St. Petersburg Pasteur Institute, Russia
Laboratory of Molecular Epidemiology and Evolutionary Genetics
(former Laboratory of Molecular Microbiology, until 14.09.2016)

Activity report, 2015-2016: Tuberculosis and other mycobacteria

Researchers of laboratory involved in these activities:

Current staff: Igor Mokrousov, Olga Narvskaya, Anna Vyazovaya, Alena Gerasimova.
Past member: Daria Starkova (until Aug. 2015).

Funded Projects

"Open Collaborative Model for Tuberculosis Lead Optimisation", 2011-2015. Funded by European Union FP7 program FP7-HEALTH-2010-single-stage, project #261378 (consortium of 12 partners, coordinated by GSK-Spain, Russian PI: Prof. O. Narvskaya).
"Evolution of pathogenetic potential of phylogenetic lineages of Mycobacterium tuberculosis", 2014-2015. Funded by Russian Science Foundation; project #14-14-00292 (PI – Dr I. Mokrousov).
"Specific features of proteins expressed by Mycobacterium tuberculosis Beijing B0 cluster in vitro and in vivo", 2014-2016. Funded by Russian Science Foundation, project #14-15-00689 (PI – Dr E. Ilina, Institute of Physico-Chemical Medicine, Moscow).
"Application of molecular epidemiological monitoring system for the control of nosocomial transmission of Mycobacterium tuberculosis strains", 2015-2016. Funded by Aitkhozhin Institute of Molecular Biology and Biochemistry, Almaty, Kazakhstan (co-PI – Dr Y. Skiba, Dr I. Mokrousov).
"Molecular analysis of Mycobacterium avium isolates from Russia", 2015. Funded by Kobe Institute of Health, Japan (co-PI – Dr T. Iwamoto, Prof. O. Narvskaya).
"Medical and social consequences of the co-epidemics of tuberculosis and HIV infection in the Siberian region", 2016. Funded by Omsk State Medical University (co-PI – Dr O. Pasechnik, Dr I. Mokrousov).

Current Collaborations

National:
Moscow. Central Research Institute for Epidemiology.
Omsk. State Medical University.
Irkutsk. Scientific Center of Family Health and Reproductive Problems.
Ekaterinburg. Ural Research Institute of Phthisiopulmonology.
Novosibirsk. Institute of Chemical Biology and Fundamental Medicine.
Kaliningrad. Anti-Tuberculosis dispensary.
Petrozavodsk. Anti-Tuberculosis dispensary.

International:
Estonia. North Estonian Medical Centre, Tallinn.
Latvia. Latvian Biomedical Research and Study Centre, University of Riga.
Spain. Hospital General Universitario Gregorio Marañón, Madrid.
Kazakhstan. Aitkhozhin Institute of Molecular Biology and Biochemistry, Almaty.
China. Beijing Children's Hospital, Capital Medical University.
Japan. Kobe Institute of Health.

Major directions of research

Emerging clones of M. tuberculosis in Russia and Eurasia

Mycobacterium tuberculosis has clonal population structure whereas its different (sub)lineages are marked with different evolutionary pathways, and some of them have undergone a dramatic global dissemination. Furthermore, clinically/epidemiologically significant compact clusters have been identified by high-resolution genotyping. I will review some emerging *M. tuberculosis* clones from different genotype families (Beijing, LAM, Ural) that started to attract attention in the recent decades and even years in Russia and other countries of the Former Soviet Union.

Within the BEIJING genotype, these include two large clonal clusters 94-32 and B0/W148. The B0/W148 was previously defined a successful Russian clone of *M. tuberculosis* (Mokrousov, 2013). Initially, it was designated B0 (Narvskaya, 2003) and W148 (Bifani et al., 2002) based on IS*6110*-RFLP. Based on 24-MIRU-VNTR typing, this cluster greatly overlaps with type #100-32 (MIRU-VNTRplus.org). Beijing B0/W148-cluster is MDR-TB associated and is a major driving force of the Russian TB epidemics. It is epidemically spread across Russia (but not in former Soviet Central Asia) and likely originated in Siberia. Recent studies independently "rediscovered" these strains and named them East-European sublineage (Casali et al., 2014), Resistant European cluster (de Beer et al., 2014), East European cluster 2 (Luo et al., 2015), and CC2 clonal complex (Merker et al., 2015). "Asian/Russian" type Beijing #94-32 is also termed Russian/Asian clone CC1 (defined by 24-MIRU-VNTR clustering) and corresponds to the IS*6110*-RFLP-defined A0-cluster (Narvskaya, 2003; Mokrousov et al., 2008). It is highly prevalent in the former Soviet Central Asia and is one of the two largest and significant Beijing subtypes in Russia (Skiba et al., 2015; Merker et al., 2015; Luo et al, 2015).

