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Research Article

### THE PREVALENCE OF M. TUBERCULOSIS STRAINS OF VARIOUS GENETIC FAMILIES IN BELGOROD REGION

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**Abstract:**

**Purpose of the Study:** To estimate the prevalence and association with multiple drug resistance of strains of *M. tuberculosis* of various genetic families in the Belgorod region, to reveal the contribution of strains of the genetic family Beijing to the epidemic process of tuberculosis; evaluate the role of strains of *M. tuberculosis* of various genetic families in the formation of "rural foci of tuberculosis" in the region.

**Materials and Methods:** Spoligotyping of 311 strains of *M. tuberculosis* isolated from patients with pulmonary tuberculosis in the Belgorod Region in 2015-2017 has been carried out.

**Results.** Among the strains studied, strains of the families Beijing and T. are most widely represented. The shares of other genetic families (H, X, LA, U) are insignificant. The strains of the Beijing family are much wider than others presented in previously treated patients; in patients of middle and young age, as well as among strains with multiple drug resistance. Some prevalence of strains of Beijing and T in "chronic" foci of tuberculosis was revealed.

**Results and Discussion:** Despite the favorable epidemic situation, one can not exclude the danger of forming "chronic" foci of tuberculosis with a decrease in attention to preventive antituberculous activities in the settlements of the region. The genotyping of strains of *M. tuberculosis* should be included in the monitoring program of foci of tuberculosis on a regular basis, which will allow predicting the risk of forming chronic «foci» and differentiating approach to antiepidemic measures in the foci of tuberculosis.

**Key words:** *mycobacterium tuberculosis*, genetic families, foci of tuberculosis.

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**INTRODUCTION:**

In the Belgorod region, during the last few years, there has been a successful epidemiological situation in tuberculosis. The level of the total incidence of tuberculosis declines and in 2014 it was 29.0 per 100 thousand of the population, in 2015 - 27.1, in 2016 - 21.5 per 100 thousand people (RF - 53.3) [1,2,3]. The death rate from tuberculosis remains the lowest among all regions of the Russian Federation; in 2016 it was 0.8 per 100 thousand of the population (RF - 7.5) [4,5].

However, despite the stability of the situation, there are some negative trends in the development of the epidemiological process. Thus, there remains a high proportion of patients with multiple drug resistance (further MDR) pathogens [6,7]. In 2014, the share of MDR among newly diagnosed bacillary patients was 21.5%, in 2015 - 17.3%, in 2016 - 26.7%; MDR among patients registered for repeated courses of treatment (relapse, failure or interruption of treatment) decreased from 53.2% in 2014 to 48.3% in 2015 and again increased to 54.6% in 2016 [8].

Against the background of decreasing morbidity in the Belgorod region, rural settlements "free from tuberculosis" appeared, where no cases of this disease have been registered for 3-5 years, despite the full preventive examinations. And at the same time, the proportion of "chronic" foci is increasing - villages where cases of tuberculosis are detected continuously for 3 or more years: endemic settlements are formed - "rural foci" of tuberculosis [9].

There is a need to search for the causes of the current situation, including those caused by the genetic characteristics of the circulating strains of *M. tuberculosis*.

According to studies published in recent years, molecular genetic monitoring is becoming increasingly important in epidemiology, tracking the population structure of infectious agents for the purpose of assessing and predicting the epidemic situation [10].

The epidemiology of tuberculosis in the Russian Federation is characterized by a significant prevalence of strains of the genetic family Beijing, which is associated with drug resistance and increased virulence and pathogenicity. Beijing is the

most common group among isolates isolated from tuberculosis patients in many regions of the Russian Federation [11,12]. However, in the Belgorod region, studies on the genetic typing of strains of the causative agent of tuberculosis have not been conducted previously.

**MATERIALS AND METHODS:**

With the help of the "SPOLIGO-BIOCHIP" kit (produced by LLC "Biochip-IMB", Moscow), 311 strains of *M. tuberculosis* isolated from patients with pulmonary tuberculosis in the Belgorod region in 2015-2017 were spoligotyped. All strains were obtained at the stage of diagnosis and were selected on the principle of "one patient - one strain." The study includes:

- 240 strains from newly diagnosed and 71 strains from previously treated patients;
- 119 strains with multiple drug resistance (MDR) and 192 - non-MDR;
- 178 strains from patients living in cities;
- 133 strains from patients living in rural settlements, including 57 strains from patients from "safe villages" and 76 strains from patients from "chronic foci".

