appeared in Yakutia on March 24, 2020, on March 25 in the Chelyabinsk region, and on March 26 in six regions of Siberia. The MOST recent covid-19 outbreak appeared in the Altai Republic on April 17, a little earlier than April 15 in the Chukotka and Nenets Autonomous districts. At present, there are almost no localities in Siberia that are free of this infect. The main sources of the disease are patients infected with SARS-Cov-2. The incubation period of the disease is 5.1 days on average, with 99% of cases limited to 14 days [24]. Based on this, 14 days were taken as a contact isolation measure in the initial stage of the pandemic. According to the literature, the incubation period can last from 2 to 21 days. Most authors consider the duration of the incubation period to be 6 days [25]. By Canadian researchers W. He et al. a comprehensive assessment of key infection indicators was carried out based on a meta-analysis of literature sources published for the period from January 24 to March 31, 2020. the following results were obtained: Ro-mean value of the baseline reproduction indicator 3.1 (95% confidence interval-CI 2.41-3.90); incubation period 5.0 (95% CI 4.7-5.3) days; specific weight of asymptomatic infection 46.0 (95% CI 18.4-73.6) the mortality rate of patients, including asymptomatic patients, was 2.7 (95% CI 1.2-4.1) % [26]. A high mortality rate of 12.6% is observed in patients older than 80 years, and more than 20.0% in patients with transplanted organs, chronic kidney diseases and cerebrovascular diseases [27], [28].

It was found that COVID-19 can be asymptomatic in a number of patients. These patients are of particular interest to researchers, due to the fact that they can contribute to the invisible spread of infection. Determining the true incidence of asymptomatic patients and knowing their role in the development of the epidemic is important in planning anti-epidemic measures. Researchers from the center for evidence-based medicine at the University of Oxford C. Heneghan et al. found 21 publications dedicated to asymptomatic COVID-19 patients. In these publications, the proportion of asymptomatic patients ranged from 5 to 81%, but a comprehensive meta-analysis allowed us to establish the proportion of asymptomatic patients at the level of 17% (95% CI 14-20%) [29]. According to another study by Oran D. P. et al., the proportion of asymptomatic diseases is 40-45%, and taking into account presymptomatic patients, 30%. The authors believe that asymptomatic patients are a significant factor in the rapid progression of the pandemic [30]. It should be noted that until now, the role of asymptomatic patients in the development of the pandemic is not fully defined. It has been established that asymptomatic patients can infect healthy people with the SARS-Cov-2 virus. The first information about infection in an asymptomatic patient of 5 people was published on February 23, 2020 in the journal JAMA [31]. The rate of COVID-19 infection from an asymptomatic patient ranges from 0 to 2.2%, and from a symptomatic patient from 0.8 to 15.4%. in General, the risk of infection from an asymptomatic patient was 42.0% lower than from a symptomatic patient [29].

System and meta-analysis of 79 scientific articles by M. Cevik et al. it allowed us to find out that despite a long period of positive PCR tests of SARS-Cov-2 RNA, a live or replicative competent virus was not isolated after 9 days after the appearance of symptoms in patients with mild and moderate severity in any published scientific article. At the same time, relatively rapid clearance of virus isolation is observed in asymptomatic patients [32]. In severe and immunocompromised patients, the live virus is released up to 15 days after the onset of

Created with BioRender.com

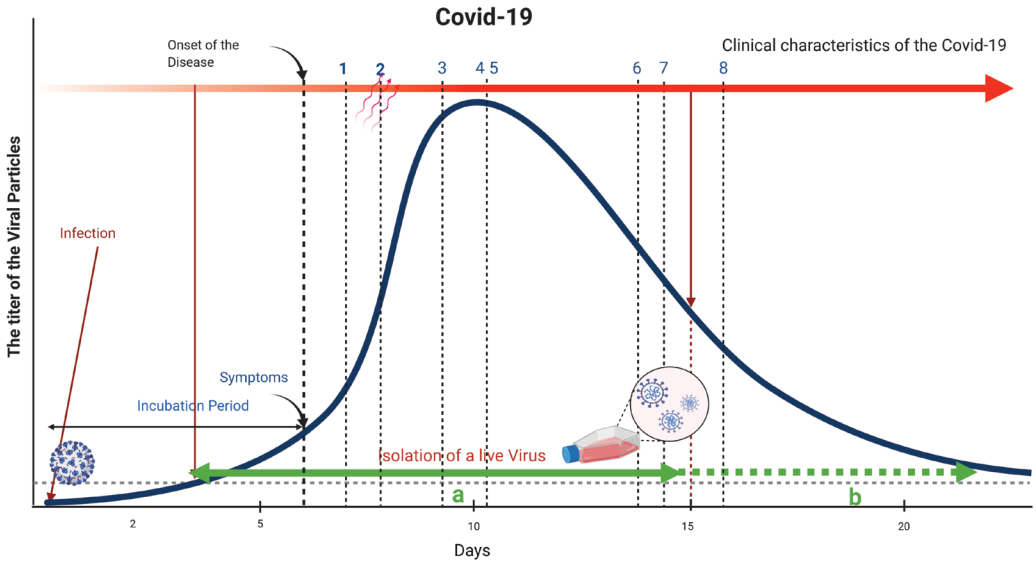

Fig. 2. Isolation of live viral particles by patients and the clinical course of COVID-19.

