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DISTRIBUTION OF CLINICAL FORMS OF NEWLY DETECTED PULMONARY TUBERCULOSIS AMONG ADULT POPULATION OF THE SAKHA REPUBLIC (YAKUTIA) DURING THE PANDEMIC OF NOVEL CORONAVIRUS INFECTION

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With an aim to study the impact of restrictive measures against COVID-19 pandemic on epidemiologic situation with tuberculosis (TB), we analyzed key epidemiological data and distribution of clinical forms of newly detected pulmonary TB (PTB) among adult population of the Sakha Republic (Yakutia), with a separate analysis for the Arctic zone, as an example of a territory with low population density and limited transport accessibility.

For the study purpose, we used data from federal statistical recording and reporting forms, and data from TB medical patient database of the Sakha Republic (Yakutia). Rates for adult newly diagnosed PTB cases were analyzed for two pandemic years (2020-2021) against two pre-pandemic years (2018-2019). Statistical methods of choice were Pearson’s correlation coefficient and data weighing by chest x-ray coverage trend.

Study findings showed that the period of strengthened anti-epidemic and sanitation measures against novel coronavirus infection (COVID-19) was followed by substantial decrease in epidemiologic rates for TB, but, at the same time, profoundly deteriorated situation with delays in TB detection.

In the Arctic zone of Yakutia, epidemiologic rates for TB were showing decrease during restrictive measures, but generally remain higher than mean republic rates.

Increase in proportion of new adult patients with advanced disease forms was observed, together with the fact the TB detection rates in the Arctic zone were lower compared to mean republic detection rates.

The scope and quality of preventive checkups for TB correlated in a statistically significant way with the distribution of clinical forms of TB among newly diagnosed patients.

In conclusion, to reduce the rate of detections of MTB-positive destructive TB forms, prevention and detection measures will need to be strengthened, and should include universal annual chest x-ray screening of the population aged 15 and above.

Keywords: pulmonary tuberculosis, detection, novel coronavirus infection, COVID-19, Yakutia, Arctic.

Introduction. Steadily for the last years, the Sakha Republic (Yakutia) has been implementing advancements in public TB services aimed to meet local needs caused by difficult transport accessibility. These efforts, which included the organisation of centralized treatment for patients with multidrug- and extensively drug-resistant (MDR, XDR) *M.tuberculosis* (MTB), high-tech surgical treatment, and early population screening for tuberculosis (TB), have led to appreciable improvement and stabilization of the epidemiologic situation with TB.

During the pandemic of novel coronavirus infection (COVID-19), global wide anti-epidemic restrictive measures caused numerous readjustments in TB case detection, diagnosis and treatment routines (2,3,5,10). Several authors have commented on lower rates of coverage with preventive checkups for TB in 2020-2021 as a cause of decrease in TB incidence rates, although, at the same time, decrease in coverage with unscheduled exams for TB among TB case contacts was noticed likewise (1,7-9).

Novel coronavirus infection pandemic that emerged in 2019 demanded complete reset of healthcare systems across the world, and emphasized the importance of mass anti-epidemic measures aimed at reducing the threat of infectious disease spread. TB services during the pandemic faced the need to adjust to restrictive measures, which were developed and implemented primarily with the purpose of deescalating the threat of infection spread, but ended up largely neglecting the algorithms of proper dealing with socially significant diseases (1,4,10). These circumstances have urged the leading federal and regional TB centers in Russian Federation to estimate risks and develop their own interventions and workflow schemes adapted to meet local needs, but they proved insufficient to maintain the stable decreasing trend in TB incidence and mortality achieved during previous years (3,8). Restrictive measures against the spread of coronavirus infection resulted in major reduction of population coverage with preventive checkups for TB, and, eventually, steep decrease in TB incidence (8,10-13,15).

A number of authors predicted the risks associated with the upsurge in numbers of advanced and sputum-positive TB cases, the groups presenting the highest epidemiologic hazard, and, as it turned

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out, these concerns were confirmed by our study findings (9,11,14).

Epidemiologic situation with TB in Sakha Republic (Yakutia) showed a gradual improvement trend until the onset of COVID-19 pandemic. During 10 pre-pandemic years (2009 to 2019) TB incidence had decreased by 30.3%, mortality from TB had decreased by 58.5%, presence of necrotic lesions in newly identified cases had decreased by 28.5%, while coverage with preventive chest x-rays for TB had increased by 23.2%.

