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Population structure of *Mycobacterium tuberculosis* from referral clinics in Western Siberia, Russia: Before and during the Covid-19 pandemic

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ABSTRACT

The dramatic change in global health imposed by the Covid-19 pandemic has also impacted TB control. The TB incidence decreased dramatically not because of the improved situation but due to undertesting, reduced resources, and ultimately, substantially reduced detection rate. We hypothesized that multiple and partly counteracting factors could influence changes in the local *Mycobacterium tuberculosis* population. To test this hypothesis, we analyzed *M. tuberculosis* isolates collected in Western Siberia, Russia, before and during the Covid-19 pandemic. A total of 269 *M. tuberculosis* isolates from patients admitted at referral clinics were studied. The pre-pandemic and pandemic collections included 179 and 90 isolates, respectively. Based on genotyping, both pre-pandemic and pandemic samples are heavily dominated by the Beijing genotype isolates (95% and 88%) that were mostly MDR (80 and 68%). The high proportion of MDR isolates is due to the specific features of the studied collections biased towards patients with severe TB admitted at the National referral center in Novosibirsk. While no dramatic change was observed in the *M. tuberculosis* population structure in the survey area in Western Siberia during the Covid-19 pandemic in 2020–2021 compared to the pre-pandemic collection, still we note a certain decrease of the Beijing genotype and an increase in the proportion and diversity of the non-Beijing isolates. However, the transmissible and MDR Beijing B0/W148 did not increase its prevalence rate during the pandemic. More generally, the high prevalence rate of the Beijing genotype and its strong association with MDR both before and during the pandemic are alarming features of this region in Western Siberia, Russia.

1. Introduction

Russian Federation is a hotspot for multi-drug resistant tuberculosis (MDR-TB), and the proportion of newly diagnosed TB patients with MDR-TB increased from 27.2% in 2015 to 32.4% in 2021 (Krasnov et al., 2018; Filippova et al., 2021). The situation is variable across different parts of the country, and the highest levels of MDR-TB (furthermore aggravated by the higher rate of TB/HIV co-infection) are recorded in the Asian part of Russia with the TB incidences of 8.9 and 6.8 per 100,000, in Siberia and Far East, respectively. In particular, the Siberian regions with the most adverse situation are the Republic of Tyva, Kemerovo, and Novosibirsk regions with 31.3% to 38.6% of primary MDR (Filippova et al., 2021).

This situation is partly explained by some differences in the molecular population structure of the circulating *Mycobacterium tuberculosis* strains which in turn has been shaped by multiple factors, both related to

human migration, health control implementation and the environment. However, these interregional differences are not dramatically significant. Previously, it was suggested that intensive human population mixing in Russia during most of the 20th century has led to the close relatedness of the geographically distant *M. tuberculosis* populations across Russia as was demonstrated by principal components analysis of the VNTR data of the Beijing and Latin-American Mediterranean (LAM) genotypes (Mokrousov, 2008; Mokrousov et al., 2016).

The geographic position of the Russian Federation as Northern Eurasia explains why its *M. tuberculosis* population is presented by two major genetic families – Beijing genotype (East Asian lineage) and LAM genotype (Euro-American lineage). Extremely rare are isolates of the Indo-Oceanic and Central Asian lineages. In its turn, the Beijing genotype in Russia is mostly represented by isolates of modern sublineage that mainly belong to the Russian epidemic strain Beijing B0/W148 and heterogeneous Central Asian Russian clade (Mokrousov, 2013; Shitikov

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et al., 2017). Regarding Euro-American lineage, its Russian isolates mainly belong to the LAM, Ural, Haarlem, and T families (Zhdanova et al., 2022; Pasechnik et al., 2018; Umpeleva et al., 2020; Sinkov et al., 2018; Chernyaeva et al., 2018; Dymova et al., 2011).