The duration of the incubation period is taken as 6 days;

a-the duration of isolation of a live (replicative-competent) virus (no more than 9 days from the beginning of the disease and 2-3 days before the first symptoms appear), b-individual cases of long-term isolation of a live virus (patients with severe course);

Clinical course of COVID-19 (according to S. Zayet et al. [25]): 1 – pain syndrome (a combination of headache, myalgia or arthralgia) in 87% of patients after an average of 1.6 days from the onset of the disease; 2 – temperature high at 76% after 1.9 days; 3 – cough 80% of patients after 3.7 days; 4 – diarrhea 40% of patients in 4.5 days; 5 – anosmia 53% of patients in 4.7 days; 6 – hospitalization 47% of patients after 7 days; 7 – shortness of breath 21% of patients in 8.7 days; ICU 15% patients in the 10.1 days after the onset of the disease.

clinical manifestations of the disease [33]. It was found that patients become infectious a few days before the onset of symptoms of COVID-19 [33]. According to most researchers, this fact was the reason for the rapid progression of the disease to a pandemic and makes it more similar to the flu than to SARS-Cov and MERS-Cov. It should be noted that outbreaks of MERS-Cov and SARS-Cov independently stopped as a result of anti-epidemic measures, because patients became infectious after the onset of symptoms. We have summarized data on the development of the infectious process and COVID-19 infection, which are shown in figure 2.

Until now, the debate continues about what is more severe than the flu or COVID-19? An international group of researchers led by E. Burn et al. (2020) conducted a comparative analysis of 34,128 COVID-19 patients and 84585 flu patients admitted to hospitals in the United States, South Korea, and Spain. Thus, according to the data obtained, COVID-19 patients were more likely to be men, younger, with fewer concomitant diseases, i.e. they were healthier and younger than the flu [34]. It should be noted that the current pandemic cannot be compared to the Spanish flu pandemic of 1918-1920, because the levels of health development were different. For example, the death rate in the United States from Spanish flu in 1918 was 6 people out of 1000 or 0.6% of the population [35], while in Yakutia in 1926 only in two Yakut districts 3286 people died from "Spanish flu", or 2.0% of the total population, and in Bayagantay nasleg 3.2% of the total population died from This disease [36]. It should be noted that at that time in the territory of Yakutia there was no developed network of the health care system.

Route of infection. The main routes of transmission of SARS-Cov-2 are respiratory droplets and close contact [37]. It has been experimentally established that the virus can be transmitted by airborne droplets, but also by fomites, but the first pathway is the main one [38]. Due to the fact that the viable SARS-Cov-2 is preserved in aerosols for 3 hours, plastic and stainless steel for 72 hours, copper for no more than 4 hours, and cardboard for 24 hours, aerosol contamination is allowed, but also by fomites [39]. Currently, the probability of transmission of infection by aerosols suspended in the air, through fomites and by fecal-oral route is not fully determined. It is believed that contact infection can be transmitted when fomites enter the mucous membranes of the eyes and mouth. It should be noted that in exper-

