

OCCUPATIONAL INTERSTITIAL DISEASES: PNEUMOCONIOSIS AND CORONAVIRUS DISEASE (COVID-19). EPIDEMIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, DIAGNOSTICS, PREVENTION

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Introduction. In the structure of occupational morbidity of the population of Ukraine, pathology of the bronchopulmonary system occupies the first place. Interstitial lung diseases are among the most common diseases of the respiratory system of occupational etiology, pneumoconiosis dominates among them. The main share of cases of the disease is registered in the coal industry (70–80 % of the total level of occupational morbidity). The disease is characterized by a progressive course and the addition of serious complications in the form of chronic obstructive pulmonary disease, tuberculosis, malignant neoplasms, etc., which leads to the loss of work capacity and disability of the patient, often at a young working age. The problem has gained wide recognition both in Ukraine and at the international level. Due to its high social and economic importance, the WHO recognized the problem of eliminating pneumoconiosis in the world as one of the priorities. In Ukraine, the acute disease of COVID-19 was included in the list of occupational diseases, approved by Resolution of the Cabinet of Ministers of Ukraine dated May 13, 2020 No. 394 «On Amendments to the List of Occupational Diseases». Healthcare workers are a professional group whose risk of infection with COVID-19 is one of the highest. The occupational incidence of COVID-19 in Ukraine remains «underrecognized» for numerous social, organizational, and medical reasons, and the consequences of an acute illness in the form of interstitial changes in the lungs of a fibrous nature are extremely rarely recognized as being related to the profession. The economic damage associated with compensation for loss of working capacity, medical expenses for the treatment and rehabilitation of patients, as well as the reproduction of the workforce, makes the problem of prevention and early diagnosis of interstitial lung diseases one of the priorities in the field of occupational medicine. At the current stage, the development of new diagnostic methods that will allow detecting pathology in the early stages, objectifying the diagnosis, and effectively monitoring its course is of the exceptional importance. Based on literary sources, this article presents modern data on the main features of the coronavirus infection associated with the SARS-CoV-2 virus, which caused a pandemic in 2019, according to the definition of the World Health Organization. We also analyzed various emerging technologies and summarized current advances in pneumoconiosis and Covid-19 research to identify potential treatment targets and areas for future research. Pneumoconiosis, in turn, remains widespread throughout the world, and in recent years it has maintained a relatively high incidence rate. It is a serious global public health problem due to the lack of prevention of dust formation in the workplace, the inability to diagnose the disease in its early stages, and the limited effective methods of treating the disease. New diagnostic methods and therapeutic goals give hope for solving the clinical problems of pneumoconiosis, and various new research methods create opportunities for in-depth study. Therefore, we summarized the latest epidemiological studies and modern methods of diagnosis and treatment of pneumoconiosis and coronavirus disease.

The aim of the study – summarize the main ideas about the etiology, pathogenesis, clinical manifestations, diagnosis and preventive measures of pneumoconiosis and coronavirus disease.

Materials and methods of research. Selection of information took place using data from scientific literature and Internet resources. Data from scientific bibliographic databases «Occupational and Environmental Resources», «PubMed» were used; International Information Center for Occupational Safety and Health.

Results. Data on the incidence of pneumoconiosis and coronavirus disease are summarized, the main risk factors for the development of the disease are determined. An analysis of the diagnostic effectiveness of methods of imaging and functional diagnosis of occupational interstitial lung diseases is presented.

Conclusions. The priority of developing methods for early diagnosis of occupational interstitial lung diseases is determined by the significant share of pathology in the group of miners and medical workers who are exposed to harmful factors of the industrial environment, the need to improve the diagnosis of diseases in the early stages of development.