LAM (Latin-American Mediterranean) family in the FSU countries is dominated by the RD115/LAM-RUS branch. Two MDR spoligotypes with partly overlapping areas of circulation have attracted attention recently (**Fig.1, Fig. 2**). Spoligotype SIT252 is emerging in European Russia and Eastern Europe and has already been described in rare isolates in Ural and Kazakhstan. The *M. tuberculosis* SIT252 strains have highly conserved 24-MIRU-VNTR profiles, similar IS*6110* fingerprints and mutations *rpoB* Asp516Ser, *katG* Ser315Thr and *inhA* -15C/T (Vyazovaya et al., 2016). Spoligotype SIT266 is still geographically limited to Belarus (Zalutskaya et al., 2013), and has been described in northwestern and central Russia and in Latvia. SIT266 is multidrug-resistant (MDR) (and perhaps extensively drug resistant [XDR]) unlike its parental SIT264 which is more widespread but at very low prevalence and is not MDR (Mokrousov et al., 2016 and references therein).

URAL family was traditionally considered to be low-virulent, low-transmissible and not linked to MDR (reviewed in Mokrousov, 2012). This may explain its low prevalence (<15%) and limited dispersal, still mainly in central Eurasia. However, recent reports described MDR Ural strains in some parts of Eastern Europe (Moldova, Lithuania) and northwestern Russia (Mokrousov, 2015 and references therein). Whole genome analysis of the Ural family genomes divided these strains into two large clusters: (i) ancestral, small and diverse group and (ii) modern, homogeneous and more abundant group. A significant predominance of pansusceptible strains in "ancestral" group ($p<0.05$) was found (Sinkov et al., 2016).

Reasons of success of different emerging clones may be different in each particular case and be related to TB control programs and strain properties. A strong association with MDR was shown for the Russian Beijing B0/W148 strain (compared to other Russian Beijing clones) and genetically, it was due to the acquisition of particular resistance mutations, and likely due to certain compensatory mutations (although beyond *rpoA/C*). The mutation N51I in the regulatory gene *relE* was suggested to be hallmark in evolution of "modern" Ural subgroup, and might promote development of drug resistance (Sinkov et al., 2014). The different capacity of certain, relatively homogeneous clonal groups, to develop particular pathobiologically relevant properties

may be a decisive factor for strain dissemination in the same human population where less hazardous parental strains have been circulating.