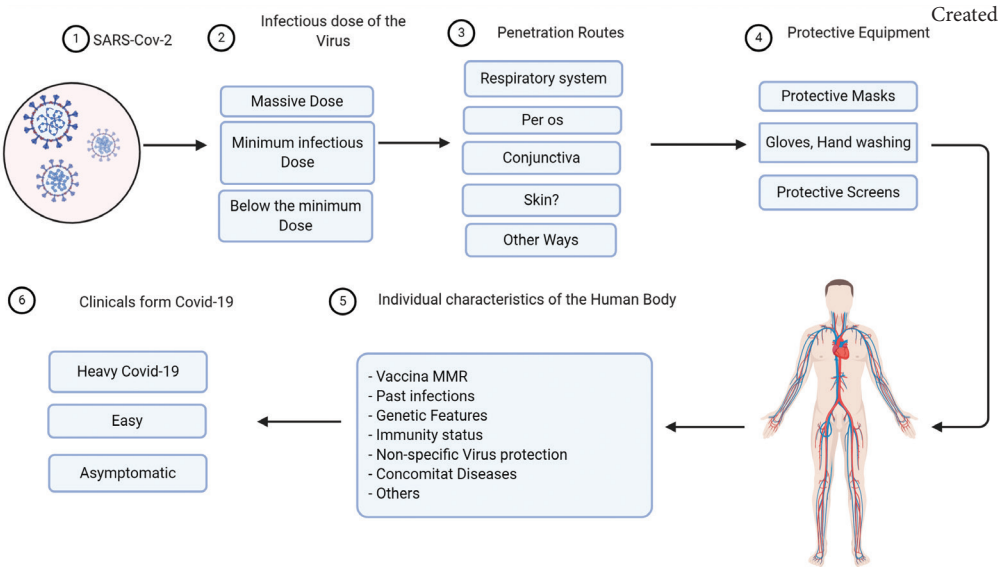

Fig. 3. Reasons for varying degress of COVID-19 susceptibility and severity of clinical manifestations

iments, SARS-Cov-2 is intensively replicated in the culture of cells of the bronchi, lung tissue and conjunctival mucosa [40], virus RNA is isolated from the conjunctival secretions of COVID-19 patients [41], and wearing face shields prevents the incidence of COVID-19 social workers in contact with patients [42], people who constantly wear glasses had a lower hospitalized incidence than those who do not wear glasses [43].

Researchers and people often ask: "Why do some patients get COVID-19 more seriously, up to a fatal outcome, others carry the disease relatively easily, and some do not feel any ailments at all?". Analysis of literature sources allows us to identify five reasons that can determine the characteristics of individual susceptibility to COVID-19 (see figure 3): 1. Virulence of the virus; 2) the Infectious dose of the virus entered the body; 3) the Use of protective equipment; 4) Individual characteristics of the human body; 5) Clinical manifestations of the disease depending on the implementation of various pathogenetic mechanisms.

Virulence. In June 2020, an article by B. Corber et al. that the mutation of the d614g spike protein gene had become the dominant SARS-Cov-2 genotype worldwide by may (see figure 4). They found that the genotype of the G614 virus causes a higher viral load of the upper respiratory tract, increasing the infectious ability of the virus, but does not lead to a heavier clinical picture of the disease. In Russia, a small amount of the d614 genotype was introduced in March, but in may it was almost completely replaced by the g614 genotype [44].

Evolution towards higher transmissivity should show repeatedly, independently occurring mutations (homoplasy's) and their positive selection. van Dorp L. et al. based on the analysis of 46723 genomic collections of the virus, no recurrent mutations leading to increased transmissivity were detected. The identified mutations were evolutionarily neutral and were caused by RNA editing by the human immunological system [45]. It should be noted that deletion of the E protein gene, which leads to extensive loss of amino acid residues in the C-terminal region, according to preliminary data leads to asymptomatic forms of COVID-19 [46].

Thus, despite the absence of more virulent strains of SARS-Cov-2 in the world to date, it is theoretically likely to be infected with a virus with a mutation that causes an asymptomatic form of the disease. On the other hand, the mass wearing of protective equipment helped eliminate massive infection with the virus, causing asymptomatic and mild forms of infection.

Infectious dose of the virus. The severity of the clinical manifestations of COVID-19 probably depends on the number of virus particles in the body [47]. An experimental model of COVID-19 on Syrian hamsters showed that the severity of the disease depended on the dose of the virus introduced into the body of the experimental animal [48]. It is known that superinfection with massive doses of the virus in the red zones of infectious hospitals led to infection, the development of severe forms of COVID-19 and the death of healthy and young doctors. So, 21.02.2020 G. The Xinhua news Agency reported that Chinese doctor Peng Yinhua died at the age of 29 from COVID-19 in a hospital in Wuhan and became the youngest doctor to die from the According to the most approximate estimate, the minimum infectious

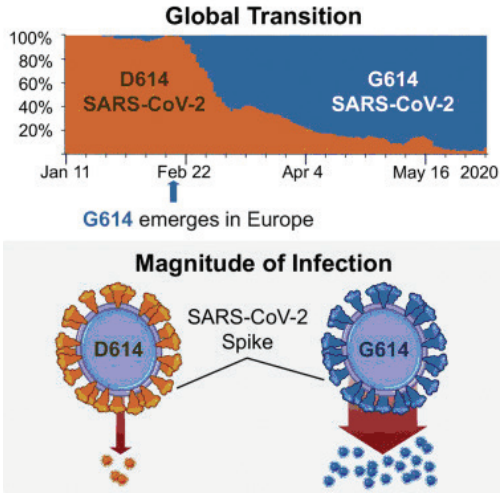

Fig. 4. Global distribution of the g614 SARS-Cov-2 genotype (According to B. Korber et al. [44])

dose of SARS-Cov-2 is more than 100 particles [50]. It should be noted that in people with reduced immunity, even a small amount of viral particles can cause the development of the disease.is disease [49].

