proposed an alternative explanation: POA is primarily active against PanD but PanD is only essential if the bacteria are expressing a stringent response, the other genes associated with resistance in some way disrupt the stringent response and eliminate the sensitive phenotype. This suggests a critical role for the stringent response in the life cycle of *M. tuberculosis* as compounds are being developed that target this pathway we suggest these compounds are particularly promising compounds for the treatment of tuberculosis.

6.4

IDENTIFICATION OF MUTATIONS OF RESISTANCE TO FLUOROQUINOLONES, AMINOGLYCOSIDES AND ETHAMBUTOL IN RIFAMPICIN-RESISTANT *MYCOBACTERIUM TUBERCULOSIS*

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The aim of the study was to identify resistance mutations to second-line anti-tuberculosis drugs in patients with *Mycobacterium tuberculosis* clinical samples resistant to rifampicin. Samples of biomaterial from 35 adult residents of the Tyumen region in West Siberia with established by GeneXpert system presence of rifampicin-resistant mycobacteria tuberculosis (MBT) were examined in our study using the MTBDRsl kit (Hain Lifescience, Nehren, Germany) according to the manufacturer's instructions. The mutations were identified in genes encoding DNA gyrase *(gryA)*, 16S RNA *(rrs)*, and arabinosyltrasferase *(embB)* associated with resistance to fluoroquinolones (FLQ), injectable aminoglycosides/cyclic peptides (AG/CH) and ethambutol (EMB) respectively.

In 9 of the examined samples (25.7%) the MBT resistance to all three groups of drugs was revealed. In the remaining 26 samples, the MBT sensitivity to one or two groups of drugs can be assumed. Samples from 24 patients (92%) were genetically susceptible to AG/CH (in 2/3 cases solo, in 1/3 — in combination with sensitivity to ethambutol (5 samples) and fluoroquinolones (1)). Most samples demonstrated genetic resistance to fluoroquinolones (97%) and ethambutol (80%), and 30% of samples are resistant to aminoglycosides/cyclic peptides.

Among the *gyrA* mutations, 11 were in codon 90 (A90V), 43 — in codon 94 (of which 4 — D94A, 6 — D94N, D94Y, 30 — D94G and 3 — D94H). No mutation in codon 91 (S91P) was detected. In 22 samples 1 mutation was detected, in 4 — 2 mutations, in 6 — 3 mutations, and in 1 — 5 mutations. Among the mutations found in the *rrs* gene, 8 are in codons 1401—1402 (A1401G, C1402T) and 10 — in codon 1484 (G1484T), all mutations in codons 1401—1402 are combined with the presence of a mutation in codon 1484. Among mutations in *embB* (codon 306) in three cases replacement of M306I = 306 ATG/ATA, M306V, in 26 — replacement of M306I = 306 ATG/ATC/ATT was revealed. In 24 cases only one variant of the mutation is found, in 2 — both, and in 18 samples in the presence of a mutation there is no marker of wild type.

In conclusion, preliminary data on the genetic structure of MBT strains resistant to rifampicin and second-line anti-tuberculosis drugs were obtained in tuberculosis patients from the Tyumen Region in Siberia.

6.5

MOLECULAR TYPING OF *MYCOBACTERIUM KANSASII* — A GLOBAL PERSPECTIVE

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To date, over 180 nontuberculous mycobacteria (NTM) species have been identified and almost 30 of these species have been reported as the causative agents of pulmonary and extrapulmonary diseases. *Mycobacterium kansasii* is the sixth most frequently isolated NTM species across the world. The isolation rate of this pathogen, among other NTM, has been calculated at 5% in Europe and 4% globally. In Poland and Slovakia, the recovery of *M. kansasii* from respiratory samples is particularly high, being 36% and 35%, respectively.

The genetic heterogeneity of *M. kansasii* is defined by the presence of seven molecular subtypes. Most of the disease-related strains belong to subtype I and II, while the others (III-VII) have usually been linked to environmental sources. Therefore, subtyping of *M. kansasii* isolates from human samples may be helpful for clinical diagnosis.

The aim of this study was to determine the distribution of *M. kansasii* subtypes among clinical isolates from 19 countries on 4 continents.

A total of 475 isolates recovered between 2000 and 2017 from as many patients with suspected *M. kansasii* disease were analyzed. The isolates were collected from 19 coun-