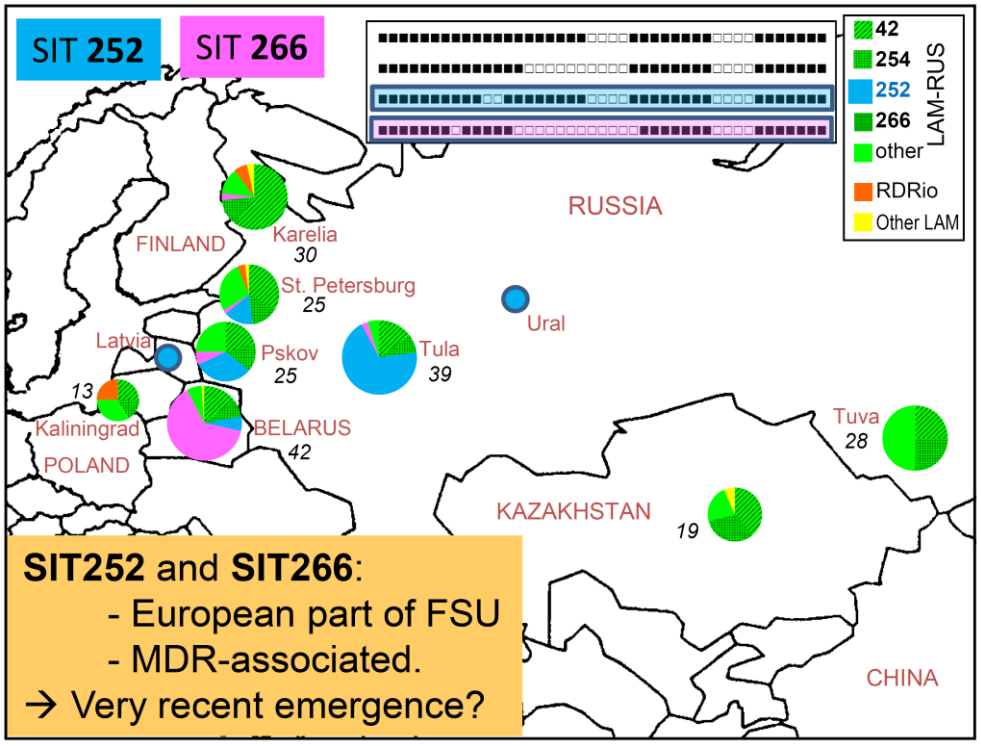

Figure 1: Distribution of the MDR-associated LAM spoligotypes SIT252 and SIT266 in the European part of Former Soviet Union.

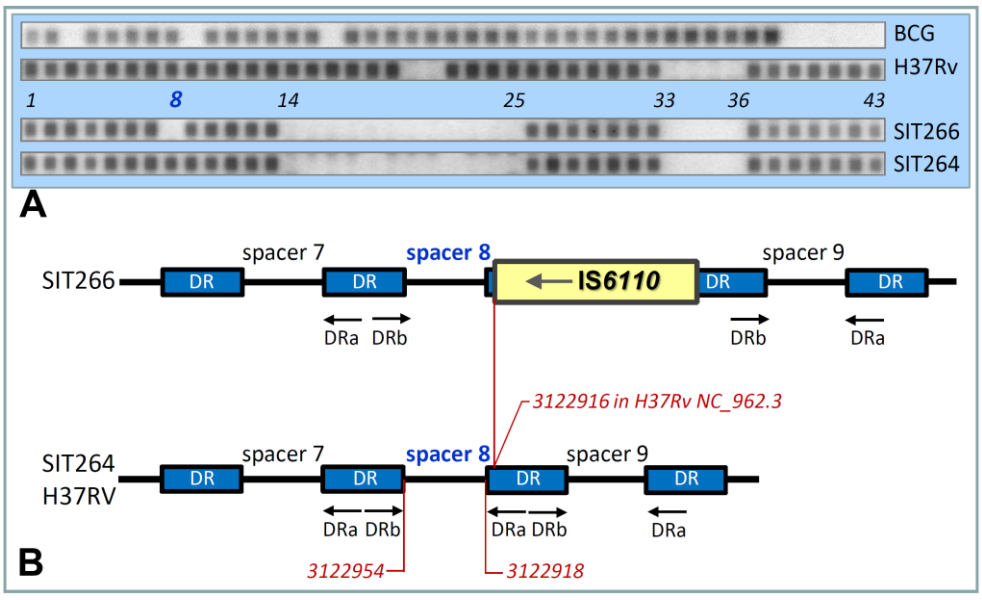

Figure 2: A) Spoligotyping hybridization profiles of H37Rv and BCG reference strains, Mycobacterium tuberculosis SIT266 and SIT264. B) Schematic view of the DR/CRISPR locus (region of spacers 7–9) in spoligotypes SIT264 and SIT266 and reference strain H37Rv, inferred from next-generation sequencing data. Reproduced from Mokrousov et al., 2016a, Copyright © Centers for Disease Control and Prevention, USA.

In addition to the emerging clones within the FSU countries we have drawn attention to one intriguing but apparently underestimated *M. tuberculosis* genotype. Until recently endemic in South Iran, it has started a wider propagation in West/South Asia, already as multidrug resistant strain. Phylogenetically, it makes a part of the large Euro-American superlineage of *M. tuberculosis.* Once consecutively (mis)assigned to the Haarlem and Ural families, it still holds an awkward designation of 'NEW-1' (MIRU-VNTRplus.org). Its convenient molecular signature relies on characteristic spoligotyping profile with absent signals 2, 29-31, 33-36 (prototype spoligotype SIT127; **Fig. 3**). In review 5 years ago, Mokrousov suggested: (i) its phylogeographic specificity for Iran, more precisely, South Iran, and (ii) a historical eastward propagation via Silk Road. However, its dispersal pattern in West Asia since 15-20 years has undergone remarkable changes both in volume (increasing prevalence in Iran) and content (association with MDR). Particular refugee migration flows make this clone of particular epidemiological and clinical concern due to likely jeopardizing impact on TB control programs in different countries. In view of the above, an in-depth pathogenomic analysis of this epidemic and potentially pandemic clone is most relevant and pertinent.