Key words: pneumoconiosis, COVID-19, diagnosis, prevention

Introduction

Epidemiological features of the formation of occupational lung disease

The coronavirus-2019 pandemic (coronavirus disease 2019 – COVID-19; formerly 2019-nCoV), caused by the SARS-CoV-2 virus, began in December 2019 in Hubei Province of the People's Republic of China, and on January, 20 the World Health Organization (WHO) Committee declared a global health emergency [6, 9, 13].

Coronaviruses are single-stranded RNA viruses that were first described in 1966 by Tyrell and Bynoe as causative agents of acute respiratory infections. There are four subfamilies of coronaviruses: alpha, beta, gamma, and delta coronaviruses. The SARS-CoV-2 virus is a beta coronavirus. The SARS-CoV-2 virus genome is highly homologous to the genome of the SARS-CoV virus that caused acute respiratory distress syndrome in thousands of people in 2003. However, COVID-19 is characterised by lower severity and mortality than SARS-CoV-associated ARDS. The SARS-CoV-2 virus predominantly affects the elderly and more often men than women [18, 22].

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Results of research and their discussion

A significant share of occupational pathology is occupied by COVID-19 in the modern day. For example, in Ukraine, the coronavirus infection Covid-19 (new type pneumonia) was first diagnosed on March, 3 2020 in Chernivtsi. And on March, 13 the first death due to coronavirus infection was recorded. As of November, 26 2022, there were 5297254 cases in Ukraine, of which 110 008 were lethal [7, 8].

In the first half of 2022, institutions of the Executive Directorate of the Fund received and registered 219 reports of deaths of certain categories of healthcare workers due to COVID-19.

Risk factors and susceptibility to COVID-19

The most vulnerable population is currently considered to be smokers, who, according to numerous meta-analyses, are expected to have a frequent severe course; men, people of Asian ethnicity

ty, the elderly and people with severe background diseases.

Healthcare workers, especially doctors, who have direct and prolonged contact with patients, are at a high risk, with a risk 8 times higher than in the general population. Frequent hospital-acquired infections were found among both healthcare workers and patients with other respiratory diseases. The duration of immunity after the disease is unknown. A study by Iranian scientists found that the increase in cases occurs rapidly in densely populated areas with low winds, high humidity and low levels of sun exposure.

From 1990 to 2019, the number of cases of pneumoconiosis increased by 81.1 %. The stan-

dardised prevalence rate by age was significantly higher in men. The incidence also increases with age, and is significantly higher in men. According to the Global Burden of Disease study in 2010, pneumoconiosis caused 125,000 deaths. The number of patients with dust-related respiratory diseases in Ukraine decreased significantly from 4,041 in 2013 to 713 in 2016. From 2017, there has been an increase in the number of patients with occupational diseases, with 1,145 registered cases.

The distribution of cases of occupational diseases by diagnosis among workers in Ukraine in 2013–2020 is shown in Tables 1 and 2.

Table 1

Distribution of cases of pneumoconiosis among workers by age and sex

Forms of pathologies	Men		Women		Both genders	
	middle age	average experience	middle age	average experience	middle age	average experience
All forms in Ukraine in total	51.3 ± 0.1	17.9 ± 0.1	50.4 ± 0.5	17.4 ± 0.4	51.5 ± 0.1	17.9 ± 0.1
Including: pneumoconiosis	54.4 ± 0.3	18.3 ± 0.1	59.0 ± 0.8	16.8 ± 1.0	53.5 ± 0.3	18.2 ± 0.1

Table 2

The share of pneumoconiosis diseases in the structure of occupational morbidity in Ukraine for 2014–2020

Years	2014		2015		2016		2017		2018		2019		2020	
Forms of pathologies	Absolute number	Specific weight	Absolute number	Specific weight	Absolute number	Specific weight	Absolute number	Specific weight	Absolute number	Specific weight	Absolute number	Specific weight	Absolute number	Specific weight
Total in Ukraine including:	5860	100.0	4352	100.0	1761	100.0	1599	100.0	1951	100.0	1903	100.0	2403	100.0
Respiratory diseases including:	4041	83.2	2801	64.4	896	50.9	713	44.6	928	47.6	955	50.2	1145	60.1
pneumoconiosis	1551	26.5	942	21.6	198	11.2	148	9.3	190	9.7	157	8.3	177	7.4