The dramatic change in global health imposed by the Covid-19 pandemic has also impacted TB control. The TB incidence decreased dramatically not because of the improved situation but due to under-testing, reduced resources, and ultimately, substantially reduced detection rate (WHO. *Global tuberculosis report, 2021*). We hypothesized that multiple and partly counteracting factors could influence changes in the local *M. tuberculosis* population, such as: (1) delayed start of treatment, inadequate treatment due to interruptions in the supply of drugs, consumables for bacteriology laboratories, e.g., there were problems with the supply of consumables for the BACTEC system, (2) patients themselves came irregularly for drugs, (3) lack of TB-specialists due to Covid-19; (4) wearing masks, restrictions on visiting public places, remote work/study can decrease the spread of *M. tuberculosis*.

All this leads to an increase in drug resistance, and since some strains develop resistance faster than others (e.g., Beijing B0/W148), their proportion in the pathogen population could increase. At the same time, the most contagious strains would spread faster, leading to a change in the structure of the *M. tuberculosis* population.

To test this hypothesis, we analyzed *M. tuberculosis* isolates collected in Western Siberia, Russia, before and during the Covid-19 pandemic. We additionally interpreted our data in the light of the previous studies on the molecular epidemiology of TB in Russia.

2. Materials and methods

The *M. tuberculosis* isolates were recovered from TB patients in the neighboring provinces of Novosibirsk, Kemerovo and Tomsk in Western Siberia, Russia in 2019 (retrospective collection) and in 2020–2021 (prospective collection, during the Covid-19 pandemic).

Pre-pandemic (2019) samples are represented by cryopreserved isolates available in Novosibirsk TB Research Institute (NTRI). NTRI provides high-tech medical care to the most complicated patients who cannot be cured in the regions of their residence. The proportion of MDR-TB patients treated in NTRI is higher than in the general population of Siberian and Far Eastern regions. *M. tuberculosis* cultures were collected from TB patients admitted to NTRI for anti-TB therapy and TB related surgery in 2019. We included all isolates from the mentioned regions available in the NTRI cryocollection.

The pandemic collection included *M. tuberculosis* isolates recovered from TB patients diagnosed with TB in 2020–2021 and admitted to NTRI or treated in Kemerovo, Tomsk, and Novosibirsk regions.

The bacterial isolates were characterized by standard bacteriological and biochemical methods and drug susceptibility testing for the first- and second-line drugs using recommended methods (*Federal Clinical Recommendations on Organization and Implementation of Microbiological and Molecular-Genetic Diagnostics of Tuberculosis, 2015*).

DNA was extracted using CTAB based method (van Embden et al., 1993). The isolates were first differentiated into Beijing and non-Beijing genotypes based on a real-time PCR assay targeting IS6110 insertion in the oriC region (Mokrousov et al., 2014). Further, Beijing strains were subdivided into two major groups known to be prevalent in Russia (B0/W148-cluster and Central Asian/Russian cluster) by testing specific SNP markers as previously described (Mokrousov et al., 2012 and 2018). The non-Beijing strains were subjected to spoligotyping as described (Kamerbeek et al., 1997) followed by a comparison with the SITVIT2 database (<http://www.pasteur-guadeloupe.fr:8081/SITVIT2/>) and assignment of the spoligotype international type (SIT) and clade.

The Hunter Gaston index was calculated as described (Hunter and Gaston, 1988). A chi-square test was used to detect any significant difference between the two groups. Yates corrected χ^2 and *P*-values were calculated with the 95% confidence interval at http://www.medcalc.org/calc/odds_ratio.php online resource.

3. Results

A total of 269 *M. tuberculosis* isolates from three regions in Western Siberia were studied. Due to the reduced detection rate during the Covid-19 pandemic, the pandemic sample included 90 isolates, mostly from 2020. The pre-pandemic collection included 179 isolates from 179 patients diagnosed with tuberculosis in 2019 and earlier.

The 179 patients in the pre-pandemic sample included 114 (63.7%) males and 65 females. The pandemic sample included 90 patients: 66 (73%) males, and 24 females.