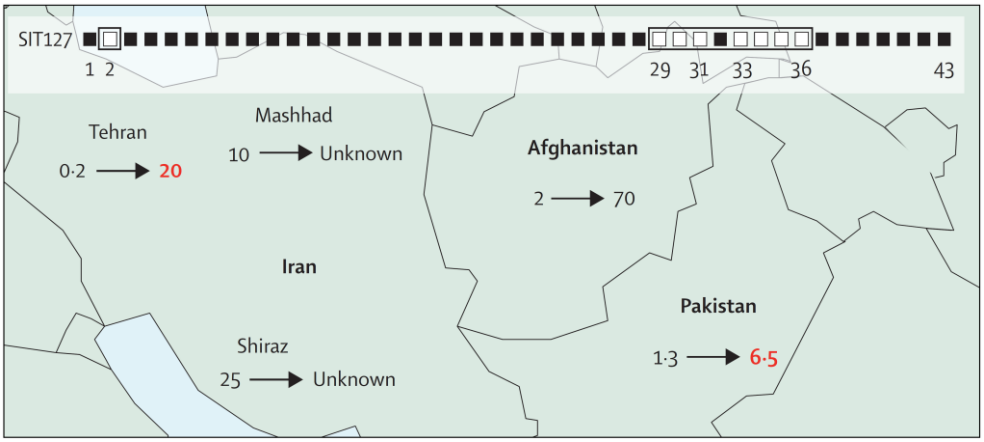

Figure 3: Changes in prevalence of the *Mycobacterium tuberculosis* NEW-1 (SIT127) genotype in Iran and neighbouring countries.
Values below a location show percentage prevalence of NEW-1 among tuberculosis cases in local population in old (2005–08) and recent (2014–16) studies. Red depicts a significant association with multidrug resistance. Reproduced from Mokrousov, 2016, Copyright © Elsevier Ltd.

Dominance of the Beijing genotype among XDR Mycobacterium tuberculosis strains in Russia

The emergence and spread of multidrug-resistant and, more recently, extensively-drug resistant tuberculosis (MDR-TB and XDR-TB) is a major concern of public health that hampers efficient TB control. The Mycobacteriology Laboratory in the St. Petersburg Research Institute of Phthisiopulmonology serves as a reference center for northwest Russia (11 provinces; 1,700,000 sq. km; population of 13.5 million); additionally, the laboratory receives strains from other regions across Russia. This study aimed to perform a molecular characterization of XDR Mycobacterium tuberculosis isolates recovered from TB patients in northwestern Russia during the time period of 2011–2013.
Materials and methods. M. tuberculosis isolates from mainly pulmonary TB patients (extrapulmonary TB, n = 7) were identified and characterized using traditional biochemical methods, including susceptibility testing for 11 anti-TB drugs (streptomycin, isoniazid, rifampin, ofloxacin, kanamycin, amikacin, capreomycin, ethambutol, ethionamide, pyrazinamide, and PAS acid). Drug susceptibility testing (DST) was done using a method of absolute concentrations according to the guidelines of the Russian Ministry of Health (order No.

109 of 21 March 2003) and/or BACTEC MGIT 960 system according to the manufacturer's recommendations. Extensive drug resistance was defined as recommended by WHO (World Health Organization) as resistance to isoniazid and rifampin (MDR) plus resistance to one of the fluoroquinolones and one of three injectable drugs (kanamycin, amikacin, capreomycin). The isolates were further subjected to spoligotyping followed by comparison with SITVIT_WEB and MIRU-VNTRplus databases. LAM family was defined by Rv0129c SNP analysis.