By the Decree of the Head of the Sakha Republic issued on March 17, 2020, a heightened preparedness regime was announced in the republic, mandating measures to be taken to counteract the spread of novel coronavirus infection (COVID-19). Anti-epidemic measures included discontinuation of national health checkup program (dispensarization) and mass preventive checkups (chest x-rays), which substantially diminished the threat of infection spread (coronavirus, and other communicable infections, TB as well), but caused a new threat – late detection of active TB cases. Two years before the pandemic, mean total incidence of TB over Yakutia was 47.9/100 000. During pandemic, the rate had decreased by 39.5%, but the proportion of destructive TB forms had escalated by 15.9%. Total population coverage with preventive checkups for TB had reduced by 18.1%, which caused changes in the distribution of clinical forms of newly diagnosed TB.

The present study was focused on the changing incidence of adult TB, while the consequences of work incapacity and mortality among adult population are directly associated with economic losses of a country, and were demonstrated in our previous study (2).

Material and methods. For this study, we used rates from federal statistical recording and reporting forms ('Form 33', 'Form 30', 'TB-03'), patient lists from 'Contingent' and 'Treatment control' databases maintained within 'Barclay' HDBMS (health database management system), and data from Federal TB Register of the Sakha Republic (Yakutia). Rates for adult patients (aged 18 or above) newly diagnosed with pulmonary TB (PTB) were analyzed for two pandemic years (2020-2021) against two pre-pandemic years (2018-2019). Data for Arctic zone of Yakutia were analyzed separately, to focus specifically on territories with low population density (0.01-0.08/km2) and limited transport accessibility. Relationships between changes in variables over time were assessed using Pearson's correlation coefficient and Kendall's Tau rank correlation coefficient. To assess associations between trends, variables were weighed by values of chest x-ray coverage. New TB case was considered an 'advanced case' if the patient was both MTB-positive and had necrotic lesions in the lungs. Calculations were performed using Microsoft Office Excel 2019, and IBM SPSS Statistics software.

Results. During COVID-19 pandemic, restrictive measures were brought to effect in Sakha Republic (Yakutia), which negatively impacted population coverage with mass chest x-rays for TB, further leading to changes in the rates reflecting effectiveness of TB detection by primary care health facilities.

Pearson's correlation analysis was used to assess the significance of changes in variables over time, during pre-pandemic (2018-2019) and pandemic (2020-2021) periods (see Table 1).

Adult population coverage with chest x-rays decreased by 18.6% (in the Arctic zone by 14.9%) (Fig. 1). Alongside with that, incidence of PTB among adult population decreased sharply, both over Yakutia and in Arctic zone: by 41.3% and 32.7%, respectively. Fig. 1 shows upsurge in mean proportions of newly diagnosed adult PTB cases with necrotic lesions, both over the entire republic (by 19.1%) and in the Arctic zone (by 5.3%). Also, rates in the Arctic zone exceeded all-republic rates by 16.6% before pandemic, and by 4.3% during pandemic.

Strong and meaningful linear cor-

Table 1

Correlation analysis of variables for adult population; Sakha Republic (Yakutia); Periods 2018-2019 and 2020-2021

Variable	Decline/growth rate (%)	Pearson's r-coefficient	Two-tailed significance level
Sakha Republic (Yakutia)			
Incidence	-41.3	0.530558	0.001043
Chest x-ray coverage	-18.6	0.776775	0.000000
Proportion of patients avoiding chest x-ray for ≥2 years	11.1	0.767547	0.000000
Proportion of advanced PTB cases	69.9	0.491074	0.002556
Arctic zone			
Incidence	-32.7	0.534530	0.059842
Chest x-ray coverage	-14.9	0.808062	0.000831
Proportion of patients avoiding chest x-ray for ≥2 years	160.0	0.839557	0.000331
Proportion of advanced PTB cases	48.6	0.264876	0.381808*

* Pearson's correlation did not show meaningful correlation (due to presence of outliers). Whenever Kendall's τ coefficient was employed, coefficient value was -0.536925, significance level was -0.013316, which were considered as the presence of association between attributes

