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Identification of Corona Virus Infection in People Infected with SARS-CoV-2

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ABSTRACT

Localization and eradication of the COVID-19 pandemic requires that a number of challenges are addressed, and diagnosis is the first of these challenges. Establishing diagnosiscan not only detect ill people, but also create a statistical database, which may help manage containment measures, realize epidemic-prevention measures and organize the work of the world community on the way to elimination of the emerged problem.

Study of the methods of COVID-19 diagnosis constitutes the aim of our research. By means of analyzing literary data and methods of laboratory studies we have managed to present variants of reactions use (polymerase chain reaction, enzyme linked immunosorbent assay) for establishing the COVID-19 diagnosis.

The authors of the article have conducted the analysis of COVID-19 diagnosis protocol files valid in the People's Republic of China, the United States of America, South Korea, the Russian Federation and Ukraine. Variants of polymerase chain reaction setup were studied (diagnostic identification of one or several viral genes). The mechanism of diagnosis in case of SARS-CoV-2 viral infection and variants of use of corresponding methods of laboratory studies are presented.

Polymerase chain reaction (PCR) remains the only diagnostic reaction acknowledged by the World Health Organisation, however, a range of laboratory and instrumental methods can be used as auxiliary, helping lower the load on PCR diagnostic laboratories. There is no protocol of PCR administration, and determining the optimal diagnostic procedure of COVID-19 diagnosis is one of the forward-looking tasks for the world academic community.

Keywords
SARS-CoV-2, laboratory diagnostics, COVID-19, Polymerase Chain Reaction, Enzyme Linked Immunosorbent Assay.

Introduction

Human evolution history has been continuously associated with the phenomenon of a pandemic undulantly embracing countries and continents. Peculiarities of the development of global infectious diseases have been studied since the time of Antiquity (Avicenna, Hippocrates). The impact pandemics have of socio-cultural development of states is truly global: Justinianic Plague in V-VII killed 125 million people, the Black Death of XVI took lives of more than 60 million people worldwide, which was 25% of the Earth population [1]. The Spanish influenza pandemic in 1918-1919 carried away more than 20 million human lives, outnumbering people losses during

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the World War 1 by two to one [2]. But except for being a curse, pandemics can also be a force for progress: comprehensive study of cholera was not of the least importance in formulation of medical hygiene postulates by N. F. Gamaleya [3]. It is worth mentioning that every pandemic, first of all, poses a question which is not why, but rather how: how to stop and how to prevent.

Literature Review

The new reality is to be accepted: viral pneumonia caused by the serotype SARS-CoV-2 quickly spread to become a pandemic. The city of Wuhan, Hubei province, China, became a staging ground for the extension of coronaviral infection. On January 9, 2020 Chinese specialists reported that a new serotype of the *Betacoronavirus* genus had been identified. On 11 February, 2020 the World Health Organization (WHO) assigned the name COVID-19 to the disease caused by the newly identified virus [4-6].

It should be taken into account that the current outbreak of coronavirus is not one of its kind. Thus, in a short period the humanity faced several serotypes of the *Coronaviridae* causing severe courses of respiratory syndrome: SARS (Severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) [7]. WHO accentuates that a ubiquitous spread is typical of four human coronaviruses: HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43. These are betacoronavisuses. The former two can cause zoonoses: MERS-CoV can be transmitted to a human from the Arabian camel, while SARS-CoV can be transmitted from horseshoe batsinhabiting caves [8].

The SARS-CoV-2 serotype is distinguished by a range of specific features contributing to its quick dissemination and therefore to COVID-19 pandemic progression. Thus, the predictedreproductive number of virus (the number of contact cases caused by a single infected person is 2.2 (from 1.4 to 6.5), which is significantly higher than that of seasonal influenza (1.8). A person starts spreading virions at a prodromal stage (absence of vivid symptoms of the disease, insignificant, nonspecific symptoms). The incubation period (from the moment of infection until first nonspecific symptoms occur) for COVID-19 lasts 6.5 days (from 2.1 to 11.1) [9-11].

