Dynamics of drug sustainability *Mycobacterium tuberculosis* in the Belgorod region for the period of 2008–2017

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ABSTRACT

Aim of the study: to assess and compare the structure and dynamics of Mycobacterium tuberculosis drug resistance to anti-tuberculosis drugs, including multiple and broad, in the Belgorod region in newly diagnosed patients and patients with relapses of tuberculosis. **Methodology:** the article analyzed the structure and dynamics of drug resistance of Mycobacterium tuberculosis to the main and reserve anti-tuberculosis drugs for the years 2008-2017 in the Belgorod region. The authors used data from statistical accounting forms 07-TB and the centralized bacteriological laboratory. For the ten-year period 2008 - 2017 in the Belgorod region, against the background of a happy tuberculosis epidemiological situation, a decrease in morbidity and mortality, there has been a general increase in the resistance of the pathogen to anti-tuberculosis drugs. An alarming tendency to an increase in the wide drug resistance of Mycobacterium tuberculosis strains is registered, which is an extremely unfavourable sign, significantly complicates the appointment of adequate therapy to patients and reduces the effectiveness of treatment. **Conclusion:** all of the above emphasizes the importance of monitoring the drug resistance of Mycobacterium tuberculosis, which is an integral part of controlling the spread of this infectious disease. It is necessary to continue this work, which will make it possible to predict the risk of spreading drug-resistant tuberculosis and differentiate the approach to anti-epidemic measures at the regional level.

KEY WORDS: Anti-epidemic measures, Antituberculosis drugs, Drug resistance, *Mycobacterium tuberculosis* strains

INTRODUCTION

The World Health Organization (WHO) notes that tuberculosis (TB) remains the most deadly infectious disease in the world today. In 2017, 10 million people became infected with TB, and for 1.6 million more, it was the cause of death.[1]

WHO confirms that the problem of multidrug-resistant TB has not been resolved yet. Annually in the world, 580 thousand patients fall ill with multidrug-resistant TB, a characteristic feature of which is high mortality. The risk of a patient with multidrug resistance to die from TB is at least 40%.

Among patients with multidrug-resistant TB, about 9–10% of patients with extensive drug resistant have been identified, which adversely affects the outcome of treatment.[2]

The spread of drug-resistant TB indicates a low efficacy of anti-epidemic measures, including a lack of control over the use of anti-TB drugs.[3,4]

The Russian Federation is among the countries with the largest number of multidrug-resistant TB, which is caused by both the relatively high incidence of TB and the high proportion of drug resistance among patients.[5,6]

Until now, the Russian Federation has not included extensive drug-resistant TB in the accounting and reporting forms of the national statistical system; therefore, representative information on the spread of extensive drug-resistant TB is available only for a few Russian subjects, where selective studies were conducted or regional monitoring systems were functioning.[7]

In the Belgorod region, there is a regional system of routine epidemiological monitoring, which provides for the collection of data on bacterial excretion and resistance to anti-TB drugs for all patients.[8,9]

The Belgorod region is characterized by a prosperous epidemiological situation with respect to TB. For

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the analyzed period, the incidence rate decreased by 70.0%, from 57.0 to 17.1/100 thousand of the population; mortality rate decreased by 80.8%, from 5.2 in 2008 up to 1.0/100 thousand population in 2017.

However, the proportion of patients with multidrug resistance does not decrease. On the contrary, this indicator increased among newly diagnosed patients from 22.0 to 29.3%; and among relapses, it remained at a high level and amounted to 72.4% in 2017.[10,11]

The above dictates the urgent need to analyze the structure and development trends of drug resistance of the TB pathogen in the Belgorod region.

MATERIALS AND METHODS

Based on the materials of the Belgorod Oblast TB Dispensary (statistical accounting forms 07-TB) and the centralized bacteriological laboratory, an analysis of the structure and dynamics of *Mycobacterium tuberculosis* resistance to the first line or main anti-TB drugs (isoniazid, rifampicin, streptomycin, and ethambutol) and the second row was carried out-reserve (kanamycin, ofloxacin, and capreomycin). Data on the drug resistance of *M. tuberculosis* strains isolated from all bacterial-excreting patients before chemotherapy for 2008–2017 were available for analysis, which made it possible to evaluate the structure and trends in drug resistance over a 10-year period.

Drug resistance of the causative agent of TB in patients was determined on the strains obtained at the stage of diagnostics before the start of treatment and selected according to the principle "one patient-one strain." The methods of determination were the methods of absolute concentrations on a Levenshtein-Jensen medium and proportions on a liquid medium in the BACTEC MGIT 960 system.