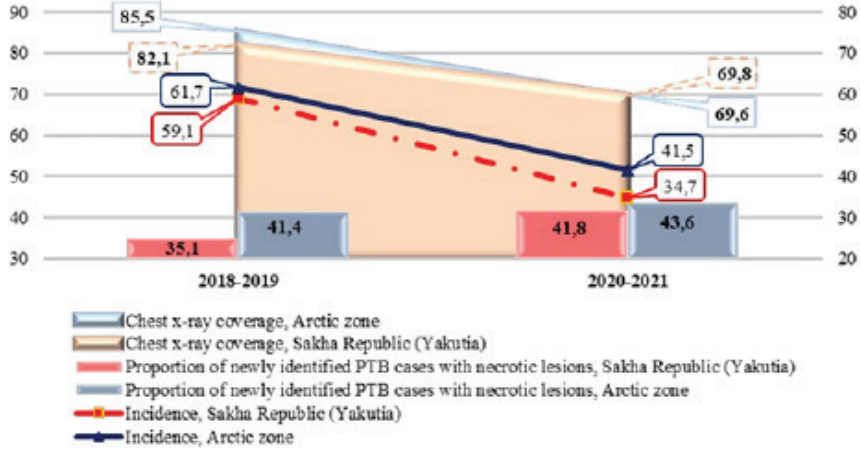

Fig. 1. Incidence of pulmonary TB (PTB), coverage with chest x-rays, and proportions of new adult PTB cases with necrotic lesions; Sakha Republic (Yakutia) and Arctic zone; Years 2018-2021

relation was observed between PTB incidence decline rates and chest x-ray coverage decline rates, among the adult population, analyzed in breakdown by municipal entities (Table 2). There was a linear correlation between chest x-ray coverage decline rates and the proportions of new PTB cases with necrotic lesions, visible in breakdown by municipal entities, but the correlation was inverse and negligible. At the same time, a strong correlation was observed between chest x-ray coverage rates and the proportions of advanced PTB cases among newly diagnosed patients (Table 2).

It is calling for attention, that during pandemic years, proportions of population avoiding chest x-rays for 2 or more years had increased by 11.1% in entire republic, and by a factor of 2.6 in the Arctic zone (Table 2). Proportion of new TB cases detected by visit to primary care facility had increased by 46.8% in the republic overall, and by a factor of 2.6 in the Arctic zone (Fig. 2).

Over time, mean proportions of advanced cases among new patients increased by 69.9% in the republic, and by 48.6% in the Arctic zone. Importantly, the proportion of patients with caseous pneumonia among newly diagnosed advanced cases had risen by 35.4% in the republic, and by 98.4% in the Arctic zone (Fig. 3).

Rates describing the proportions of MTB-positive (MTB+) patients and proportions of patients with MDR/XDR TB were controversial, and require further evaluation. In the Arctic zone, these rates showed negative trend (decrease by 24.0 and 29.6%, respectively), compared to mean all-republic rates (decrease in proportion of MTB+ cases by 9.1%, and increase in proportion of MDR/XDR cases by 29.6%). After subjecting the data to correlation analysis, we found no significant differences in variable changes over time periods (Table 2).

Presented in Table 2 is paired correlation analysis of variables with their significance levels, for chest x-ray coverage, incidence of TB, and delays in TB detection.

Reduced population coverage with preventive chest x-ray was a statistically significant cause of reduced TB incidence, and was related to the rise in proportion of advanced cases among new PTB cases, both over the entire republic, and over Arctic districts. Increase

Table 2

Paired correlation analysis of decline/growth rates for new adult cases of pulmonary TB (PTB); Sakha Republic (Yakutia) and Arctic zone; Periods 2018-2019 and 2020-2021*

Paired variables (decline/growth rates)	M±m	Pearson's r-coefficient	Two-tailed significance level
Sakha Republic (Yakutia)			
Chest x-ray coverage/Incidence	19.3±0.29 83.4±4.51	0.122412***	0.004817
Chest x-ray coverage/ Proportion of advanced PTB cases	19.3±0.29 91.7±5.17	0.289103***	0.000000
Proportion of population avoiding chest x-rays for 2 or more years/ Proportion of new cases with necrotic lesions	109.7±10.72 35.7±5.17	-0.124006***	0.004290
Proportion of population avoiding chest x-rays for 2 or more years/ Proportion of cases discovered by visit to health facility	109.7±10.72 51.5±4.39	0.143629***	0.000925
Incidence/ Proportion of advanced PTB cases	83.4±4.51 91.7±5.17	-0.091671**	0.035070
Incidence/ Proportion of MDR/XDR cases	83.4±4.51 5.5±3.38	-0.120161***	0.005661
Proportion of cases discovered by visit to health facility/ Proportion of advanced PTB cases	51.5±4.39 91.7±5.17	0.520253***	0.000000
Arctic zone			
Chest x-ray coverage/Incidence	20.5±0.50 60.8±6.37	0.355492***	0.000000
Chest x-ray coverage/ Proportion of advanced PTB cases	20.5±0.50 133.3±10.01	0.760004***	0.000000
Proportion of population avoiding chest x-rays for 2 or more years/ Proportion of new cases with necrotic lesions	220.5±24.23 -5.93±4.51	0.407058***	0.000000
Proportion of population avoiding chest x-rays for 2 or more years/ Proportion of cases discovered by visit to health facility	220.5±24.23 71.7±6.45	-0.073506 (нет корреляции)	0.302107
Incidence/ Proportion of advanced PTB cases	60.8±6.37 133.3±10.01	0.169259**	0.016838
Incidence/ Proportion of MDR/XDR cases	60.8±6.37 -5.4±4.73	-0.423332***	0.000000
Proportion of cases discovered by visit to health facility/ Proportion of advanced PTB cases	71.7±6.45 133.3±10.01	0.386985***	0.000000