World Health Organization (WHO) provides a list of possible transmissions of the virus: contact (close contact and a contact via fomites), aerosol transmission, air-dust, fecal-oral, through blood, mother-to-child and animal-to-human transmission [12-15]. Disease transmission in the condition of healthcare settings deserves particular attention. Thus, WHO pays a particular attention to the aerosol transmission. Administration of medical procedures facilitates elevation of virus into the air, where it mingles with liquid droplets, which are numerous in procedure rooms. This mechanism is specifically characteristic of poorly aired rooms. Thus, not only virions are spread inside the closed space of a room and, subsequently, infection of the personnel, but also different surfaces, as well as suturing instruments, which leads to additional virus transmission outside the room [16-18].

Contamination with SARS-CoV-2 in most cases provokes a respiratory disease, the course of which can vary from a mild to a severe illness entailing complications or even death [6, 12, 19]. Moreover, some infected persons do not observe any symptoms associated with COVID-19 and do not seek medical attention. This, in its turn, does not allow receive a complete picture of virus spread [18, 19]. Another characteristic feature hindering diagnosis establishment is absence of a distinctive list of symptoms evidencing SARS-CoV-2 persistence in a human body. Thus, a number of people infected with the virus may not experience any symptoms. Besides, medical statistics shows that not a symptom is registered in 100% of respondents. Thus, the following symptoms were observed in patients: body temperature rise (from sub-febrile to high

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temperature)—98%, dry cough (74%), fatigue (49%), dyspnea (36%), throat irritation (27%), smell and taste dysfunction (23%), nausea (10%), headache (9%), rash (3%), diarrhea (3%) [6]. Separate attention must be provided to blood viscosity which is an important factor in the case of the development of such virus pathology [20].

There is also a part of population who rarely or never seek medical help. This is responsible for a group of undiagnosed COVID-19 cases, which, firstly, does not allow obtain a complete picture of infection among population and, secondly, makes for an uncontrolled dissemination of the virus and widens the circle of exposed persons, who can potentially be considered infected [21, 22]. What is more, a percentage of false diagnosis as a result of the similarity of symptoms with other diseases or presence of chronic illnesses [23]. That is why laboratory diagnostic is crucial in diagnosis establishment. Laboratory diagnostics is also important, because without test results no country can determine the number of citizens infected with the virus. Test results constitute statistical data and, therefore, create a picture of the COVID-19 pandemic development [24].

The aim of the research was to study methods of COVID-19 diagnosis establishment as well as determine expedience, timeliness and sequence of application of certain methods used to establish the COVID-19 diagnosis.

Materials and Methods

Methods used to establish the COVID-19 diagnosis were studied by analyzing and studying guidelines.

Choosing the vector of the study

General medical examination and realization of a number of standard diagnostic laboratory examinations combined with computer tomography (CT) remains relevant when SARS-Co-2 infection is suspected [25-29], but specific laboratory diagnostics—gene amplification assay, or polymerase chain reaction (PCR)—comes to the fore. It is this reaction with makes it possible to not only identify a disease growing progressively worse at the acute stage, but also incipient persistence (prodromal stage) of the SARS-CoV-2 virus in a human body, and also determine infection in exposed persons [8, 30-31].

PCR testing in case of SARS-CoV-2 (one RNA strand in the genome) infection is administered with the method of reverse transcription. This is a two-stage process. The first stage implies acquiring complementary deoxyribonucleic acid (cDNA) on a matrix of ribonucleic acid (RNA) of a virus. At that a certain test fragment of a coronavirus genome is replicated. What occurs while the second testing stage is being held is amplification of the produced DNA-copy of the vRNA. Results of the analysis are registered in real time with the method of fluorescent signal detection on a computer screen. The intensity of the fluorescence is directly proportional to the quantity of a pathogen in the sample [31-34].

WHO recommends selecting material from respiratory passages as the main diagnostic material for COVID-19 sample tests.