In terms of the clinical form of TB, the dominant forms were fibrous-cavernous and infiltrative TB, followed by disseminated TB and tuberculoma. There is an increase in fibrous-cavernous TB and a decrease in tuberculoma subgroups in the pandemic sample although non-significant ($P = 0.056$ and 0.068 , respectively) (Table 1).

Analysis of the molecular structure defined by genotyping and distribution of drug resistance among genotypes demonstrated that both pre-pandemic and pandemic samples are heavily dominated by the Beijing genotype isolates (95% and 88%) that were mostly MDR (80 and 68%) (Table 2). On the whole, the prevalence rate of the Beijing genotype decreased and this change was significant ($P = 0.04$). Reciprocally, there was a significant increase of the non-Beijing isolates from 5% to 12% although they remain in a very low proportion. The two major Beijing clusters B0/W148 and Central Asian Russian remained in similar proportions before and during the pandemic (Table 2).

All non-Beijing isolates belong to the spoligotypes of Lineage 4 (Euro-American lineage). HGI of non-Beijing spoligotypes was 0.9167 (pre-pandemic) versus 0.9455 (pandemic), i.e. the diversity of the non-Beijing genotypes increased in the pandemic collection. The spoligotyping of the 20 non-Beijing isolates identified 12 spoligotypes that represented three genetic families LAM, T, Ural (16 isolates), and 4 unclassified isolates. All these isolates belonged to the Euro-American lineage. Nine pre-pandemic isolates were divided into 6 spoligotypes; of them, three SIT (SIT53/T, SIT253/T, SIT1257/Unknown family) included 2 isolates each. Both SIT253 pre-pandemic isolates were MDR. Eleven pandemic non-Beijing isolates belonged to 8 spoligotypes; of them, three SIT (SIT42/LAM, SIT253/T, SIT335/LAM) included 2 isolates each. All but one clustered pandemic non-Beijing isolates were MDR.

The percent of MDR among Beijing strains decreased from 80% to 68.4% but this could be because the pre-pandemic sample included chronic patients. However, the percent of MDR decreased more visibly among B0/W148 isolates (from 87.9% to 70.7%) compared to the Central Asian Russian isolates (70.9% and 66.7%), although in both clusters it remained very high.

Because of the small number of isolates per particular non-Beijing family, no changes in their MDR rate could be meaningfully detected. For this reason, the non-Beijing isolates were analyzed together. Thus, the percent of the MDR isolates increased from 44.4% to 63.6% in the non-Beijing collection ($P = 0.04$).

4. Discussion

Western Siberia is an important region with a high MDR-TB rate. This

Table 1
TB diagnosis and clinical forms of the enrolled patients.

TB diagnosis (clinical form)	Pre-pandemic, n = 179 Number and %	Pandemic, n = 90 Number and %	<i>P</i>
Focal	2; 1.1	2; 2.2	
Infiltrative	54; 30.2	24; 26.7	
Disseminated	24; 11.7	12; 13.3	
TB pleuritis	1; 0.5	0; 0.	
Tuberculoma	36; 20.1	10; 11.1	0.068
Fibrous-cavernous	62; 33.5	42; 46.7	0.056

Table 2
M. tuberculosis genotypes and drug resistance in this study.

Genotype	Pre-pandemic collection, n = 179		Pandemic collection, n = 90		P, genotype prevalence	P, MDR rate
	Number; % of all collection	Number of MDR; % of MDR in this genotype	Number; % of all collection	Number of MDR; % of MDR in this genotype		
Beijing all	170; 95.0	136; 80.0	79; 87.8	54; 68.4	0.04	0.046
B0/W148	83; 46.4	73; 87.9	41; 45.6	29; 70.7	0.6	0.02
Central Asian	79; 44.1	56; 70.9	36; 40.0	24; 66.7	0.5	0.6
Russian						
Other	8; 4.5	7; 87.5	2; 2.2	1; 50.0	0.4	
Non-Beijing all	9; 5.0	4; 44.4	11; 12.2	7; 63.6	0.04	0.04
LAM	2; 1.1	1; 50.0	5; 5.6	5; 100.0	0.05	
T	5; 2.8	3; 60.0	2; 2.2	1; 50.0	0.5	
Ural			2; 2.2	0; 0.		
Unknown and new	2; 1.1	0; 0.0	2; 2.2	1; 50.0	0.4	