Ways of penetration. The severity of the clinical manifestations of COVID-19 depends on the ways the virus enters the human body. The most severe lesion is caused by lung infection [51], [52]. According to a number of researchers, infection of experimental animals through the conjunctiva leads to a lighter manifestation of the disease [53], and infection through the gastrointestinal tract requires very high doses of the virus to cause clinical manifestations [54]. It is likely that the primary lesion of the gastrointestinal tract causes a milder infection [55], [56]. Especially noteworthy are the "COVID fingers" of hands and feet in children. It is known that keratinocytes contain angiotensin-2 and ACE (ACE) receptors [57], who knows how SARS-Cov-2 will behave if it gets on the skin? Chinese researchers q. Xu et al. we found abundant expression of ACE and TMPRSS2 receptors in skin cells. In addition, a fluorescent method was used to detect the SARS-Cov-2 nucleocapsid protein in the cytoplasm of the epidermis in patients with COVID-19. Based on the data obtained, the authors consider the potential transmission of the virus through damaged skin [58]. 20.4% of COVID-19 patients have skin manifestations, and about 55.1% of them are localized on the hands and feet. It was found that erythematous maculopapular rashes and urticaria in 59.0% of cases appear in the earliest periods of the disease, and in approximately 6.0% of cases before the onset of the disease. Histological examination of biopsy preparations reveals perivascular lymphocytic or monocytic infiltrates [59]. I. Colmenero et al. a positive reaction to SARS-CoV-2 was detected by immunohistochemical method in epithelial cells of the skin eccrine glands, which was confirmed by electron microscopic detection of viral particles in the cytoplasm of endothelial cells [60]. Thus, it can be assumed that the virus can penetrate the pores of the eccrine glands of healthy skin.

Protective means. According to a study conducted among health workers conducted by employees of Brigham and Women's Hospital (BWH) in Boston (Massachusetts, USA), it was found that during the initial period of the COVID-19 pandemic from March 1 to March 24, 2020, when the mandatory wearing of masks by medical workers was not yet prescribed, the incidence of COVID-19 increased by 1.16% per day and doubled every 3.6 days. After prescribing the mandatory wearing of masks by medical workers from March 25 to April 5, the incidence among them has stabilized. Starting from April 6, patients were required to wear masks, and starting from April 11, the incidence of COVID-19 began to decrease linearly by 0.49% per day, and the change in the trend slope level was 1.65% [61]. Researchers at the University of California (California State University) B. T. Haas and M. Greenhawt conducted a survey of 801 doctors, of which 663 were receiving patients and suspects on COVID-19. Of the 663 doctors, 43 (5.4%) subsequently contracted an infection and became ill. At the same time, those who wore surgical masks became ill in 10.1% of cases, disposable N95-100 masks 6.3%, reusable N-95-100 masks 2.9%, and powered air purifying respirator (PAPR) 0 %. It should be noted that doctors who wore n-95-100 masks when receiving asymptomatic patients were twice as likely to get sick as doctors who wore surgical masks, and the risk of getting sick was higher for doctors who received patients who did not wear masks than those who did [62]. Thus, according to this study, protective masks prevent infection depending on their type, but they are more effective only when everyone is wearing them.

Hand washing with soap and the use of disinfectants is recommended by who to prevent the spread of COVID-19. Who warns about the limited effectiveness of wearing gloves, according to the recommendations, gloves can be worn when coming into contact with Covid-12 patients, when caring for patients, and when coming into contact with the patient's biological fluids [63]. Many researchers warn about the problems of wearing gloves, but it should be noted that if you use gloves correctly to prevent SARS-Cov-2 infection, they can undoubtedly be useful. A dentist surgeon we know got sick with COVID-19, despite observing all safe-

ty measures at work. After being hospitalized, she observed that doctors in the red zone put double gloves on their hands, and she thought that she might have been infected because she only wore one glove when working with patients. There are recommendations to wear double gloves when performing surgery in infectious patients, but, unfortunately, these recommendations are not applied everywhere. While the scientific world is arguing about the probability of fecal-oral transmission of infection and does not notice how the entrance gates of the skin, practical doctors of the red zones of infectious hospitals have quickly learned the hard way the importance of eliminating the contact of the virus with any part of the body. Thus, the use of protective equipment can contribute to the development of milder forms of the disease by reducing the intake of an infectious dose of the virus.