The Aim of the Study

The aim of the study was to evaluate and compare the structure and dynamics of drug resistance of *M. tuberculosis* to anti-TB drugs, including multiple and broad, in the Belgorod region in newly diagnosed patients and patients with relapses of TB over the 10-year period of 2008–2017.

RESULTS

During the analyzed period, patients with newly diagnosed TB experienced a general increase in the resistance of the pathogen to all drugs [Table 1].

The highest indicator of drug resistance of the pathogen is marked to streptomycin – a drug that has been used in the treatment of TB for 70 years. For the years analyzed, resistance to streptomycin increased almost constantly and increased by 16.9% from 39.6 to 46.3% by the end of the 10-year period.

Resistance to two main first-line drugs, isoniazid and rifampicin, showed a similar trend. Isoniazid resistance increased by 24.6–41.0%, rifampicin – by 31.4% and amounted to 29.3% in 2017. The resistance to ethambutol increased by 28.2% and amounted to 19.1%.

As for the second-line drugs, their resistance at the beginning of the analyzed period was very low, but by 2017, the rates increased several times and amounted to 7.4% for kanamycin, ofloxacin, and capreomycin – by 4.3% each.

In patients with recurrent TB, drug resistance rates significantly exceed those in newly diagnosed patients [Table 2].

Indicators of resistance to the first-line drugs in patients with relapses by the end of the 10-year period were as follows: To isoniazid, 72.4%, which is 76.6% higher than in newly diagnosed patients; to rifampicin – 72.4% (2.5 times higher); to streptomycin – 75.9% (up 63.9%);

Table 1: Drug resistance of *Mycobacterium tuberculosis* in patients with newly diagnosed tuberculosis, 2008–2017 (%)

A drug	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Isoniazid	32.9	32.9	35.3	36.2	38.9	40.8	44.9	33.3	38.1	41.0
Rifampicin	22.3	20.2	18.5	20.5	24.9	22.5	28.3	23.3	27.5	29.3
Streptomycin	39.6	38.3	38.7	39.1	43.8	42.3	43.9	36.5	40.7	46.3
Ethambutol	14.9	17.5	15.7	15.7	19.4	18.3	22.9	17.8	20.1	19.1
Kanamycin	2.7	3.2	2.6	4.5	4.2	3.3	5.4	4.1	7.4	7.4
Ofloxacin	1.7	1.9	0.6	1.6	1.7	2.8	1.0	2.3	5.8	4.3
Capreomycin	0.5	1.3	0.9	2.9	2.4	1.9	2.0	1.4	2.1	4.3

Table 2: Drug resistance of *Mycobacterium tuberculosis* in patients with recurrent tuberculosis, 2008-2017 (%)

A drug	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Isoniazid	80.4	61.3	71.8	74.0	73.1	60.0	71.0	55.6	71.4	72.4
Rifampicin	72.9	53.8	56.3	64.9	65.7	48.0	66.1	47.2	71.4	72.4
Streptomycin	78.5	67.7	71.8	75.3	73.1	60.0	74.2	63.9	64.3	75.9
Ethambutol	60.3	48.4	42.3	49.4	44.8	44.0	37.1	47.2	53.6	58.6
Kanamycin	22.9	14.0	14.1	28.6	7.5	10.0	21.0	5.6	17.9	31.0
Ofloxacin	15.0	8.6	5.6	10.4	7.5	8.0	12.9	16.7	21.4	20.7
Capreomycin	8.4	6.5	5.6	15.6	3.0	6.0	3.2	2.8	7.1	10.3

and to ethambutol – 58.6% (3.1 times higher than in newly diagnosed patients). However, during the years analyzed, the figures varied with a certain tendency to decrease. Thus, resistance to streptomycin decreased by 3.3%, to isoniazid – by 10.0%, to rifampicin – by 0.7%, and to combutol – by 2.8%.

In contrast, indicators of resistance to the second-line drugs increased. Resistance to kanamycin increased by 35.4% and amounted to 31.0%, of ofloxacin – by 38.0% and amounted to 20.7% in 2017. The index of resistance to capreomycin increased by 22.6% and amounted to 10.3%. All these indicators are higher than those in newly diagnosed patients: kanamycin – 4.2 times, ofloxacin – 4.8 times, and capreomycin – 2.4 times.

We analyzed the tendency of changes in the indicators of multidrug resistance of the TB pathogen in both newly diagnosed patients and in patients with relapses [Figure 1].

During the analyzed period, the indicator of multidrug resistance in newly diagnosed patients varied with a tendency to increase, increased by 33.1% by 2017 and amounted to 29.3%.