* Data sets were subjected to weighing. ** Correlation was significant at 0.05 (two-tailed significance). *** Correlation was significant at 0.01 (two-tailed significance).

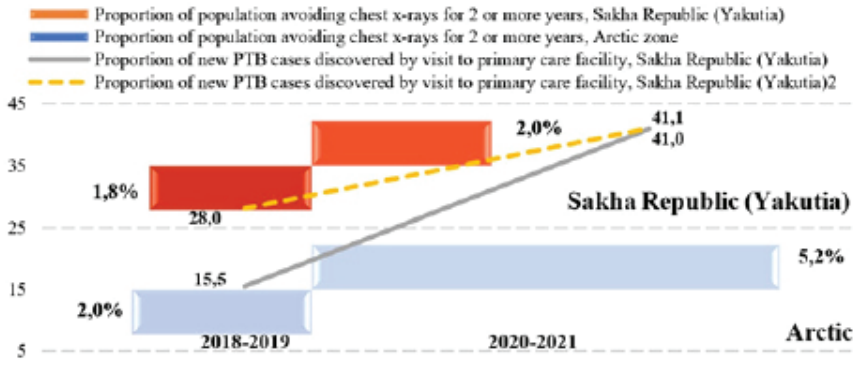

Fig. 2. Proportions of population avoiding chest x-rays for ≥2 years compared to proportions of new PTB cases discovered by vizit to primary care facility; Sakha Republic (Yakutia) and Artic zone; Periods 2018-2019 and 2020-2021

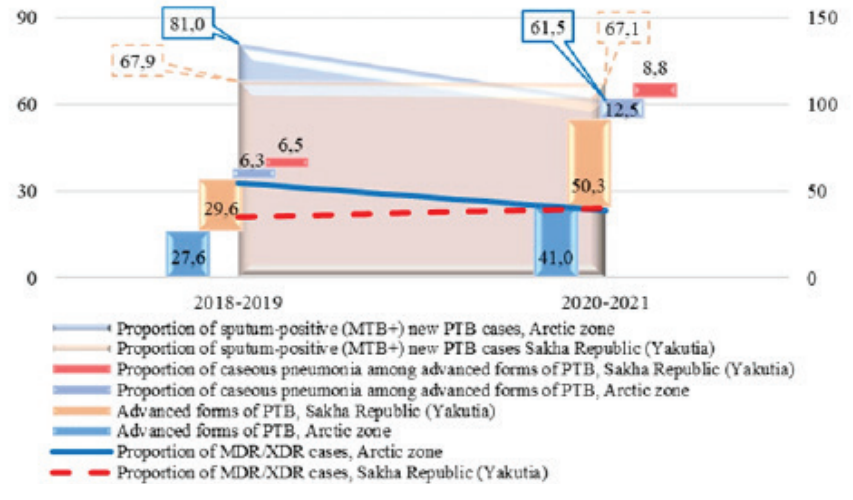

Fig. 3. Changes in clinical forms of new adult (aged 18 and above) pulmonary TB (PTB) cases over time; Periods 2018-2019 and 2020-2021 (%)

in proportion of population avoiding chest x-rays for 2 or more years was significantly associated both with the proportion of new cases with necrotic lesions, and with the proportion of cases discovered by visit to health facility. In the Arctic zone, the latter two rates showed no correlation.

Correlations presented above point at statistically significant association existing between reduced population coverage with chest x-ray screening and lower quality of TB detection. Furthermore, a marked aggravation among new cases of PTB was observed in our study, which was reflected by meaningful correlation between TB incidence rates and both the proportions of advanced cases, and proportions of patients with MDR/XDR TB.