Individual characteristics of the body. There is a striking difference in individual susceptibility to the COVID-19 virus and the development of severe forms of the disease. Susceptibility to infection is closely related to the severity of clinical manifestations, but, on the other hand, the severity of the disease depends in part on the timeliness and professionalism of the medical care provided. We have identified 7 groups of factors that contribute to a significant difference in the susceptibility and severity of clinical manifestations of the disease: the effect of vaccination, especially the titer of antibodies against mumps [64]; cross-immunity from past infections, such as other human and animal coronaviruses [65]; genetic predisposition, including blood type A [66]; state of immunity; non-specific protection against viruses, BCG vaccine [67]; concomitant diseases [68], etc.

The most interesting feature of COVID-19 is the extremely low incidence, asymptomatic or mild course of infection in children. A more convincing explanation of this phenomenon is the hypothesis about the protective role of the MMR vaccine (measures, mumps, rubella) [69]. So, in our country, mass vaccination against measles began in 1973, mumps in 1981, and rubella in 1997. Of these three diseases, patients with COVID-19 have a dose-dependent correlation of morbidity with the level of anti-mumps antibody titers. Thus, in patients who recovered from COVID-19, the level of IgG titers of mumps was inversely correlated with the severity of the disease, while a dose-dependent effect was observed. The IgG titer level reached 172.4 UE/ml (AU/ml) in the infection-tolerant subjects (in the authors ' terminology, "functionally immune patients"). In this category, the authors included people who had close contact with patients with a reliably established diagnosis of COVID-19, while they did not wear masks and did not keep a distance, but they never tested positive for SARS-Cov-2 and did not have any symptoms of the disease. In asymptomatic patients, the IgG titer level was 101.3 UE/ml, in moderate patients – 61.9, in moderate patients – 34.8, and in severe patients-8.0 UE / ml (AU / ml) [64]. In this regard, it should be noted that in our country, according to 2013 data, 8% of children aged 9-10 and 14-25% of adults aged 15-50 are immunologically seronegative to mumps [70]. This circumstance may explain the difference in the incidence and severity of infection among people under 40 years of age, because mass vaccination of the Russian population against mumps began 39 years ago. On the other hand, a certain number of people are protected by cross-immunity from other human coronavirus infections (HCov-229E, HCov-NL63, HCov-OC-43, HCov-HKU-1), as well as animal coronavirus infections [65].

Epidemiological studies have identified a number of risk factors for the development of severe forms of COVID-19: male gender, old age, and concomitant diseases (obesity, hypertension, diabetes, etc.). But it should be noted that the proportion of young people in mortality from infection is high in Mexico and in India [71]. In some cases, a severe variant of the disease can be caused by genetic factors. So, in the Netherlands, four young patients from two families aged 21 to 32 years suffered a severe form of COVID-19, which required ventilation, one of them died. Sequencing of the exome part of the genome in these families revealed a mutation in the TLR7 gene. In the first family, a 4-nucleoid deletion of the gene was detected, which led to the loss of its function. One of the brothers with this mutation died. A harmful missense mutation was found in the second family. A mutation in the TLR7 gene led to a violation of the interferon I and II response [72]. It was found that approximately 3.5% of patients with life-threatening pneumonia had genetic defects in the regulation and induction of interferon I [73]. Genome - wide Association studies GWAS revealed two loci in the third chromosome (genes: SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1) and blood group A as potential genetic risk factors for COVID-19 [66]. Another major factor that increases the risk of severe infection is the presence of autoantibodies to interferon. Such autoantibodies are detected in 10.2% of patients with severe coronavirus pneumonia [74].

Conclusion. SARS-Cov-2 has pandemic potential and is estimated to be more severe than pandemic influenza viruses. Active isolation of the virus before the onset of symptoms, including by asymptomatic patients (including children), causes the rapid spread of infection and reduces the effectiveness of anti-epidemic measures. The presence of a significant segment of the population with cross-immunity to SARS-Cov-2, including and as a result of vaccination, it is the most likely cause of a high percentage of asymptomatic and mild forms of the disease among children and young people. Effective protection against coronavirus infection in 2019 can only be achieved by taking comprehensive measures to prevent the virus from entering the body through the respiratory tract, per os, conjunctiva and skin, although the latter pathway is not taken into account anywhere in the world.

In conclusion, it should be noted that COVID-19 cannot be classified as a particularly dangerous infection, but its high contagiousness, the likelihood of multiple entry gates of the virus into the human body, multi-organ lesions and a high mortality rate of risk groups make it a special infection that requires significant human efforts to eliminate it.

Funding. This work was carried out within the framework of the State Assignment of the Ministry of Education and Science "Genome-wide studies of the gene pool of the indigenous population of the Arctic coast of Yakutia" (FSRG-2020-0016).

Disclosure statement. The authors reported to potential conflicts of interest.

Authors' contributions. Conceived, designed and manuscripts drafting Tikhonov D.G. Discussed and critically edited manuscript: Tikhonov D.G., Vladimirtsev V.A. Translation into English Vladimirtsev V.A. All authors have read and approved the final version of the manuscripts before publication.