P values are not shown for separate non-Beijing families and “other Beijing” due to their very small sample sizes.

is also a likely region of origin of the epidemic Russian Beijing strain B0/W148, which is strongly MDR-associated and transmissible (Mokrousov, 2013). The increased transmission capacity of the B0/W148 strain was shown by its higher prevalence in the prison setting, the increased clustering, and the increased prevalence in the urban versus rural setting (Mokrousov, 2013; Vyazovaya et al., 2020). In 1999, Portaels et al., 1999 reported about the simultaneous detection of the same strain with a characteristic IS6110-RFLP profile (it was B0/W148) in different prisons in Siberia, including the Kemerovo region. Currently, the region is marked by a high primary MDR rate of 35% (Filippova et al., 2021).

In this study, we analyzed the dynamics of the *M. tuberculosis* population in three neighboring regions in Western Siberia (Kemerovo, Novosibirsk, and Tomsk) before and during the Covid-19 pandemic. We hypothesized that the general population of the circulating *M. tuberculosis* strains could change during the Covid-19 pandemic compared to the pre-pandemic period due to various reasons related to TB control implementation and linked to the particular strain characteristics.

In more general terms, the striking findings of this study are a very high rate of MDR in both pre-pandemic and pandemic collections, as well as the very high rate of the Beijing genotype. Previous studies in Western Siberia demonstrated that Beijing genotype is more frequently found in MDR-TB samples (71%) compared to general TB (47%) (Dymova et al., 2011; Dymova et al., 2014). This can explain the higher rate of the Beijing genotype (95% and 88%), and consequently, a high prevalence rate of MDR in both pre-pandemic (78.2%) and pandemic (67.8%) collections in our study.

The dominance of the Beijing genotype is a known feature of the *M. tuberculosis* population in Russia. However, non-Beijing genotypes of

the Euro-American lineage have also been described across Russia in the visible prevalence rate, collectively accounting for 45% to 70% in Northwestern and Central Russia (Vyazovaya et al., 2020; Dubiley et al., 2010), and 31% in Eastern Siberia (Zhdanova et al., 2022). In this sense, their very low prevalence in this study is remarkable although the increase from 5 to 12% was significant.

Two major Russian Beijing subtypes had a similar rate in this study, i. e. the Beijing B0/W148-cluster was identified with a higher rate, compared to the other parts of Russia (Table 3). A strong MDR prevalence was noted in these Beijing subtypes. This is different from the other Russian studies carried out in both European and Asian parts of the country where B0/W148 was less prevalent than Central Asian Russian cluster but was significantly more frequently MDR (Pasechnik et al., 2018; Vyazovaya et al., 2020). These findings can be explained by the specific features of the samples collection. Most of the isolates was collected from patients admitted to NTRI, which provides medical care to the most seriously ill TB patients.

Monoresistance may be considered as an indirect marker of patient's non-compliance and/or inadequate treatment. In this study, the pre-pandemic sample (n = 179) included 13 (7.3%) monoresistant isolates including B0/W148-3 /83 (3.6%), Central Asian Russian cluster -7 / 79 (8.9%). The pandemic sample (n = 90) included 9 (10%) monoresistant isolates: B0/W148-6/41 (14.6%) and Central Asian Russian cluster -1 / 36 (2.8%). Thus, the proportion of monoresistant isolates slightly and non-significantly increased overall from 7.3% to 10.0%, and the underlying reason was a significant increase in the B0/W148 group (P = 0.04). The proportion of monoresistant isolates decreased in the Central Asian Russian group (P = 0.26).

We additionally compared the distribution of the main genotypes

Table 3
Prevalence rate and proportion of MDR isolates of the Beijing subtypes and major non-Beijing genotypes in Russian regions.