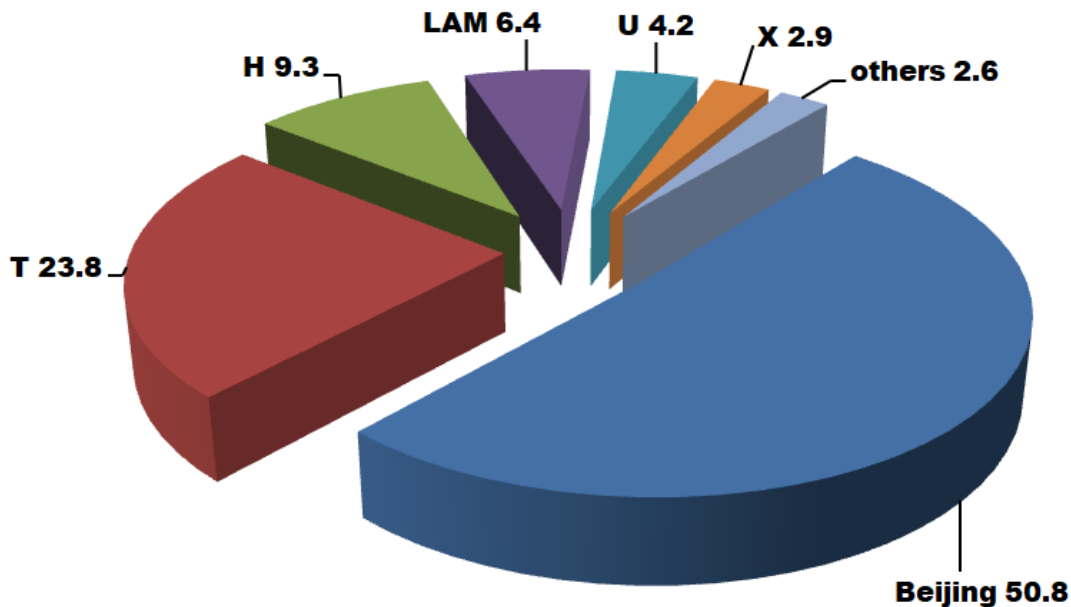
The drug resistance of these strains was determined by the absolute concentration method on the Levenstein-Jensen medium and on a liquid medium in the BACTEC MGIT 960 system.

**Goal of research**

To assess the prevalence and association of multiple strains of *M. tuberculosis* of different genetic families in the Belgorod Region, including patients of different categories and ages; to identify the contribution of *M. tuberculosis* strains of the genetic family Beijing to the epidemic process of tuberculosis; to assess the role of strains of *M. tuberculosis* of various genetic families in the formation of "rural foci of tuberculosis" in the territory of the Belgorod region.

**RESULTS:**

The most widely studied strains of the Beijing family are 158 strains or 50.8% (Figure 1).



**Fig 1: Shares of M. tuberculosis strains of various genetic families circulating in the Belgorod Region (%)**

In second place in the frequency of occurrence is the family of T-74 strains (23.8%). The shares of other genetic families are much lower: H - 29 strains (9.3%), LAM - 20 strains (6.4%), U - 13 strains (4.2%), X - 9 strains (2.9%). Isolated 8 strains of rare families - MANU, CAS and others.

Significant differences were found between the shares of the Beijing family in newly diagnosed and previously treated patients - 45.0% and 70.4%, respectively (Table 1).

**Table 1: Genetic families of M. tuberculosis in different groups of tuberculosis patients in the Belgorod Region (%)**

	Genetic families						
	Beijing	T	H	LAM	U	X	others
The newly diagnosed patients	45.0	26.3	10.8	6.7	5.0	3.3	2.5
Previously treated patients	70.4	15.5	4.2	5.6	1.4	1.4	2.8
Patients with non-MDR-TB	31.3	34.4	13.5	7.3	6.8	3.1	3.6
Patients with MDR-TB	82.4	6.7	2.5	5.0	-	2.5	0.8

The genetic family of T is more widely represented in newly diagnosed patients - 26.3%, while in previously treated patients it is 15.5%. More common in newly diagnosed patients and the genetic family H - 10.8%, and in previously treated - 4.2%. The shares of other families in both categories of patients are not so significant and range from 1.4% to 6.7%.

Among the strains with multidrug-resistant strains, the share of the Beijing family is 82.4%, while among strains with preserved sensitivity to antituberculosis drugs, or mono- and multidrug resistance (non-MDR), only 31.3%.

Families of T and H are more common among non-MDR strains: 34.4% and 13.5%, respectively, and among MDR - 6.7% and 2.5%. Other genetic families (LAM, X, etc.) are among the strains with multiple drug resistance from 0.8% to 5.0%. Among 13 strains of the U family, none have been found with multiple drug resistance.

In our opinion, it is interesting to analyze the occurrence of different genetic families in newly diagnosed patients of different ages (Figure 2).