Results. A total of 115 XDR M. tuberculosis isolates were included in this study. They presented 41 different patterns of drug resistance. XDR was complemented with resistance to streptomycin (n = 114), and/or ethambutol (n = 93), ethionamide (n = 80), pyrazinamide (n = 43), or PAS acid (n = 40). Of the three injectable drugs, XDR was mainly due to kanamycin resistance alone (n = 39, 34%), followed by combined kanamycin and amikacin resistance (n = 13), amikacin and capreomycin resistance (n = 11), kanamycin and capreomycin resistance (n = 9). Spoligotyping assigned the isolates to 3 genetic families: Beijing (98; 87%), LAM (SIT42, n = 6; SIT252, n = 2; SIT496, n = 2) and Ural (SIT262, n = 7). SIT1 was predominant among Beijing isolates. The proportion of isolates resistant to any of 5 drugs (including, streptomycin, isoniazid, rifampin, ofloxacin and/or kanamycin, amikacin, and capreomycin) was 1.7% (n = 2), to 6 drugs – 7.8% (n = 9), to 7 drugs – 19.1% (n = 22), to 8 drugs – 26.9% (n = 31), to 9 drugs – 25.2% (n = 29), to 10 drugs – 12.1% (n = 14). Eight isolates of the Beijing genotype were resistant to all 11 tested drugs.

Conclusions. XDR M. tuberculosis population in northwestern Russia is heavily dominated by Beijing genotype isolates (87%).

Latin-American-Mediterranean lineage of Mycobacterium tuberculosis

At present, *Mycobacterium tuberculosis* isolates of Latin-American Mediterranean (LAM) family may be found far beyond those geographic areas that coined its name 15 years ago. We organsied a multicenter study of LAM family, and elaborated the framework phylogeny of this geographically intriguing and pathobiologically important bacterial lineage and hypothesized how its phylogeography was influenced by human demographics and migration. Phylogenetic analysis of LAM isolates from all continents based on 24 minisatellite loci and other markers identified three globally distributed sublineages marked with certain geographic affinities and defined by large deletions RD115, RD174, and spoligotype SIT33 (**Fig. 4**). One minor sublineage defined by spoligotype SIT388 is endemic in Japan. The VNTR signatures were detected for particular sublineages and served for their geographic mapping. Based on results obtained by different kind of analysis, we suggest that LAM family originated in Western Mediterranean. The most widespread RD115 seems the most ancient sublineage, that encompasses genetically and geographically distant branches on all continents, including extremely drug resistant KZN in South Africa and homogeneous LAM-RUS recently widespread in Northern Eurasia. The RD174 sublineage likely started its active spread in Brazil; its earlier branch is relatively dominated by isolates from South America whereas the derived one – by Portuguese and South/Southeastern African isolates. Finally, the relatively most recent SIT33-sublineage is marked with enigmatic gaps and peaks across the Americas and also includes South African clade F11/RD761 which likely occurred in the SIT33 subpopulation only after its arrival to Africa. In addition to SIT388-sublineage, other deeply rooted, endemic sublineages of LAM may exist that yet to be discovered.