REFERENCES

1. WHO. Pneumonia of unknown etiology China [Electronic resource] // WHO. Global website. 2020. URL: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/ (accessed: 27.05.2020).

2. WHO. Previously unknown coronavirus China [Electronic resource] // WHO. Global website. 2020. URL: https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/ (accessed: 27.05.2020).

3. Wu F. et al. A new coronavirus associated with human respiratory disease in China // Nature. 2020. Vol. 579, № 7798. P. 265–269.

4. Gorbalenya A.E. et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2 // Nat. Microbiol. 2020. Vol. 5, № 4. P. 536–544.

5. World Health Organization (WHO). Novel coronavirus - China 11-fev 2020 // WHO Bull. 2020. № February 11.

6. WHO. COVID-19-chronology of who actions [Electronic resource] / / who. Global web 2020. 2020. P. 1-4. url: https://www.who.int/ru/news-room/detail/27-04-2020-who-timeline---covid-19 (accessed: 27.05.2020).

7. Huang C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China // Lancet. 2020. Vol. 395, № 10223. P. 497–506.

8. ICTV. International Committee on Taxonomy of Viruses (ICTV) [Electronic resource] // Virus Taxonomy: 2019 Release. 2019. URL: https://talk.ictvonline.org/taxonomy/ (accessed: 21.11.2020).

9. Gaunt E.R. et al. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method // J. Clin. Microbiol. 2010. Vol. 48, № 8. P. 2940–2947.

10. Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Hu, Y., Song Z.-G. et al. A novel coronavirus associated with a respiratory disease in Wuhan of Hubei province, China. GenBank, 2020.

11. Bestle D. et al. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells // Life Sci. Alliance. 2020. Vol. 3, № 9. P. e202000786.

12. Kim D. et al. The Architecture of SARS-CoV-2 Transcriptome // Cell. 2020. Vol. 181, № 4. P. 914-921. e10.

13. Gui M. et al. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a pre-

requisite conformational state for receptor binding // Cell Res. Nature Publishing Group, 2017. Vol. 27, № 1. P. 119–129.

14. Wei C. et al. HDL-scavenger receptor B type 1 facilitates SARS-CoV-2 entry // Nat. Metab. Springer US, 2020.

15. Cantuti-Castelvetri L. et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity // Science (80-.). 2020. Vol. 860, № November. P. eabd2985.

16. Teesalu T. et al. C-end rule peptides mediate neuropilin-1-dependent cell, vascular, and tissue penetration // Proc. Natl. Acad. Sci. U. S. A. 2009. Vol. 106, № 38. P. 16157–16162.

17. Xia S. et al. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin // Signal Transduct. Target. Ther. 2020. Vol. 5, № 1.

18. Ji H.L. et al. Elevated plasmin(Ogen) as a common risk factor for COVID-19 susceptibility // Physiol. Rev. 2020. Vol. 100, № 3. P. 1065–1075.

19. Kharchenko I.P. Koronavirus SARS-Cov-2: osobennosti strukturnykh belkov. kontagioznost i vozmozhnyye immunnyye kollizii [Coronavirus SARS-Cov-2: features of structural proteins, contagiousness and possible immune collisions] // Epidemiologiya i Vaktsinoprofilaktika. 2020. Vol. 7, № 812. P. 13–30 [in Russian]

20. Boni M.F. et al. Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic // Nat. Microbiol. Springer US, 2020. Vol. 5, № 11. P. 1408–1417.

21. Wu Z. et al. Novel Henipa-like virus, Mojiang Paramyxovirus, in rats, China, 2012 // Emerg. Infect. Dis. 2014. Vol. 20, № 6. P. 1064–1066.

22. 李旭 (Xu L. 未知病毒引起重症肺炎6例分析 (The Analysis of Six Patients With Severe Pneumonia Caused By Unknown Viruses) // Master's thesis. 2013. Vol. 2020. P. 1–66.

23. Worldometer. COVID-19 CORONAVIRUS PANDEMIC [Electronic resource] // Worldometers. 2020. URL: https://www.worldometers.info/coronavirus/ (accessed: 16.11.2020).

24. Lauer S.A. et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application // Ann. Intern. Med. 2020. Vol. 172, № 9. P. 577–582.

25. Zayet S., Gendrin V., Klopfenstein T. Natural history of COVID-19: back to basics // New Microbes New Infect. Elsevier Ltd, 2020. Vol. 38. P. 100815.

26. He W., Yi G.Y., Zhu Y. Estimation of the basic reproduction number, average incubation time, asymptomatic infection rate, and case fatality rate for COVID-19: Meta-analysis and sensitivity analysis // J. Med. Virol. 2020. Vol. 92, № 11. P. 2543–2550.