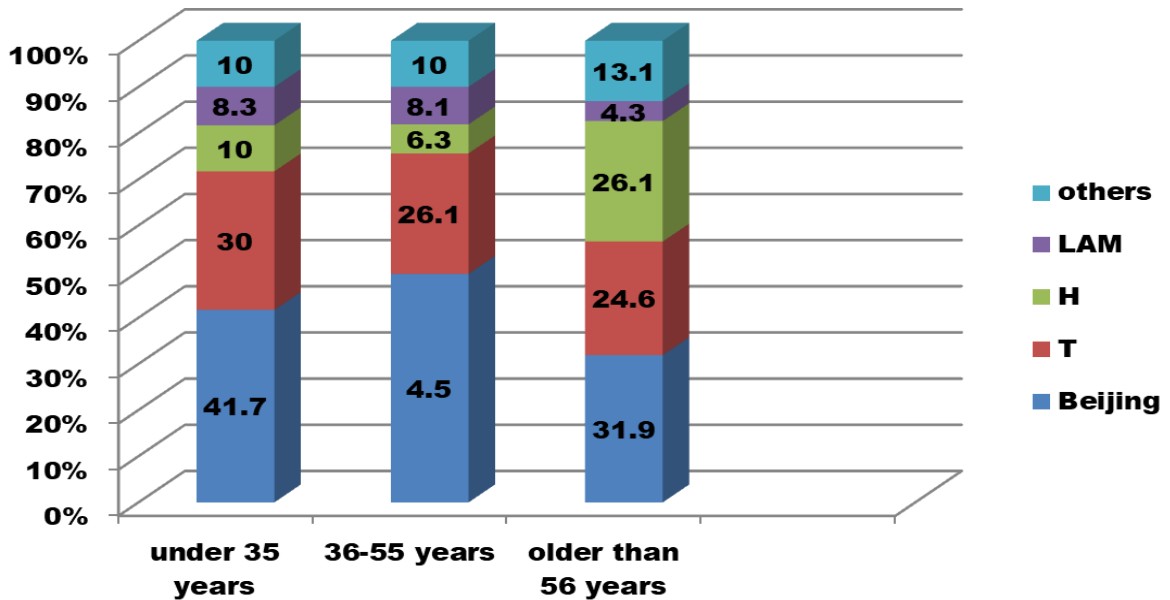


Fig 2: Genetic families of M. tuberculosis in different age groups of newly diagnosed tuberculosis patients in the Belgorod Region (%)

Thus, strains of Beijing are less common in patients older than 56 years old - 31.9%, whereas in middle-aged patients (36-55 years) - 49.5%, young age (under 35 years) - 41.7%. The proportions of the T family are approximately the same at different ages, with some predominance at a young age of 30.0% (26.1% on average and 24.6% at the senior age). The

share of the H family is significantly higher in the older age group - 26.1% (average 6.3%, young - 10.0%). Apparently, this can indirectly indicate the intensity of circulation in the territory of different genetic families at different times.

Some prevalence of strains of Beijing and T in "chronic" outbreaks was revealed (Figure 3).

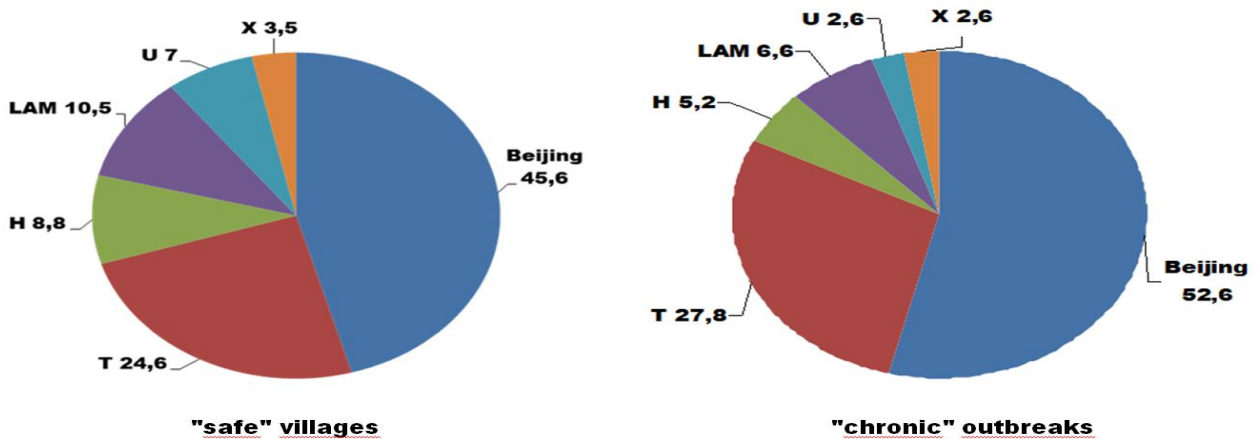


Fig 3: The shares of strains of M. tuberculosis of various genetic families circulating in "safe" villages and in "chronic" outbreaks (%)