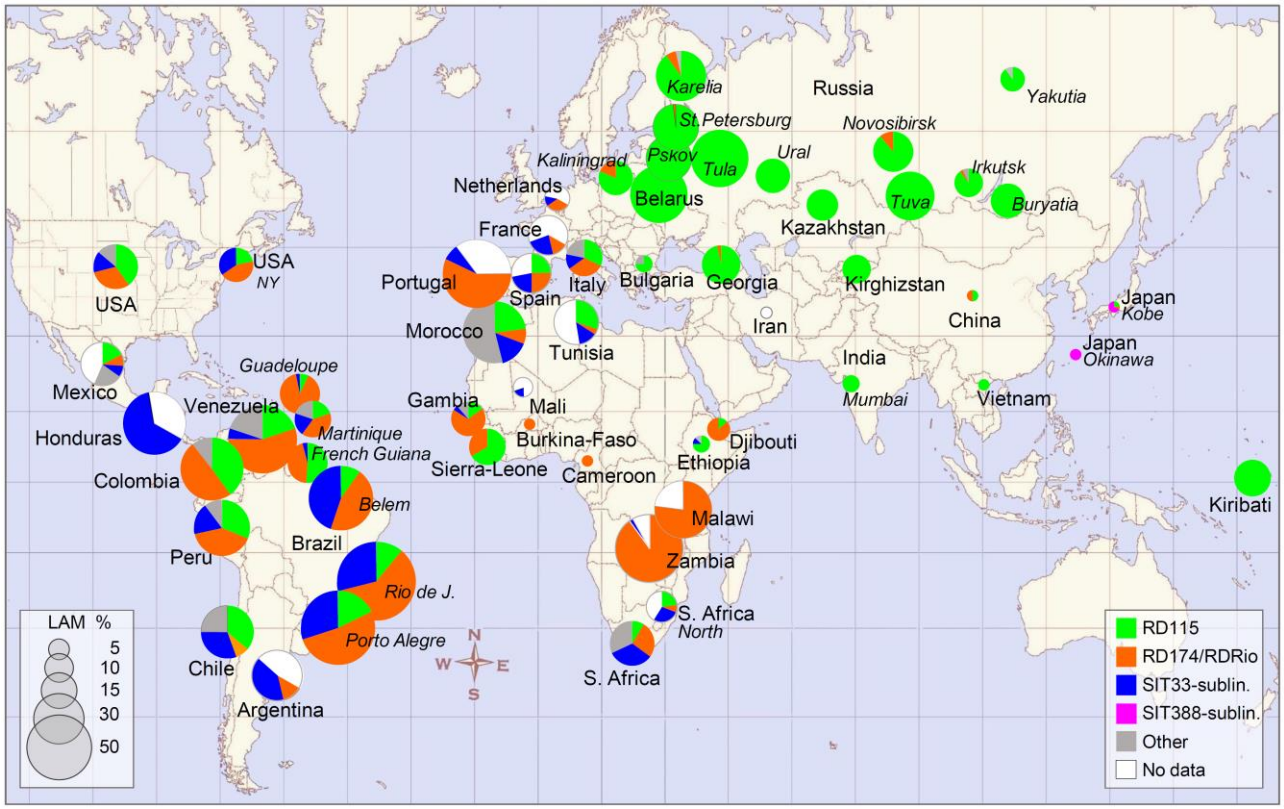

Figure 4: Geographic worldwide distribution of the *M. tuberculosis* LAM sublineages. Reproduced from Mokrousov et al., 2016b, Copyright © Elsevier Inc.

In order to explore all available VNTR information and ultimately to gain more insight into the LAM history and phylogeography, we analyzed relationships between geographic populations targeted in our study, by means of multidimensional scaling (MDS) (**Fig. 5**). We considered relative positions of the studied populations and we determined correlation between the populations in the MDS graph versus geography. On the MDS graph, a high divergence of the four geographically close Western Mediterranean populations should be noted. At the same time, in spite of such remarkable divergence, their relative position correlated with geography (Iberian peninsula vs. Maghreb). Together, this may reflect the ancestral position of this region that could be an area of origin of the LAM lineage. LAM populations in the vast area of Northern Eurasia (i.e., former Soviet Union) form a relatively well delimited cluster separated from the rest of the graph by a grey zone of the intermediate, invisible populations/countries not included in this analysis. Mass human population mixing in the course of the 20th century may explain some homogeneity of these LAM populations.

