## HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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CLOUD SERVICE FOR THE DIFFERENTIAL CLINICAL DIAGNOSTICS OF ACUTE RESPIRATORY VIRAL DISEASES (INCLUD-ING THOSE ASSOCIATED WITH HIGHLY CONTAGIOUS CORONAVIRUSES) WITH AN APPLICATION OF METHODS OF ARTIFICIAL INTELLIGENCE

DOI 10.25789/YMJ.2020.70.13 УДК 550.382.3:612.014.4

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Increasing population density and mobility contribute to the high incidence of the acute respiratory viral infections and the emergence of dangerous epidemic situations associated with them. The XXI century began with an epidemic (November 1, 2002 - July 31, 2003) caused by the coronavirus of Severe Acute Respiratory Syndrome (SARS-CoV) (Coronaviridae, Betacoronavirus); this was later followed by a pandemic was registered in 2009 (June 11, 2009-August 10, 2010) of the so-called Swine Influenza (H1N1) pdm09 (Orthomyxoviridae, influenzavirus A); in 2012, the Middle East Respiratory Syndrome coronavirus (MERS - COV) (Coronaviridae, Betacoronavirus) showed its epidemic potential. December 2019 was the month of the beginning of epidemic of the modern COVID-19 (Coronavirus Disease 2019), etiologically related to SARS-CoV-2 (temporarily named 2019-nCoV - 2019 novel coronavirus). March 11, 2020 World health organization has announced the beginning of the COVID-19 pandemic. The modern paradigm of mass differential diagnosis of acute respiratory diseases is based on the indication of the pathogen using polymerase chain reaction (PCR), but this, firstly, does not exclude the establishment of a preliminary differential diagnosis based on clinical data, and secondly, differential clinical diagnosis comes to the fore during major epidemic outbreaks (especially in developing countries), the scale of which exceeds the practical possibilities of laboratory diagnostics. This is the reason why diagnostic decision-making support systems are one of the most promising areas of digitalization in the medical practice. This paper presents the results of the development of a medical diagnostic service that is based on a model of medical knowledge and an intelligent decision-maker. The model of medical knowledge, in turn, includes models of definitions, medical diagnosis, medical history, and justification of the decisions made. An intelligent decision-maker generates a structured report using common medical definitions about diseases that have either been confirmed or rejected by the system, and a detailed justification of the decisions made. The developed cloud service allows users to accumulate data on the clinical manifestations of acute respiratory viral infections and to use artificial intelligence methods to generate solutions that can significantly facilitate and speed up the establishment of the preliminary diagnosis.

**Keywords:** acute respiratory viral infections, highly contagious coronaviruses, differential clinical diagnostics, cloud services, artificial intelligence.

**Introduction.** Both increasing population density and intensification of the passenger mobility that brings together distant territories of Earth contribute to a high prevalence of acute respiratory viral infections and the emergence of dangerous epidemic situations associated with these infections [8, 9, 10].

The XXI century began with an epidemic (November 1, 2002 – July 31, 2003) caused by a coronavirus of Severe Acute Respiratory Syndrome (SARS-CoV) (*Coronaviridae*, *Betacoronavirus*), which had lethality of 9,6 % (774 / 8096). The epidemic process began in the South-Eastern provinces of China after the penetration of SARS-CoV from the bats, which function as its natural reservoir (*Chiroptera*: *Microchiroptera*) first in the population of intermediate hosts - Himalayan civets (Paguma larvata) and later in the human population [10,13,18]. In 2009, a pandemic (June 11, 2009-August 10, 2010) of the so-called Swine Influenza A (H1N1) pdm09 began, which due to an application of modern vaccine technologies and the presence of etiotropic chemotherapeutic drugs became the least devastating of all the influenza pandemics known since the beginning of the XX century [6, 9, 12]. In 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Coronaviridae, Betacoronavirus) has showed its epidemic potential. Its natural foci associated with bats (Chiroptera) are located on the Arabian Peninsula, and its intermediate hosts are one-humped camels (Camelus dromedarius). "Smoldering infection" of MERS-CoV according to the World Health Orga-



nization (WHO) at the beginning of 2020 had the lethality of 34,4 % (866 / 2519), including imported cases of infection in 27 countries around the globe. The largest epidemic outbreak resulting from the import of MERS-CoV occurred in the Republic of Korea (May 11 - July 10, 2015) where lethality has reached the level of 18,5 % (35 / 189) [11, 14].