The main pathogenetic milestones in the development of pneumoconiosis and coronavirus infection

The pathogenesis of PC is based on the accumulation of dust containing fine particulate matter, such as silicon dioxide. Upon entering the lungs, some of the dust interacts with epithelial cells, thereby causing further activation of the NLRP3 protein, a cryopyrin of the NLR family that contains three inflammatory pathways and causes the production of proinflammatory cytokine (IL)-1 β through activation of the apoptosis-associated protein caspase enzyme, free radicals and fibroblast activation factor, which leads to fibrosis [14, 19, 27].

The substrate of the pneumoconiosis process is the so-called silicotic nodule or granuloma, which develops as a consequence of macrophage alveolitis. The nodule located in the interalveolar septum is a histiocytic granuloma devoid of giant cells. Subsequently, the granuloma transforms into a fibrohyaline nodule with an acellular centre. Silicon particles are located along the periphery of the nodule, i.e. in the zone of the youngest fibrosis [12, 22].

The excessive development of fibrosis in pneumoconiosis leads to the replacement of lung parenchyma with foci of sclerotically transformed tissue, which are partially or completely excluded from the gas exchange process. As a result, there is a decrease in volume of useful gas exchange space, which is manifested by clinical signs in the form of shortness of breath, decreased exercise tolerance, etc. Similar pathogenetic changes occur in patients with Covid pneumonia and have similar CT signs of lung parenchymal damage to pneumoconiosis, in particular, the frosted glass symptom, which occurs due to a decrease in the «airiness» of the alveoli, their partial descent or thickening of the walls [33].

SARS viruses, including SARS-CoV-2, use the transmembrane exopeptidase angiotensin-converting factor 2 (ACE2-angiotensin converting enzyme) to enter the cell, localised in a small population of well-differentiated type II alveolar cells (pneumocytes) and small intestinal enterocytes (which is why respiratory symptoms are accompanied by gastrointestinal symptoms in at least 1/3 of cases: nausea, vomiting, etc). Organs that are considered to be more sensitive to SARSCoV-2, due to their levels of ACE2 expression, are: lungs, heart, oesophagus, kidneys, bladder and ileum [27, 30]. SARS-CoV strains isolated from different hosts differ in their ability to bind to human ACE2 and, consequently, in their infectivity to humans. Epidemic strains typically have a high affinity for human ACE2 and therefore have a high potential for effective human-to-human transmission [28]. Similar to SARS-CoV, SARS-CoV-2 causes acute respiratory distress syndrome (ARDS) and acute lung failure, which are the main causes of death. It is known that gas exchange occurs through the alveoli of the lungs. Red blood cells are saturated with oxygen in the capillaries of the alveolar membrane. The alveolar walls are formed by type I and type II pneumocytes and alveolar macrophages. Type I pneumocytes cover 95 % of the alveolar surface area and provide gas exchange with blood in the lung capillaries. Pneumocytes type II are the precursors of pneumocytes type I. They are responsible for the formation of pulmonary surfactant, which prevents the alveolar walls from sticking together during breathing by reducing the surface tension of the film covering the alveolar epithelium [16, 18]. SARS viruses, infecting pneumocytes, cause their desquamation in the alveoli, contribute to alveolar dysfunction, edema and bleeding, disrupt gas exchange and lead to respiratory failure. At the same time, the amount of surfactant decreases,

and, accordingly, the ability of the lungs to expand and contract during the breathing act decreases. This process can lead to lung collapse during exhalation. As the alveoli fill with fluid, respiratory failure increases. Death occurs when the integrity of the alveolar membrane is compromised, leading to the accumulation of liquid exudates in the alveolar space, and mechanical ventilation is useless [22, 28, 30]. Very severe pneumonia develops due to the induction of an intense cytokine response by SARS-like viruses. Proinflammatory cytokines and chemokines, including IL-6, TNF α , IL-1 β , attract inflammatory cells to the site of infection. Neutrophils and cytotoxic T cells, along with cytokines, cause damage to lung tissue, including increased vascular permeability and stimulation of pulmonary fibrosis.