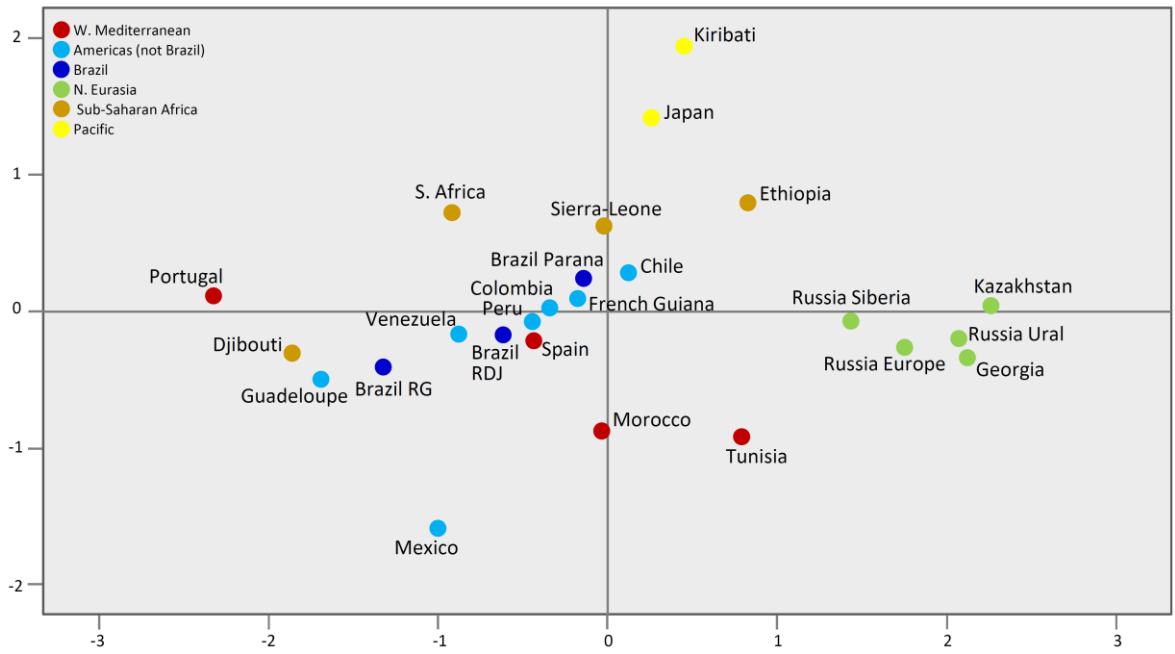

Figure 5: MDS graph of 25 *M. tuberculosis* LAM populations based on 12 MIRU-VNTR alleles. Reproduced from Mokrousov et al., 2016b, Copyright © Elsevier Inc.

Molecular epidemiology of drug-resistant tuberculosis in Republic of Karelia, Russian Federation

Tuberculosis (TB) in Russia remains a major national health problem. However, one of the markers of an unequal social and economic development of different regions within the country is the disparity with regard to the burden of TB. The Republic of Karelia is located at the Russian-Finnish (de facto European Union) border (800 km) and contains most of the historical Karelia land inhabited with autochthonous Karels and more recently migrated Russians. Although tuberculosis (TB) incidence in Karelia is decreasing, it remains high (45.8/100 000 in 2014) with the rate of multi-drug resistance (MDR) among newly diagnosed TB patients reaching 46.5%. Since the collapse of the USSR, the population morbidity via Finnish-Karelian border has been intensified which may have some impact on the epidemiology of TB in Finland.

Past migration of human populations in this area in Northern Europe and historically more recent trans-border exchange shaped both human and human pathogens' local population structures. In modern Karelia the proportion of Karels (autochthonous people close to Finns) decreased from 37.4% in 1926 to 7.4% in 2010. This occurred through massive influx from the neighboring Russian regions between 1920s and 1940 and from more distant and diverse areas across the USSR in 1946-1954 [14]. Furthermore, the borders and population of the Soviet Republic of Karelia have undergone changes since 1920s through (i) incorporation of the ethnically Russian districts, and (ii) annexation of parts of Finnish Karelia by the Soviet Union in 1940/1944.

The study aimed to genetically characterize *Mycobacterium tuberculosis* isolates obtained at different time points from TB patients from Karelia to gain insight into the phylogeographic specificity of the circulating genotypes and to assess trends in evolution of drug resistant subpopulations.

Methods. The sample included 150 *M. tuberculosis* isolates: 78 isolated in 2013-2014 ("new" collection) and 72 isolated in 2006 ("old" collection). Drug susceptibility testing was done by the method of absolute concentrations. Spoligotyping was used to test genotype-specific markers of a Latin-American-Mediterranean (LAM) family and its sublineages as well as a Beijing B0/W148-cluster.

Results. The largest spoligotypes were SIT1 (Beijing family, n=42) and SIT40 (T family, n=5). Beijing family was the largest (n=43) followed by T (n=11), Ural (n=10) and LAM (n=8). Successful Russian clone, Beijing B0/W148, was identified in 15 (34.9%) of 43 Beijing isolates; all B0/W148 isolates were drug-resistant. Seven of 8 LAM isolates belonged to the RD115/LAM-RUS branch, 1 - to the LAM RD174/RD-Rio sublineage. MDR was found in Beijing (32/ 43), Ural (3/10), and LAM (3/8). In contrast, all T isolates were pansusceptible. Comparison of drug resistant subgroups of the new and old collections showed an increasing prevalence of the B0/W148 clonal cluster, from 18.0% (mainly polyresistant) in 2006 to 32.6% in 2014 (mainly MDR and pre-XDR). The West-East increasing gradient is observed for the Ural genotype that may be defined a 'Russian' strain. In contrast, the spoligotype SIT40 of the T family appears to be a historical Karelian strain.
Conclusions. Despite decreasing incidence of TB in Karelia in the last years, the situation with drug resistant TB continues to worsen. The most hazardous strains and clones (Beijing B0/W148 cluster being the major threat) furthermore dominated by MDR and pre-XDR isolates, increasingly spread within the population. Contrasting phylogeographic patterns have been revealed for the Ural genotype and SIT40 spoligotype; they may reflect a complex demographic history of Karelia within the course of the 20th century.