Serum diagnostics can be applied in order to confirm a patient to be infected with SARS-CoV-2 and to control the development of a pathological process via antibody titer monitoring (retrospective diagnostics) [8].

Retrospective diagnostics cannot determine an illness at its early stages (prodromal stages), however it helps obtain monitoring data regarding the patients who have already recovered from COVID-19, or to determine staging of the process by determining different immunoglobulin classes (the M class is characteristic of an acute course of an illness, the G class defines a convalescence or a post-convalescence period) [35].

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The essence of the method is that a viral antigen is introduced into a tested sample. Immunoglobulins (Ig) bind to the antigen, creating stable substances, which are then identified through inserting stable enzyme markers, which ensure a color effect of the reaction [36].

Results and Discussion

A trend on mobility, developed transport communication on a world scale together with the absent fear of pandemics and high contagiosity of the pathogen contributed to the rapid spread of SARS-CoV-2. Governments of all the countries were faced with the challenge of the outbreak localization, prevention of the pathogen transmission and sustention of the epidemiological well-being inside the borders.

Since while in the process of its persistence the SARS-CoV-2 virus does not manifest any characteristic symptoms to be observed in 100% cases [6], only a result of a laboratory stury can be considered a confirmation of the COVID-19 diagnosis. Many countries have efficiently designed a protocol of COVID-19 diagnostics and laboratory diagnostics in particular [36-39]. The main method of COVID-19 diagnostics is polymerase chain reaction [8]. It should be stated that PCR can provide a false-negative result, so other laboratory and instrumental methods are used in the diagnostics. Computer tomography, among all, deserves special attention [40] as well as C-reactive protein [41]. CT allows diagnose pathological changes in the structure of lungtissue, which are a result of viral infiltration [40], while C-reactive protein can be viewed as an anti-inflammatory immune trigger, activating production of cytokines and proteins of the complement system by monocytes (IL-1, IL-6 and TNF-α) [32]. But, however, PCR remains the primary diagnostic reaction.

Protocols of PCR administration in different countries vary by the discovered genes (Table 1). It should be noted that determination of the optimal protocol requires further, more elaborate research.

Table 1. A summary table of the research protocols and SARS-CoV-2 genes included into the research*

Research establishment	Studied viral genes
China CDC, China	ORF1ab and N
Institut Pasteur, Paris, France	Two targets in RdRP
US CDC, USA	Three targets in N gene
National Institute of Infectious Diseases, Japan	Pancorona and multiple targets, Spike protein
Charité, Germany	RdRP, E, N
HKU, Hong Kong SAR	ORF1b-nsp14, N
National Institute of Health, Thailand	N

*According to the official data on the web-site of WHO.

Diagnosis of a presence of one viral gene is a determinative indicator, and determination of a second gene is used as a confirmation test. At the same time, the protocols demanding identification of 3 (and more) genes infer that the result is positive when all the diagnosed nucleotide sequences are identified [37, 38, 43-45].

Thus, the diagnostics protocol used in China, the country which was first to suffer from the COVID-19 pandemic, requires identification of at least 2 viral genes. The protocol was developed with National Institute of Viral Disease Control and Prevention. Material for study is a

swab from the throat of a tested person. In the process of diagnostics ORF1ab is the firsts target to be identified: forward primer (F) — CCCTGTGGGTTTTACACTAA; reverse primer (R) — ACGATTGTGCATCAGCTGA; fluorescent probe (P) — 5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. The second target (confirmation test) is viral nucleocapsid protein N: forward primer (F) — GGGGAACTTCTCCTGCTAGAAT; reverse primer (R) — CAGACATTTTGCTCTCAAGCTG; fluorescent probe (P) — 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. The guideline distinguishes 3 types of result interpretation: negative, questionable and positive, depending on a *cycle threshold* (Ct). The value of Ct fewer than 37 was defined as a positive result. A negative is the result with Ct higher than 40. A questionable result requiring another testing is the one with Ct from 37 to 40 [45, 46].