Genotype / Region	Komi, Northwestern Russia (Vyazovaya et al., 2020) newly diagnosed	Moscow, Central Russia, (Afanas'ev et al., 2011), newly diagnosed, 2005–2006	Yekaterinburg, Ural (Umpeleva et al., 2016), 2009–2011	Eastern Siberia and the Far East (Zhdanova et al., 2022), newly diagnosed	Omsk, Western Siberia (Pasechnik et al., 2018), newly diagnosed	Kemerovo, Novosibirsk, Tomsk - Western Siberia (this study) Pre-pandemic	Kemerovo, Novosibirsk, Tomsk - Western Siberia (this study) Pandemic
BEIJING	56.2	60.1	55.0	69.0	62.0	95.0	87.8
B0/W148	18.5 (83.3)	26.3 (100)	29.1 (78.3)	23 (63)	14 (85.7)	46.4 (87.9)	45.6 (70.7)
Central Asian Russian	33.8 (27.3)	15 (91.7)	15.2 (nd)	30 (37)	39 (28.8)	44.1 (70.9)	40.0 (66.7)
Other	3.9 (20.0)	18.8 (80.0)	10.7 (nd)	16 (48)	9 (85.7)	4.5 (87.5)	2.2 (50.0)
NON-BEIJING	43.8	39.9	45.0	31.0	38.0	5.0	12.2
LAM	12.3 (6.3)	13.8 (0)	12.9 (34.8)	15 (53)	15 (23.3)	1.1 (50.0)	5.6 (100.0)
Ural	6.9 (11.1)	2.5 (0)	11.9 (19.0)	5 (47)	6 (41.7)	–	2.2 0.
L4 other	24.6 (9.4)	23.6 (0)	20.2 (8.3)	11 (16)	17 (5.6)	3.9 (42.9)	4.4 (50.)

% of MDR isolates is shown in brackets. nd - no data.

and subtypes identified in this study with published data on other Russian regions (Table 3). We looked at the proportion of the genotypes in the local populations and the rate of the MDR isolates. When interpreting those data, it should be kept in mind that some of the cited studies were carried out 10–15 years ago, and some studies were biased towards resistant isolates. In this study, the pre-pandemic collection included both chronic and newly diagnosed patients and this may partly account for the extremely high rate of the Beijing genotype (95%). The prevalence rate of the B0/W148 strain was the highest in the studied regions and was much higher compared to other parts of Russia. At the same time, other important Beijing subtype (Central Asian Russian) was almost as highly MDR as B0/W148 (at least, 66%) and this differed from most other Russian regions where MDR rate in the Central Asian Russian cluster was smaller and ranged from 27% to 37%.

The limitation of this study was that the studied *M. tuberculosis* sample was limited to the collections available at the National referral center and its clinics in Novosibirsk, where severe TB patients are admitted. However, both collections were based on the same criteria and thus are comparable.

5. Conclusions

While no dramatic change was observed in the *M. tuberculosis* population structure in the survey area in Western Siberia during the Covid-19 pandemic in 2020–2021 compared to the pre-pandemic collection, still we note a certain decrease of the Beijing genotype and an increase in the proportion and diversity of the non-Beijing isolates. However, the transmissible and MDR Beijing B0/W148 did not increase its prevalence rate during the pandemic. More generally, the high prevalence rate of the Beijing genotype and its strong association with MDR both before and during the pandemic are alarming features of this region in Western Siberia, Russia.

The time window of two years of the Covid-19 pandemic may be insufficient to detect more significant changes in the *M. tuberculosis* population structure and further prospective surveillance is required.

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CRediT authorship contribution statement

Anna Vyazovaya: Methodology, Investigation, Formal analysis, Writing – review & editing. **Irina Felker:** Methodology, Investigation, Formal analysis, Writing – review & editing. **Yakov Schwartz:** Conceptualization, Writing – review & editing, Funding acquisition. **Igor Mokrousov:** Formal analysis, Writing – original draft.

Declaration of Competing Interest

None.

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