27. Raja M.A. et al. COVID-19 in solid organ transplant recipients: A systematic review and meta-analysis of current literature // Transplantation Reviews. Elsevier Inc, 2021. Vol. 35, № 1. 100588 p.

28. Stawicki S.P. et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper // J. Glob. Infect. Dis. Wolters Kluwer - Medknow, 2020. Vol. 12, № 2. P. 47–93.

29. Byambasuren O. et al. Estimating the Extent of True Asymptomatic COVID-19 and Its Potential for Community Transmission: Systematic Review and Meta-Analysis // SSRN Electron. J. 2020.

30. Oran D.P., Topol E.J. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review // Ann. Intern. Med. 2020. Vol. 173, № 5. P. 362–367.

31. Li Q. et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia // N. Engl. J. Med. 2020. Vol. 382, № 13. P. 1199–1207.

32. Cevik M. et al. SARS-CoV-2, SARS-CoV-1 and MERS-CoV Viral Load Dynamics, Duration of Viral Shedding and Infectiousness: A Living Systematic Review and Meta-Analysis // SSRN Electron. J. The Author(s). Published 李旭 by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license, 2020. Vol. 5247, № 20. P. 1–10.

33. Rhee C. et al. Duration of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectivity: When Is It Safe to Discontinue Isolation? // Clin. Infect. Dis. 2020. Vol. 2, № Xx Xxxx. P. 23–28.

34. Burn E. et al. Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study // Nat. Commun. 2020. Vol. 11, № 1. P. 1–11.

35. Crosby A.W. America's Forgotten Pandemic. The Influenza of 1918. 2nd ed. Cambridge: Cambridge University Press, 2003.

36. Tikhonov D. Arkticheskaya meditsina [Arctic medicine]. Yakutsk: YaSC SB RAS, 2010. 317 p. [In Russian].

37. World Health Organization (WHO). Transmission of SARS-CoV-2: implications for infection prevention precautions [Electronic resource] // Scientific Brief. 2020. URL: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions (accessed:

29.11.2020).

38. Sia S.F. et al. Pathogenesis and transmission of SARS-CoV-2 in golden Syrian hamsters // Nature. 2020. Vol. 583, № 7818. P. 834–838.

39. van Doremalen N. et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1 // N. Engl. J. Med. Massachusetts Medical Society, 2020. Vol. 382, № 16. P. 1564–1567.

40. Hui K.P.Y. et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures // Lancet Respir. Med. Elsevier Ltd, 2020. Vol. 8, № 7. P. 687–695.

41. Xia J. et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection // J. Med. Virol. 2020. Vol. 92, № 6. P. 589–594.

42. Bhaskar M.E., Arun S. SARS-CoV-2 Infection Among Community Health Workers in India Before and After Use of Face Shields // JAMA. 2020. Vol. 324, № 13. P. 1348–1349.

43. Zeng W. et al. Association of Daily Wear of Eyeglasses with Susceptibility to Coronavirus Disease 2019 Infection // JAMA Ophthalmol. 2020. P. 1–4.

44. Korber B. et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus // Cell. 2020. Vol. 182, № 4. P. 812-827.e19.

45. van Dorp L. et al. No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2 // Nat. Commun. Springer US, 2020.

46. Kumar B.K. et al. Deletion in the C-terminal region of the envelope glycoprotein in some of the Indian SARS-CoV-2 genome // Virus Res. Elsevier B.V., 2020. Vol. 291, № June 2020. P. 198222.

47. Guallar M.P. et al. Inoculum at the time of SARS-CoV-2 exposure and risk of disease severity // Int. J. Infect. Dis. 2020. Vol. 97. P. 290–292.

48. Imai M. et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development // Proc. Natl. Acad. Sci. U. S. A. 2020. Vol. 117, № 28. P. 16587–16595.

49. Xinhua. Wuhan hospital doctor dies from coronavirus [Electronic resource]. 2020. URL: http://www.xinhuanet.com/english/2020-02/21/c_138805730.htm (accessed: 03.12.2020).

50. Karimzadeh, S.; Bhopal, R.; Nguyen Tien H. Review of Infective Dose, Routes of Transmission, and Outcome of COVID-19 Caused by the SARS-CoV-2 Virus: Comparison with Other Respiratory Viruses // Preprint. 2020. № October. P. 1–21.

51. Schaller T. et al. Postmortem Examination of Patients with COVID-19 // JAMA - J. Am. Med. Assoc. 2020. Vol. 323, № 24. P. 2518–2520.

52. Ackermann M. et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19 // N. Engl. J. Med. 2020.

53. Deng W. et al. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques // Nat. Commun. 2020. Vol. 11, № 1. P. 1–7.

54. Sun S.H. et al. A Mouse Model of SARS-CoV-2 Infection and Pathogenesis // Cell Host Microbe. Elsevier Inc., 2020. Vol. 28, № 1. P. 124-133.e4.