In patients with recurrent TB, the indicator of multidrug resistance of the pathogen is much higher. In 2017, it was 72.4%, which is 2.5 times higher than the rate of newly diagnosed patients.

It is worth noting that the indicator of multidrug resistance in relapses practically did not change in 10 years. This fact, as well as some tendency to reduce the resistance to the first-line drugs in patients with relapses, may be related to the implementation in 2008–2010 of the Green Light Committee project on the treatment of patients with multidrug-resistant patients. During this project, a significant number of such patients were treated with a 2-year course of chemotherapy with high-quality drugs, which could change the structure and slow down the increase in drug resistance in patients with relapses.

At present, there is an alarming trend toward the growth of broad drug resistance of strains isolated from various categories of patients [Figure 2].
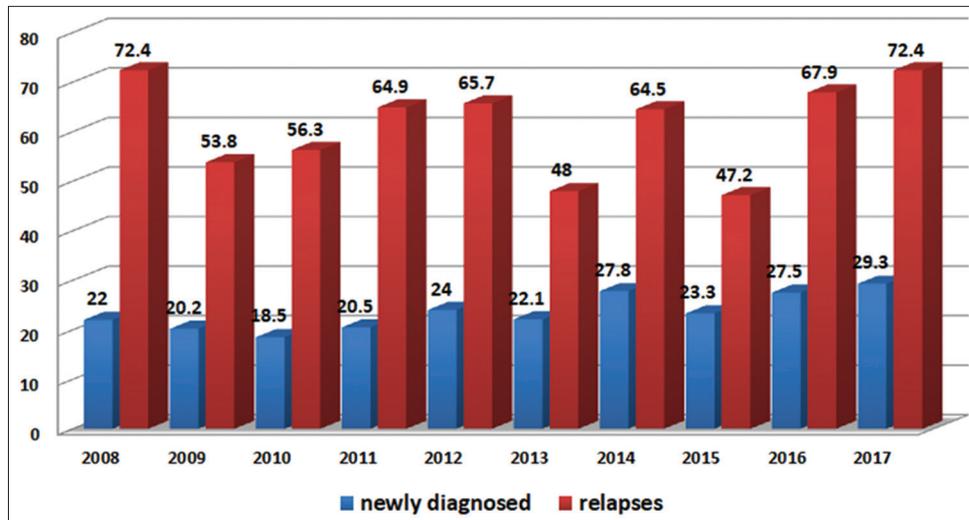

Figure 1: The dynamics of multidrug resistance *Mycobacterium tuberculosis*, 2008–2017 (% of all strains isolated)
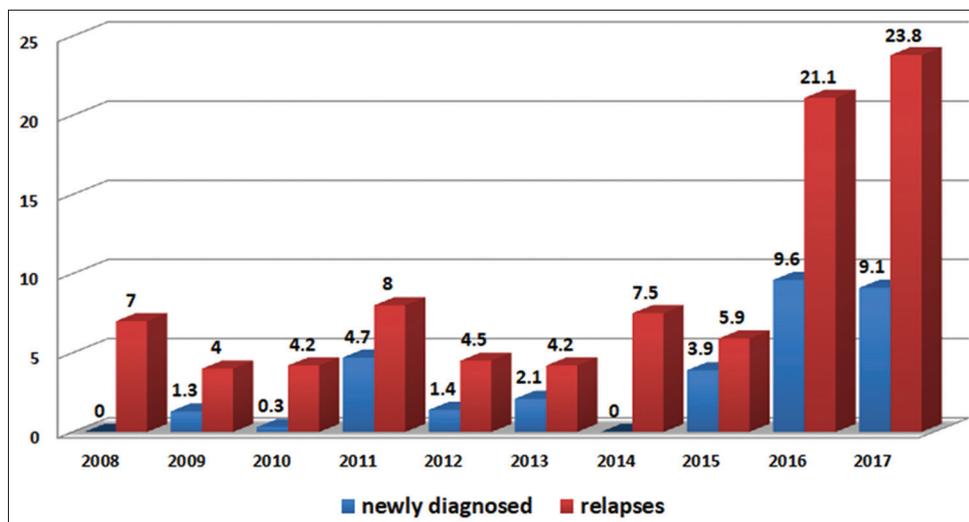

Figure 2: Dynamics of extensive drug resistance *Mycobacterium tuberculosis*, 2008–2017 (% of all multidrug-resistant strains)

Despite the singularity of the cases of TB with extensive drug resistance, their proportion among newly diagnosed patients increased almost 7 times, from 1.3 to 9.1%, among relapses – 3.4 times, from 7.0% to 23.8 %, which is an extremely unfavorable sign.