The first patient with a new disease, named COVID-19 (Coronavirus Disease 2019), was officially registered in Wuhan, the administrative center of the Eastern Chinese province of Hubei on December 8, 2019. In early January 2020, it was established that the etiological agent of COVID-19 is a new Type 2 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2)1 (Coronaviridae, Betacoronavirus), which together with the previously described SARS-CoV and the Chinese rufous horseshoe bat coronavirus (RsBtCoV - Rhinolophus sinicus coronavirus) form subgenus Sarbecovirus. The natural reservoir of SARS-CoV-2 is bats [16]. Intermediate hosts have not yet been reliably established but they appear to be pangolins (Pholidota) [17]. Currently, SARS-CoV-2, which has entered the human population, is spreading from person to person by airborne wavs.

March 11, 2020 World health organization has announced the beginning of the COVID-19 pandemic: for this date in all parts of the world, including imported cases and related epidemic outbreaks in 113 countries, the lethality for COVID-19 has reached a figure of 3,6 % (4292 / 118319) [18].

The modern paradigm of mass differential diagnosis of acute respiratory diseases is based on the indication of the pathogen using a polymerase chain reaction [4, 7, 8, 9]. However, first, this does not preclude making a preliminary differential diagnosis based on clinical data. Second, differential clinical diagnosis comes to prominence during major epidemic outbreaks (especially in developing countries), which exceed the practical capabilities of laboratory diagnostics. This is the reason why diagnostic decision-making support systems are one of the most promising areas of digitalization in the medical practice.

The purpose of this work is to develop a cloud service with an application of artificial intelligence methods to search for hypotheses about a possible differential diagnosis of patients with acute respiratory disease with justification of the decisions made by the system, which is followed by prescribing of recommendations of the possible options for clarification of the diagnosis.

**Materials and Methods.** The medical diagnostics service is based on a soft-ware shell that includes models of medical knowledge and data and an intelligent solver (decision-maker). This models of medical information include a terminology model, a model of medical diagnosis, a model of medical history, and a model of explanation of hypoteses on decision [1, 2, 3, 5] (Fig. 1).

The terminology model is designed to describe all concepts used by doctors, called findings or observations or signs, which are necessary for making diagnosis. Such definitions include descriptions of possible symptoms (complaints). methods of the physical examination of the patients, definitive and structural descriptions of laboratory and instrumental studies. The model of medical diagnostics describes the structure and causeand-effect relationships necessary to describe the clinical evidence of the diseases in dynamics of the pathological process, as well as taking into account the impact of treatment measures, and other possible events. The medical history model describes the structure used in medical institutions to describe information about a patient and includes a description of general data (sex and age of the patients, their complaints at admission, history of current disease, results of physical examination, etc.). The decision explanation model describes the structure where the intelligent solver generates a structured report using vocabulary of medical concepts. It not only contains information about the diseases either confirmed or rejected by the system, but also a detailed explanation of hypoteses on decision made specifying: what findings of the disease are / are not included in the clinical evidence of hypotheses

about diseases, and if additional observations are needed for confirmation/rejection, the system tells the doctor what observations should be obtained additionally [1,2].

Results and Discussion. The cloud service, consisting of such a software shell and knowledge base, is implemented on the IACPaaS platform in the certified Data Center of the Far Eastern Branch of the Russian Academy of Sciences. IACPaaS simultaneously supports three cloud service models: Platform as a Service (PaaS), Software as a Service (SaaS), and Desktop as a Service (DaaS).