Features of clinical manifestations of coronavirus infection and pneumoconiosis

The spectrum of clinical symptoms of coronavirus disease is quite wide, ranging from mild symptoms to extremely severe disease with the development of ARDS and multiple organ failure. The disease can be asymptomatic [31], but the percentage of such cases is unknown. The most common clinical finding was fever (98 %), followed by cough (76 %), and myalgia/fatigue (44 %). Headache, sputum and diarrhoea were less common. The clinical course was characterised by dyspnoea in 55 % of patients and lymphopenia in 66 %. All patients with pneumonia had abnormal lung imaging findings. Acute respiratory distress syndrome developed in 29 % of patients [24], and the «frosted glass» symptom was the most common diagnostic sign on CT lung scans [15]. It is now clear that the main source of infection is the infected patient, particularly during the incubation period of the disease. Although complete information on the duration and intensity of immu-

nity to this virus is not available, it can be assumed that immunity in COVID-19, as in other infections caused by other coronavirus families, is unstable and reinfection is possible.

Ling Mao and colleagues [33] showed that 78–88 % of patients with severe COVID-19 showed signs of central nervous system (CNS) damage in the form of impaired consciousness and cerebrovascular disorders (dizziness, headache), decreased taste (hypogausia) and olfactory sensitivity (hyposmia). Loss of consciousness is mostly observed in cases where the course of COVID-19 was accompanied by the development of an ischaemic or haemorrhagic stroke. However, the potential for CNS damage by SARS-CoV-2 virus remains poorly understood. The presence of the SARS-CoV-2 virus gene in the cerebrospinal fluid of a patient with COVID-19 and neurological disorders was first identified on 4 March 2020 by researchers from Beijing Ditan Hospital (China) [7, 12, 21]. Experimental studies using transgenic mice have shown that coronaviruses can penetrate the brain when injected intranasally. It is assumed that the SARS-CoV-2 virus, like other coronaviruses, first infects peripheral nerve endings and then penetrates the CNS tissue via the transsynaptic transfer mechanism, mainly affecting cells in the thalamus and brainstem [14, 18].

Clinical manifestations of PC are not specific. In the initial stages, they are almost always absent, and the first complaints often appear when a secondary infection is present.

Often the disease is detected incidentally by X-ray diagnostics during preventive examinations. The patient may be disturbed by mild dyspnoea or cough. In the early period of the disease, a mild pleural friction noise is often heard in the lower chest due to inflammatory and sclerotic processes in the pleura [11, 12].

As the disease progresses and a secondary infection occurs, the cough intensifies and is accompanied by sputum production, and shortness of breath increases. During this period, the examination of the patient reveals signs of bronchitis and pulmonary emphysema. Against the background of rigid breathing, dry, and with the progression of the process, subcretic and moist rales are heard. Emphysema determines the appearance of a box percussion tone. Rupture of subpleural emphysematous bullae sometimes leads to spontaneous pneumothorax. Often at this stage, PC is complicated by bronchiectasis.

In the mechanism of respiratory failure, along with impaired bronchial patency, increased deforming bronchitis, and the development of pulmonary emphysema, reactive processes, gradual death of nerve fibres and ganglia, leading to disintegration of the function of the lung receptor systems, play a role. Progressive pulmonary insufficiency leads to an increase in the symptoms of chronic pulmonary heart disease [13, 14].