CONCLUSIONS

In the 10-year period 2008–2017, in the Belgorod region, patients with newly diagnosed TB showed a general increase in the resistance of the pathogen to anti-TB drugs. The highest indicator of drug resistance of the pathogen is marked to streptomycin. Resistance to other main and reserve drugs increased almost constantly.

In patients with relapses, although significantly higher rates of drug resistance are observed than in those newly diagnosed, there was a slight decrease in drug resistance in the 2008–2017 period. In contrast, the indicators of resistance to the second-line drugs increased.

The rate of multidrug resistance in newly diagnosed patients increased by 33.1% by 2017. In relapses, it did not practically change in 10 years. This fact, as well as the reduction in resistance to the first-line drugs in patients with relapses, may be related to the implementation in 2008–2010 of the Green Light Committee project in the region.

There is an alarming tendency in the region to increase the wide drug resistance of strains isolated from various categories of patients, which is an extremely unfavorable sign, significantly complicates the appointment of adequate therapy to patients and reduces the effectiveness of treatment.

Thus, over the study period in the Belgorod region, against the background of a successful TB epidemiological situation, a steady decline in morbidity and mortality, there is an increase in the indicators of drug resistance of *M. tuberculosis*, including multiple and widespread resistance.

All of the above emphasize the importance of monitoring the drug resistance of *M. tuberculosis*, which is an integral part of controlling the spread of this infectious disease. It is necessary to continue this work, which will make it possible to predict the risk of spreading drug-resistant TB and differentiate the approach to anti-epidemic measures in the Belgorod region.

REFERENCES

1. World Health Organization. Calls for Urgent Action to end TB. Available from: http://www.who.int/news-room/detail/18-09-2018-who-calls-for-urgent-action--to-end-tb. [Last accessed on 2019 May 15].
2. World Health Organization. Global Tuberculosis Control Report 2017. Available from: http://www.who.int/tb/publications/global_report/gtbr2017_executive_summary_ru.pdf?ua=1. [Last accessed on 2019 May 15].
3. Vorobeva OA. Drug resistance of mycobacterium tuberculosis modern views on the problem. Siberian Med J 2008;2:5-8.
4. Ershov VI, Kashnikov SY, Martynova NE. Analysis of the Structure and Development Trends of Drug Resistance of the Causative Agent of Tuberculosis in Russia and Abroad. Electronic Epidemiological Atlas of the Volga Federal District; 2014. Available from: http://www.epid-atlas.nniiem.ru. [Last accessed on 2019 May 15].
5. Sterlikov SA. The problem of combating drug-resistant tuberculosis in the Russian federation. Public Health and Habitat 2014;6:21-3.
6. Nechaev OB. The Epidemic Situation of Tuberculosis in Russia; 2016. Available from: http://www.mednet.ru/ru/czentr-monitoringa-tuberkuleza/o-czentre.html. [Last accessed on 2019 May 15].
7. Vasilieva IA, Belilovsky EM, Borisov SE, Sterlikov SA. Multidrug-resistant tuberculosis in the countries of the world and in the Russian federation. Tuberc Lung Dis 2017;95:5-17.
8. Malykhina TI. Effectiveness of Monitoring Tuberculosis in the Region in Stabilizing the Epidemic Situation: Dissertation Candidate of Medical Science: 14.01.16/T.I. Malykhina Kursk: 2011. p. 183.
9. Zemlyanski OA, Turina EB, Malykhina TI. Information Control of Bacteriological Diagnosis of Tuberculosis (Bacteriological Monitoring) as Part of a Regional System for Monitoring Tuberculosis in the Belgorod Region. Collection of Theses of the II Congress of the National Association of Phthisiatricians, St. Petersburg: 2013. p. 82-3.
10. Zemlyanski OA, Bashkirev AA. Features of the epidemiological process of tuberculosis in the Belgorod region. Sci Bull Bel SU 2012;16:100-3.
11. Amelchenko AA. Characteristics of the Dynamics of the Main Indicators of the Epidemiological Monitoring of Drug Resistance of *M. tuberculosis* in Various Groups of Patients in the Belgorod Region for 2010-2016-Materials of the Interregional Scientific-Practical Conference Modern Opportunities and Prospects for the Implementation of the WHO New Strategy for the Elimination of Tuberculosis in the Era of Sustainable Development Goals, the Contribution of the Subjects of the Russian Federation (Belgorod, 10-11 August 2017). Belgorod: "Graphite": 2017. p. 64.