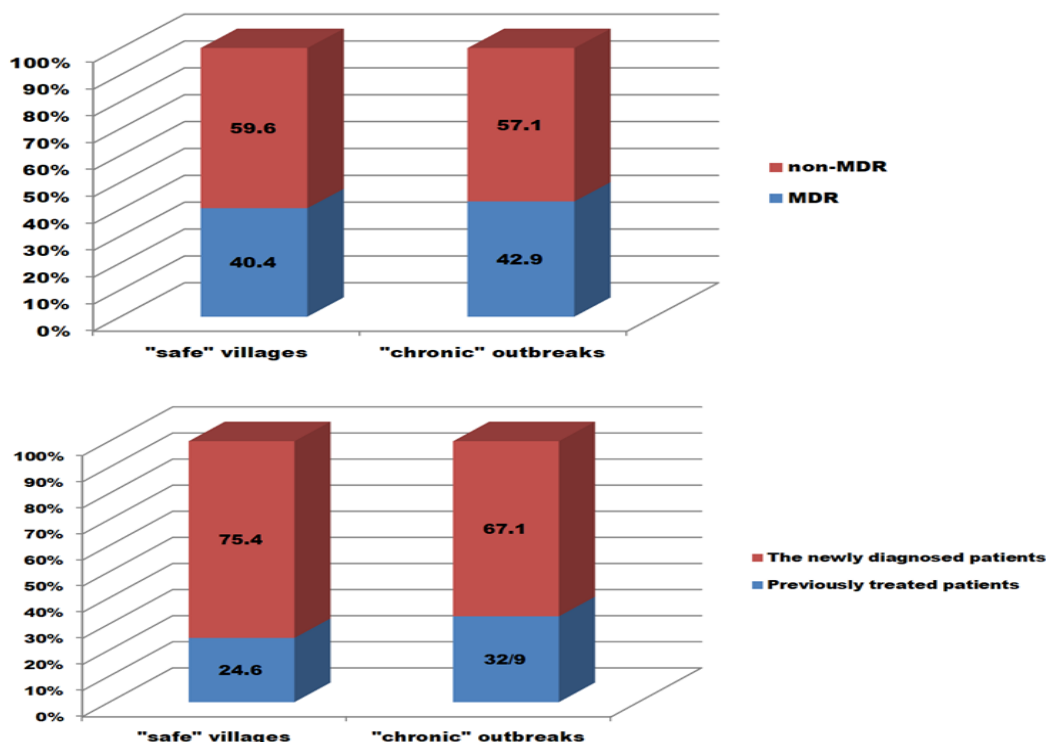


Fig 4: *M. tuberculosis* strains circulating in "safe" villages and in "chronic" outbreaks (%).

So, strains of the genetic family Beijing in "chronic" outbreaks were 52.6%, and in "well-off" tuberculosis villages, 45.6%; strains of the T family - 27.8% and 24.6%, respectively. However, in four of the 90 "chronic" foci, the absolute predominance of Beijing strains is recorded, in two - strains of T. The shares of other genetic families in all rural settlements are approximately the same and range from 3.0 to 10.5%. Strains with MDR slightly prevail in "chronic" outbreaks - 42.9% versus 40.4% in "safe" villages (Figure 4).

The predominance of strains isolated from patients with repeated treatment of tuberculosis (relapses, seizures, failures, etc.) is more pronounced - in the "chronic" foci of such strains 32.9%, in "safe" villages - 24.6%.

#### CONCLUSIONS:

In the territory of the Belgorod region, *M. tuberculosis* strains of the genetic family Beijing are most widely spread, which has a pronounced association with multiple drug resistance and contributes significantly to the epidemic process. The strains of this genetic family are much wider than

others, presented in previously treated patients; in patients of middle and young age, as well as among strains with multiple drug resistance.

However, despite the available data in the literature on the increased ability to epidemic spread of Beijing strains, the predominance of these strains in the "chronic" outbreaks of tuberculosis in the Belgorod region is not so significant.

The following genetic families of T and H are more widely represented in newly diagnosed patients among non-MDR strains. Strains of the T family have some predominance in the "chronic" foci along with Beijing.

Strains with multiple drug resistance and strains from patients with re-treatment of tuberculosis are also more widely represented in "chronic" outbreaks.

The proportion of the H family is significantly higher at the older age.

The results of this study require further study jointly by microbiologists and epidemiologists.

Despite the favorable epidemiological situation, it is impossible to exclude the danger of forming "chronic" foci of tuberculosis with a decrease in attention to preventive antituberculous activities in the settlements of the region.

The data of spoligotyping and drug resistance of strains of *M. tuberculosis* should be permanently included in the monitoring program for foci of tuberculosis, which will allow predicting the risk of formation of chronic «foci» and differentiating approach to antiepidemic measures in the foci of tuberculosis.

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