Analysis and evaluation of the effectiveness of diagnostic methods for pneumoconiosis and coronavirus infection

To detect COVID-19 pneumonia, its complications, differential diagnosis with other lung diseases, as well as to determine the severity and dynamics of changes, and to assess the effectiveness of therapy, radiological diagnostic methods are used: plain radiography of the lungs (PR), computed tomography of the lungs (CT) (Figure), and ultrasound of the lungs and pleural cavities (US). Standard PR has a low sensitivity in detecting initial lung changes in the first days of the disease and therefore cannot be used for early diagnosis. Informativeness of PR increases with the duration of pneumonia. The method allows to

confidently detect severe forms of pneumonia and pulmonary edema of various nature. Using a portable X-ray machine, the examination can be performed on bedridden patients. In severe cases of pneumonia in COVID-19, unilateral or bilateral pulmonary infiltrates are noted on the images [8, 11]. CT scan has the highest sensitivity in detecting lung changes characteristic of COVID-19 pneumonia. The use of CT is advisable for the initial assessment of the chest cavity in patients with severe progressive forms of the disease, as well as for the differential diagnosis of the detected changes and assessment of the dynamics of the process. CT scan reveals characteristic changes in the lungs of patients with COVID-19: multiple bilateral partial and subsegmental areas of opacities in the form of frosted glass or compaction (usually peripheral or posterior, mostly in the lower lobes, less often in the right lower lobe), a «chaotic paving stone» pattern, pulmonary bronchograms, reversed halo patterns around the lobe/reversed perilobular patterns interlobular or septal thickening (smooth or irregular), adjacent pleural thickening, subpleural lesions, pleural effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, round cystic changes. Older people, compared to younger patients, have more extensive lung lobe involvement, interstitial changes, and pleural thickening [14, 19]. Due to the technical difficulty of performing PR and CT in patients on mechanical ventilation, it is recommended to use ultrasound with portable devices to monitor the lung condition. If the correct methodology is followed, reasonable indications are chosen and trained medical personnel are available, this examination is highly sensitive in detecting interstitial changes and consolidations in the lung tissue with subpleural location [10].

Specific diagnostic methods

1. Reverse transcription polymerase chain reaction for detection of coronavirus nucleic acid in material from a patient (gold standard). Molecular testing is required to confirm the diagnosis. Overall sensitivity is 89 %. Samples are taken from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs or washings) in outpatients and/or lower respiratory tract samples (sputum and/or endotracheal aspirate or bronchoalveolar lavage) in patients with more severe respiratory disease. Additional clinical specimens (e.g. blood, faeces, urine) may be collected. Samples should be collected with appropriate infection prevention and control measures, and the high risk of aerosolisation during lower respiratory tract sampling should be taken into account [15, 19].

2. A rapid test for the detection of antibodies to coronavirus in the blood using an immunochromatographic method (a positive result can be obtained on the 5th-6th day after the onset of the disease). The sensitivity of this method is low [12].

The main method of PC diagnosis is radiological. The current classification of PC codes the existing radiological changes in the lungs by form (nodular, interstitial, nodular), degree of their spread per unit area or category. There are 12 categories of pneumoconiosis, which are determined by comparing the available radiographs with standard radiographs. In addition, changes in the pleura are subject to registration: localised pleural thickening, diffuse pleural thickening and obliteration of the costodiaphragmatic sinus.

A more accurate and informative method of diagnosing PC is CT scanning. Scientific studies on its use for the diagnosis of PC mainly concern such forms as silicosis and asbestosis [8, 14]. Studies conducted in patients with disseminated lung diseases have established a higher informativeness of CT scan for the detection of small opacities located in subpleural areas, as well as for the diagnosis of pleural thickening [7]. There is often a diffuse (usually perilymphatic) distribution of small nodules throughout the lungs, which tend to favour the upper lungs. About 30 % of patients