Conclusion. Presented study results together with summarized experience reported by other authors showed that restrictive measures caused by COVID-19 pandemic had, without doubt, prevented the spread of this highly dangerous infection and the spread of other communicable infections as well, including TB. But the aspect largely missed out was that discontinuation of mass preventive checkups for TB fueled the threat associated with late TB detection, emergence of hidden (undetected) infection sources, including infection with MDR/XDR MTB as causative agent, all of which can adversely impact the incidence of TB and the prevalence of advanced clinical forms of the disease.

COVID-19 pandemic in the Sakha Republic (Yakutia) was associated with noticeable reduction in epidemiologic rates for TB incidence, mortality, and prevalence. But simultaneously, we observed escalation in proportions of patients with advanced forms of TB (rise in detections of necrotic lesions and MDR/XDR MTB), and in proportions of patients with TB discovered by visit to primary care facility.

In our view, to reduce the rate of detections of PTB forms presenting high epidemiological danger, and to reduce mortality from TB, we will need to strengthen efforts for early detection of TB by universal chest x-ray screening of the population aged 15 and above.

Further analysis of trends in epidemiologic rates and distribution of clinical forms of PTB is needed to assess the performance of primary care services in terms of TB prevention and early TB detection, and next, to adopt necessary managerial decisions at the level of regional healthcare authorities.

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ASSOCIATION OF DELETION POLYMORPHISMS OF THE *GSTM1* AND *GSTT1* GENES WITH THE DEGREE OF LUNG DAMAGE IN ELDERLY PEOPLE AFTER COVID-19

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A feature of the SARS-CoV-2 virus, unlike other respiratory infections affecting the human body, is a rather high virulence and mortality. It has been established that severe forms of the disease are more common in elderly people with concomitant diseases. It has been established that free radical lipid oxidation plays an essential role in the pathogenesis of COVID-19. The body's antioxidant defense system prevents damage to cells and tissues from initiating free radical reactions. The family of enzymes glutathione-S-transferase (GST; EC 2.5.1.18) is interesting for research. The aim of this work was to analyze the association of polymorphisms of the *GSTM1* and *GSTT1* genes with the degree of lung damage in elderly people who had COVID-19. A survey of 51 elderly volunteers who had coronavirus infection aged 60 to 75 years (average age: 64.470± 0.602 years) was conducted. Informed consent to the study was obtained from all participants of the study (according to the protocol of the Ethics Committee of the YSC CMP No. 52 dated March 24, 2021, decision 1). Identification of samples by the GSTT1 and GSTM1 genes was carried out using polymerase chain reaction (PCR) according to the method described in the work of Zehra et al. (2018). According to the data obtained by us, 74.50% of all surveyed elderly people suffered a coronavirus infection with a mild degree of lung damage, and 25.49% with a severe degree. The results of our study show that the combination of zero deletion genotypes GSTM1 and GSTT1 are a risk factor for the development of severe lung lesions in elderly people in Yakutia.

Keywords: glutathione-S-transferase, *GSTM1* and *GSTT1* genes, deletion polymorphisms, COVID-19, SARS-CoV-2.

Introduction. The SARS-CoV-2 virus differs from other respiratory infections by its rather high virulence and mortality. Many researchers have found that severe forms of the disease are more common in elderly people with concomitant diseases: diabetes mellitus, cardiovascular, etc. [4].

It has been established that free radical lipid oxidation plays an essential role in the pathogenesis of COVID-19 [1]. The SARS-CoV-2 virus initiates the production of free radicals and inhibits antioxidant protection by suppressing the expression of the transcription factor Nrf2 (nuclear factor E2-related factor 2) [17]. Toxic products of lipid peroxidation are involved in damage to cells and tissues. Neutralization of toxic products of lipid peroxidation is carried out by the enzyme glutathione S-transferase, reducing the intensification of free radical oxidation of lipids [6,15].

Glutathione-S-transferases (GST; EC 2.5.1.18) are a large and widespread family of enzymes that are divided into three main groups: cytosolic; mitochondrial; microsomal. In humans, GST enzymes are mainly represented by the cytosolic family. There are 7 classes of cytosolic GST enzymes (α, μ, π, θ, σ, ω, ζ), which include 17 isoforms of the enzyme, each encoded by a separate gene or a group of genes located on different chromosomes [2]. The enzymes encoded by the GSTM1 and GSTT1 genes are the most studied, well expressed in human lung tissues, their genes are located on chromosomes 1p13.3 and 22q11.23, respectively [14]. A feature of these *GSTM1*

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