The protocol currently operating in the United States of America (the USA) is an example of a protocol requiring identification of 3 genes. The diagnosis is established when E-gene (codes coat protein), N-gene (codes nucleocapsid) and RdRP (RNA-dependent RNA polymerase) are simultaneously discovered in a sample (epipharyngeal, oropharyngeal or a nasal swab). It is obligatory to include 3 control points in the test: designedly positive, designedly negative and an internal control (to confirm synthesis of ribonucleic acid). The control points are necessary to prevent false-positive or false-negative results from occurring (elimination of mistakes in the process of a reaction setup). A test is considered positive when all three viral genes are identified and controls are positive. Interpretation of results is conducted with account taken of Ct: <37 – the test is positive; ≤40 – the test is negative; a questionable result requiring another testing – Ct=37-40. In case of 1 of the genes being identified the test is considered negative (or indefinite) [32, 38].

Many countries, for example, South Korea, do not recommend medical laboratories to use any tests other than PCR for identification of COVID-19 [38, 47].

In Russia the process of COVID-19 diagnostics is regulated by the temporary methodological recommendations of the Ministry of Health of the Russian Federation ‒Preventive measures, diagnostics and treatment of the new coronavirus infection COVID-19‖ (version 7 of June 3, 2020). PCR is recommended to be used as a diagnostic reaction, enzyme linked immunosorbent assay (ELISA) reaction can be used as an auxiliary reaction to identify immunoglobulins (Ig) of the G class. At that, the guideline offers a wider variation of study materials. Thus, the recommendations note that epipharyngeal or oropharyngeal swabs, pflegm, endotracheal aspirate,bronchoalveolar lavage, as well as blood (serum, whole blood) and urine can be used as diagnostic material [48].

ELISA reaction should be carried out when a repeated PCR test is negative and, according to the data of the conducted CT pneumonia is absent. In such a case diagnosis confirmation is done retrospectively, taking clinical presentations and IgG growth. According to the provided data, IgG appear in the blood serum of a patient in 14-21 days after they contracted infection and correlates with clinical presentations of the disease [49, 50].

In Ukraine nowadays PCR is also the main diagnostic reaction for COVID-19 establishment. The protocol implies identification of 3 viral genes: open reading frame 1 a/b — ORF1a/b gene, and also the genes confirming correctness of a received result (nucleopsid protein gene N and supercapsid protein E). Positive is a result confirming presence of three viral genes or a combination of the confirming genes N and E. At the same time it is advisory to administer parallel PCR-testing of samples from respiratory passages and feces or blood. Thus, the recommendations contain information that in patients with established viral persistence (swab from an epipharynx) viral RNA was also found in blood (30-40% of cases) and feces (50-60%). Urine tests proved to provide little information [41].

At the same time, Ministry of Health of Ukraine advises using ELISA-diagnostics (identification of Ig of the G and M classes) in order to avoid overloading PCR laboratories, but PCR remains the only reaction which can confirm the diagnosis [34, 49].

Thus, world scientific community recommends using PCR-diagnostics as a prevailing method of diagnosing COVID-19. Other laboratory and instrumental research methods can be used solely as auxiliary ones. And it is also worth mentioning that the COVID-19 pandemic is a real threat to the whole humanity, but, relying upon the system of WHO's timely information broadcasting to all the citizens of the Earth, many people who have contracted the disease, are recovering, which cannot but please [50].

Conclusion

1. Coronavirus infection (COVID-19) is an epidemiological problem of a global scale.
2. Polymerase chain reaction, based on gene sequestering and reverse transcription, remains a base for COVID-19 diagnosis establishing, although it does not exclude other laboratory and instrumental studies. World scientific community has faced the task to determine an optimal set of viral genes to be identified through PCR and design an optimal protocol of the study of virus containing material.
3. ELISA reaction can be used to control a disease course and immunity stress in post- convalescence period. It is permissible to use ELISA test as an auxiliary reaction in COVID-19 diagnostics.
4. Laboratory diagnostics does not only allow identify the ill (PCR) or those who have already recovered (ELISA), but also create a statistical database of the disease dissemination at both local and global scale.

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