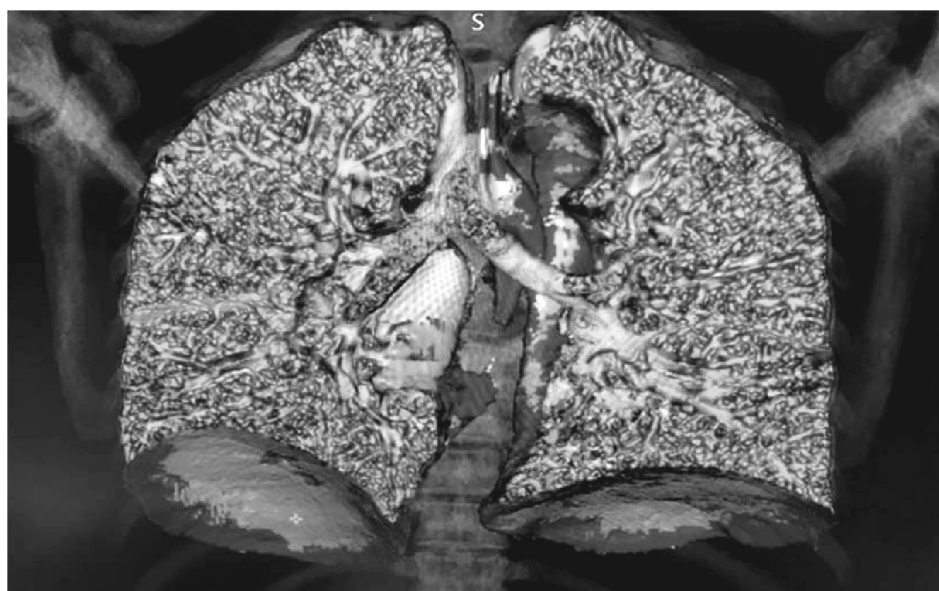


Figure. 3D SCT-Canon lung parenchyma

have calcifications with nodules on CT scan. Enlargement of the thoracic or mediastinal lymph nodes has also been reported in 30 % of patients.

N. L. Muller found that out of 50 miners without radiological signs of PC, 11 (23 %) had CT signs of the disease. Moreira V.B. showed that in 77.5 % of cases, CT scanning was more informative for the diagnosis of silicosis compared to X-ray examination [15, 18].

Pulmonary densitometry is also used to assess the condition of the lungs after lobectomy, when spirometry was diagnostically ineffective, as well as as a predictor of pulmonary hypertension in systemic sclerosis, and to determine perfusion defects in pulmonary embolism [8, 9].

V. Petroulia, 2018 also showed the effectiveness of the computerised densitometry technique in patients with idiopathic pulmonary fibrosis. The results of the study showed a significant difference in the index when performing this method on inspiration and expiration, and also explained the presence of signs of parenchymal damage in visually unchanged areas of the lungs. The study confirmed the theory of alveolar collapse resulting from pulmonary fibrosis.

It should be noted that scientific developments on the use of computerised densitometry for the diagnosis of occupational interstitial lung diseases are few. For example, there is a study on the dependence of pulmonary densitometry parameters on the parameters of the forced oscillation technique (FOT) in patients with silicosis. The authors note that the method allows detecting heterogeneity of the lung parenchyma and proves the relationship between the size of non-aerated parenchyma zones according to FOT parameters, but at the same time note that more detailed studies are needed to definitively determine the effectiveness of the technique [27, 30, 31].

Chinese authors, in particular P. Liu, 2002, found a decrease in the percentage of zones with a density index of -983 (-) -779 HU according to computerised densitometry from 87.31 % in the control group to 72.99 % in patients with stage III pneumoconiosis ($p < 0.01$). Another study by L. Hia, 2012, confirmed a higher density of lung parenchyma in patients with pneumoconiosis compared to the control group when analysing CT scans at 3 levels. These studies did not include a study of the dependence of densitometry on clinical and functional studies.