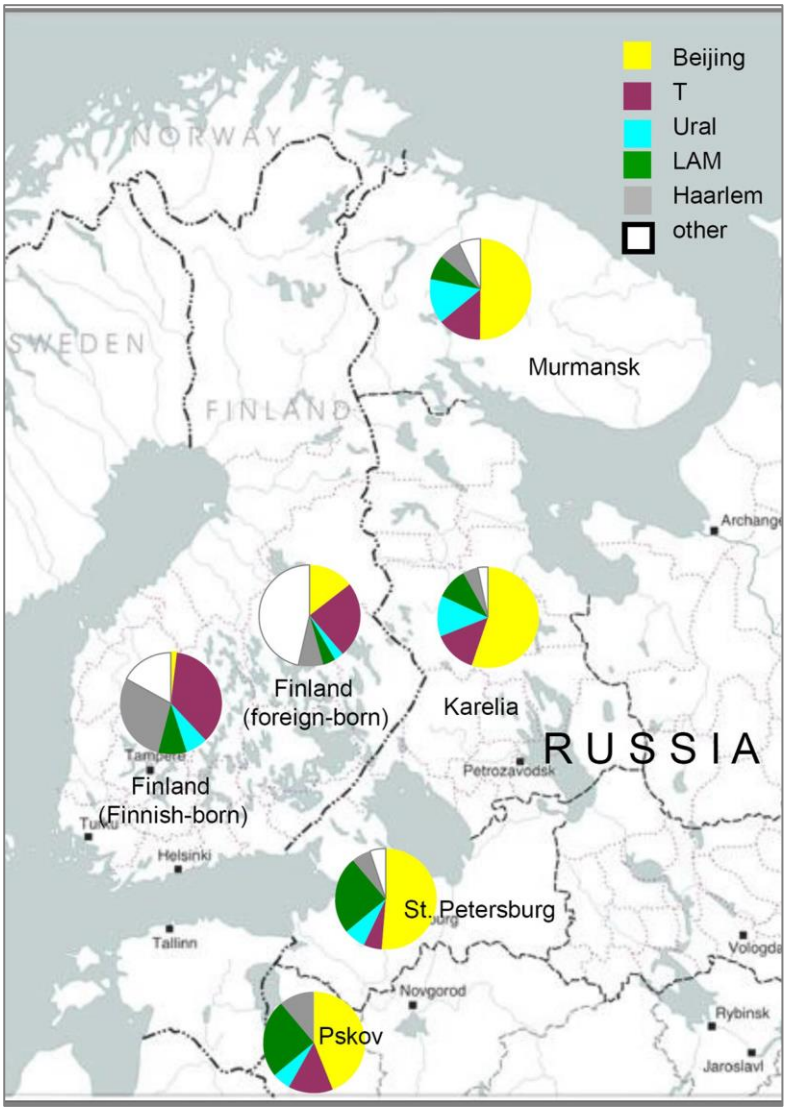

Figure 6: Distribution of *M. tuberculosis* genotypes in Karelia (collection 2013-2014) in its neighboring regions in Russia, and in Finland. Reproduced from Mokrousov et al. 2015. BMC Microbiology (© Mokrousov et al. 2015).

PUBLICATIONS in 2015-2016

Articles in journals/monographic series included in Web of Science or Scopus

In English: 15 articles (13 in Web of Science, cumulative IF = 97.736; mean IF = 7.518), 1 book chapter.

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2. Mokrousov I. Emerging clones of Mycobacterium tuberculosis in Russia and former Soviet Union countries: Beijing genotype and beyond. Int J Mycobacteriol. 2016 Dec;5 Suppl 1:S69-S70.
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In Russian: 1 article.
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5. Umpeleva TV, Vyazovaya AA, Eremeeva NI, Kravchenko MA, Narvskaya OV, Skornyakov SN [Genetic features of the causative agent of tuberculosis in the Ural Federal District, Russia] Tuberk Bolezn Legk. 2016. (8):60-65. In Russian.