The medical diagnostic model has the following features: description of the sets of symptoms of the diseases, including categories of users and reference ranges for laboratory and instrumental studies; formation of alternative sets of symptoms with different approaches to identify manifestations or diagnostic criteria of the disease that may differ across various medical institutions; description of the diagnosis taking into account etiology, pathogenesis, types of the course for the differential diagnosis of the diseases and selection of appropriate treatment methods; the ability to specify the measures of fuzziness of attributes such as modality, with the values "needed", "typical", "possible", and a scale the probabilities of matching characteristics to a hypothesis about the diagnosis, which can be used if the experts have an agreement on what manifestations are appropriate to use when making decisions; consideration of values and characteristics of the signs, the effects of the events to account for external influences on the patient's body at different stages of the disease; consideration of different variations of dynamics of symptom values.

Formation of a knowledge base for the diagnosis of diseases is carried out by clinicians. For this purpose, the platform has a medical knowledge base editor with an intuitive interface (Fig. 2) developed on its basis. More specifically, the symptoms of viral infections were selected according to [8, 9, 10]. Data for the new COVID-19 disease are taken from [4, 15]. About 26 disease markers



**Fig. 1.** Cloud service architecture for differential clinical diagnostics of acute respiratory viral diseases with an application of artificial intelligence methods.

<sup>&</sup>lt;sup>1</sup>The original temporary name of this virus was 2019-nCoV (novel coronavirus).

were used to describe the manifestations of acute respiratory viral infections. The periods of manifestations of these stages and clarification of the features of each symptom are identified, which allows in particular to differentiate SARS, MERS, and COVID-19 from other infections of the respiratory tract of viral etiology. At the same time, for these particularly dangerous coronaviruses, it was possible to identify a set of markers of an early stage, the peak of the disease, a light (erased) course, a medium-severe form, and a severe complication in the form of primary viral pneumonia. To confirm the development of pneumonia, the following markers should be detected by X-rays: shadows in the lungs, unilateral and bilateral dense infiltrates, areas of necrotic changes, growth of connective tissue, fibrous scars, etc.

Using data that characterize several stages of disease development, the diagnostic service checks the facts from the patient's medical history, comparing them with all variations of the clinical manifestations. The results of the verification process may indicate confirmation of the hypothesis about the disease or indicate all the diseases that this patient might theoretically have.

Conclusion. The cloud service that was developed allows users to accumulate data on the clinical manifestations of acute respiratory viral infections (including those associated with particularly dangerous coronaviruses MERS-CoV, SARS-CoV, and SARS-CoV-2) and to use artificial intelligence methods to generate solutions that can significantly facilitate and speed up the establishment of preliminary diagnosis. In this case, the service can be used globally since both the information collection unit and the decision-making rules can be adjusted with consideration of specific national standards.

► * D	ry throat [Sign] 🤌 🕕
▶*\$	Cough [Sign] 🥐 🐵
▼ ‡ St	ate of the language [Sign] 🦑
▼ A	compound sign 🥐
▼	1 [Period of dynamics] 🥏
	<ul> <li>2.0 [the lower bound of the duration (sort: Real)]</li> <li>4.0 [the upper bound of the duration (sort: Real)]</li> <li>⇒ \$ 1 day [unit (sort: String)]</li> </ul>
	▼ * The color of the language [A characteristic or trait] 🤌 🕕
	▼ Settings 🧼
	▼ 1 [Option values] 🦑
	▼ Quality values 🦑
	◊ * pale [the value (sort: String)] 🕕
	▼ modality 🥏
	◊ specificity (type: String)
▼	2 [Period of dynamics] 🦑
	2.0 [the lower bound of the duration (sort: Real)]

**Fig. 2.** Fragment of a symptom description in the medical knowledge database editor.

The research was carried out with partial financial support from the Russian Foundation for Basic Research (Projects 18-29-03131 and 19-29-01077), and The Program of the Priority Research Projects for the Comprehensive Development of the Far Eastern Branch of the Russian Academy of Sciences (Project 18-5-060).