Studies have also been conducted on CT and pulmonary densitometry in non-working miners with no signs of pneumoconiosis and with category 0/1 disease, which revealed a higher density of lung parenchyma in the group of miners with the highest dust exposure. At the same time, the authors emphasise the limited reliability of the data due to the variability of lung density in healthy individuals [18, 19].

MRI signs of pneumoconiosis usually appears as a low signal intensity lesion on T1 and T2 weighted images. This is in contrast to neoplastic processes, which have high signal intensity on T2-weighted images. When contrast is administered, pneumoconiosis lesions often show peripheral enhancement.

The role of PET-CT in the diagnosis of malignancies in the setting of pneumoconiosis remains unclear, as both lung cancer and fibrous masses of complicated pneumoconiosis can demonstrate increased FDG uptake.

Key measures to prevent pneumoconiosis and COVID-19

Prevention of pneumoconiosis consists of the above-mentioned general measures implemented to address a specific problem.

Methods that focus on the production process:

- 1) eliminating harmful factors from production processes or significantly reducing their impact. The first direction is the rejection of open-pit mining and the refusal to use explosives in mining operations, which will significantly reduce the level of dust generation, the second direction is the reduction of dust generation and dedusting of the air, which is achieved through wet drilling, adequate ventilation and dust deposition;
- 2) mechanisation and automation of production. In modern mining operations, large machines are increasingly used, for example, for the construction of transport tunnels, the technological level of which allows to completely avoid problems associated with excessive dust generation. Unfortunately, their large size does not yet allow them to be used for mining.

Given the specifics of mining, there is little centralisation of management.

Methods aimed at protecting employees:

- 1) initial and periodic medical examinations are conducted in accordance with paragraphs 3.1 and 3.2 of Annex 4 to Order of the Ministry of Health of Ukraine No. 246. In addition to general examinations, employees are examined by an otorhinolaryngologist, a phthisiologist, and, if necessary, a dermatologist and an oncologist. Employees undergo X-ray radiography and external respiratory function tests. In addition to the general contraindications to working with hazardous factors, additional contraindications for those working with silica dust include atrophic changes in the upper respiratory tract, chronic diseases of the bronchopulmonary system, allergic diseases and tuberculosis;

- 2) use of personal protective equipment – respirators, helmets or suits with clean air supply, etc;
- 3) joint ultraviolet irradiation, alkaline inhalations, joint and breathing exercises are recommended; special nutrition is organised to normalise protein metabolism and inhibit the coniotic process.

The primary prevention measures for COVID-19 include the following:

- maintaining a safe distance from other people (at least 1 metre), even if they do not appear to be ill;
- wearing a mask when among people, especially when you are indoors or cannot physically distance yourself;
- preferring open areas and well-ventilated rooms. If you are indoors, open a window;
- wash hands with soap and water or use an alcohol-based hand sanitizer;
- vaccination, which remains the most effective strategy for preventing severe illness and death due to COVID-19 infection with the recent and currently circulating variants, i.e. Delta and Omicron. Hospitalisation rates in the US in autumn 2021 were 8–10 times higher in unvaccinated people than in vaccinated people. Unvaccinated individuals also had a 20-fold higher risk of dying from COVID-19 than vaccinated individuals during this time period. Data from South Africa shows that 2 doses of the Pfizer-BioNTech vaccine are 70 % effective against the Omicron variant.

In most situations, mRNA vaccines are preferred to adenovirus vector vaccine for initial series and booster doses because of the risk of serious adverse events. There is a plausible causal link between adenovirus vector vaccine and the rare and serious adverse event of vaccine-induced thrombopenic syndrome.

Conclusions

1. Despite the large number of scientific studies that extensively cover the etiological and pathogenetic aspects of occupational interstitial diseases and clinical manifestations of pathology, there are still a number of issues that are not fully covered and need to be improved. This primarily concerns the diagnosis of pathology at late stages of development, when the reversal of the disease is impossible or too difficult, and treatment and rehabilitation are ineffective.

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