55. Yang T.Y. et al. Clinical characteristics of patients with COVID-19 presenting with gastrointestinal symptoms as initial symptoms: Retrospective case series // World J. Clin. Cases. 2020. Vol. 8, № 14. P. 2950–2958.

56. Тихонов Д.Г., Владимирцев В.А. Коронавирусная пандемия. Поражение органов пищеварительного тракта при COVID-19. Причина или следствие? // Сибирские исследования. 2020. Vol. 4, № 2.

57. Steckelings U.M. et al. Human skin: Source of and target organ for angiotensin II // Exp. Dermatol. 2004. Vol. 13, № 3. P. 148–154.

58. Sun Y. et al. Skin is a potential host of SARS-CoV-2: A clinical, single-cell transcriptome-profiling and histologic study // J. Am. Acad. Dermatol. 2020/08/19. by the American Academy of Dermatology, Inc., 2020. Vol. 83, № 6. P. 1755–1757.

59. Daneshgaran G., Dubin D.P., Gould D.J. Cutaneous Manifestations of COVID-19: An Evidence-Based Review // Am. J. Clin. Dermatol. Springer International Publishing, 2020. Vol. 21, № 5. P. 627–639.

60. Colmenero I. et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases // Br. J. Dermatol. 2020. Vol. 183, № 4. P. 729–737.

61. Klompas M. et al. Universal Masking in Hospitals in the Covid-19 Era // N. Engl. J. Med. 2020. Vol. 382, № 21. P. e63.

62. Haas B.T., Greenhawt M. Clinical Communication: Association between Type of Personal Protective Equipment Worn and Clinician Self-Reported COVID-19 Infection // J. Allergy Clin. Immunol. Pract. American Academy of Allergy, Asthma & Immunology, 2020. P. 1–4.

63. Anedda J. et al. Changing gears: Medical gloves in the era of coronavirus disease 2019 pandemic // Clin. Dermatol. Elsevier Inc., 2020. № xxxx.

64. Gold J.E. et al. Analysis of Measles-Mumps-Ru-

bella (MMR) Titers of Recovered COVID-19 Patients // MBio / ed. Pirofski L. 2020. Vol. 11, № 6. P. e02628-20.

65. Mateus J. et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans // Science (80-.). 2020. Vol. 370, № 6512. P. 89–94.

66. Ellinghaus D. et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure // N. Engl. J. Med. 2020. Vol. 383, № 16. P. 1522–1534.

67. Miyasaka M. Is BCG vaccination causally related to reduced COVID-19 mortality? // EMBO Mol. Med. 2020. Vol. 12, № 6. P. 10–12.

68. Matsushita K. et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis // Glob. Heart. 2020. Vol. 15, № 1. P. 1–14.

69. Gold J.E. MMR Vaccine Appears to Confer Strong Protection from COVID-19 : Few Deaths from SARS-CoV-2 in Highly Vaccinated Populations MMR Vaccine Appears to Confer Strong Protection from COVID-19 : Few Deaths from SARS-CoV-2 in Highly Vaccinated Populations // Res. Gate. 2020. Vol. 7, № May. P. 3.

70. Terentyeva Zh.V. et al. Aktualnyye voprosy serologicheskogo monitoringa v sisteme epidemiologicheskogo nadzora za epidemicheskim parotitom [Topical issues of serological monitoring in the system of epidemiological surveillance of mumps] // Epidemiologiya. mikrobiologiya. infektsionnyye i parazitarnyye bolezni. / 2013. Vol. 1, № 46. P. 79–81 (in Russian).

71. Ioannidis J.P.A., Axfors C., Contopoulos-Ioannidis D.G. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters // Environ. Res. Elsevier Inc., 2020. Vol. 188. P. 109890.

72. Van Der Made C.I. et al. Presence of Genetic Variants among Young Men with Severe COVID-19 // JAMA - J. Am. Med. Assoc. 2020. Vol. 324, № 7. P. 663–673.

73. Zhang Q. et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19 // Science. 2020. Vol. 370, № 6515.

74. Bastard P. et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19 // Science. 2020. Vol. 370, № 6515.

Information about authors

1. TIKHONOV Dmitry Gavrilievich, MD, Professor, Senior Research Officer of the Scientific research Center of the medical Institute of the North-Eastern Federal University, 677009, Yakutsk, St. Bld. 8, Russia, https://orcid.org/0000-0003-3385-9471, e-mail: Tikhonov.dmitri@yandex.ru.

2. VLADIMIRTSEV Vsevolod A., PhD. Free Researcher. https://orcid.org/0000-0002-5480-3592, e-mail: sevelot@mail.ru.