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DOI 10.25789/YMJ.2020.70.14 УДК 616-022.7+616-093/-098

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## MICROBIOLOGICAL CHARACTERISTICS OF STREPTOCOCCUS PNEUMONIAE STRAINS ISOLATED IN YAKUTSK

Pneumococcus and pneumococcal infections are still among actively discussed problems, while there is a lack of information about the population structure in the North-East of Russia.

**Objective**: the identification of microbiological and molecular genetic characteristics of S. pneumoniae strains found during nasopharyngeal carriage in Yakutsk.

**Materials and methods**: we studied *S. pneumoniae* isolates, obtained from the discharges of nasopharynx in 69 patients from the age of 6 months to 85 years living in Yakutsk and undergoing a survey for acute and chronic diseases of the ENT organs (rhinitis, sinusitis, otitis), repeated acute respiratory viral infections and nasopharyngitis. Identification of the isolated cultures was performed using the time-of-flight mass spectrometry method on a Vitek MS analyzer. For uncertain results, we used test systems to detect *S. pneumoniae* DNA on PCR-RV. Identification of sensitivity to antimicrobial agents was determined by the disk diffusion method with an interpretation according to the EUCAST recommendations and the Clinical recommendations for determining the sensitivity of microorganisms to antimicrobial agents (version 2018-03). The microbiological analyzer Vitek II Compact was used to specify the phenotype of sensitivity / resistance.

Confirmation of species identification was carried out by amplification of the autolysin gene (lytA). Identification of serological types of the isolated *S. pneumoniae* strains was carried out using multiplex PCR. We were determining presence of genetic determinants of resistance to macrolide antibiotics *erm, mef* and *msr* as well as genes associated with the pathogenicity island PPI1 (*per, npIT, FtsW*).

**Results**: more than 80% of *S. pneumoniae* strains circulating among the population of Yakutsk are represented by serotypes 6A and 19F. In 50% of pneumococci 6A and 100% of serotype 19F pneumococci were detected all 3 genes associated with the pathogenicity island PPI1. Macrolide resistance was observed in all isolates of serotype 6A, while 80% of serotype 6A and 100% of serotype 19F showed the *ermB* resistance gene (MLSB phenotype) and 20% of serotype 6A pneumococci had the *mef* gene (M phenotype).

**Conclusions**: obtained data indicate the prevalence of virulent antibiotic resistant strains of *S. pneumoniae* among the population of Yakutsk and dictate the need for further epidemiological and microbiological studies of this problem.

Keywords: pneumococcus, nasopharyngeal carriage, virulence, resistance.

**Introduction.** Despite the insertion of mass vaccination, pneumococcus (*Streptococcus pneumoniae*) is one of the main causative agents of acute bacterial infections in children, especially under the age of 5 years [2-4].

The high incidence of pneumococcal infections is combined with a steady increase of the pneumococcus resistance to the antibacterial drugs that are most widely used in clinical practice.  $\beta$ -lactams and macrolides are the drugs of choice in the treatment of pneumococcal infections, therefore, the increase in *S. pneumoniae* resistance to these antibiotics becomes a significant clinical problem [4].

The resistance of S. pneumoniae to penicillin and other  $\beta$ -lactam antibiotics is due to a change in penicillin binding proteins (PBPs), enzymes that participate in

the final stages of cell wall synthesis [13].

The resistance to macrolides is mediated by two main mechanisms, which include changes in the binding target and antibiotic efflux from a bacterial cell. The first mechanism is due to the modification of the macrolide binding site with 23S-rR-NA as a result of its methylation, which disrupts the interaction of the antibiotic with the target. The methylation is carried out by the methylase enzyme, which is encoded by the erm gene (erythromycin ribosome methylation) and causes a high level of resistance to macrolides. About 20 varieties of erm are described, however, the ermB variant plays the greatest role in the formation of resistance in pneumococcus. Most pneumococci with ermB demonstrate cross-resistance to all macrolides, as well as to lincosamides