

Epidemiological analyses of tuberculosis in Archangelsk, Russia and implementation of a rapid assay for detection of resistance in this high burden setting

ELISEEV P.¹, MARYANDYSHEV A.¹, NIKISHOVA E.¹, TARASOVA I.², GORINA G.², CHRYSSANTHOU E.³, RIDELL M.⁴ and LARSSON L-O.⁵

Northern State Medical University, Archangelsk, Russia,¹ Regional Clinical Antituberculosis Dispensary, Archangelsk, Russia,² Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden,³ Department of Microbiology and Immunology, Institute of Biomedicine, University of Gothenburg, Göteborg, Sweden,⁴ Department of Medicine, Division of Respiratory Medicine, Karolinska University Hospital, Stockholm, Sweden.⁵

Running head: TB epidemiology and rapid detection of MDR-TB in Archangelsk

The aim was twofold: to perform epidemiological analyses of tuberculosis (TB) in the Archangelsk region with particular focus on multidrug-resistant (MDR) TB and to evaluate the molecular method MTBDR*plus* assay in this high burden setting.

In total 812 TB cases (incidence 65/100000) were registered in the Archangelsk region in 2010. Among all these cases 144 (22%) were relapses. Furthermore, 151 were registered in the penitentiary system in which the epidemiological situation thus was particularly severe (incidence 1162/100 000). A majority of the patients were men and most of the cases had pulmonary TB (94%). Out of the 812 cases, 341 (42%) were smear positive and thus contagious and 173 (21%) had MDR-TB. In addition one TB patient had a strain being monoresistant to rifampicin. The number of patients being both contagious and MDR-TB was 157 representing 19% of all cases (incidence 12.5/100000) and 44% of all the relapses belonged to this group.

Specimens from 173 patients with smear positive pulmonary TB were analysed with both MTBDR*plus* and Bactec MGIT and the result corresponded in 98.8%. The study demonstrates that MTBDR*plus* is of major value in high burden settings.

Key-words: *Mycobacterium tuberculosis*, Multidrug-resistant, Russia, Genotype MTBDR*plus* assay

Correspondence to: Platon Eliseev, Northern State Medical University, Troitsky av.51, 163000 Arkhangelsk, Russian Federation, pediatrics@yandex.ru

Tuberculosis (TB) is a great problem worldwide (1). Particularly severe is the fact that the number of multidrug resistant tuberculosis (MDR-TB) cases has increased during the last decades (1, 2). Russian Federation is a high burden country in this respect; 18% of all new TB cases were MDR-TB in 2010(1). A high prevalence of MDR-TB decreases the treatment success rates (2, 3) and thus represents a severe public health problem. Rapid diagnosis of contagious MDR-TB, as well as an early start of appropriate treatment, is of major importance since it prevents further spread of the disease and shortens the time of hospitalisation as well. There is an imperative need for rapid drug susceptibility testing methods considering the increase of resistant *Mycobacterium tuberculosis* strains worldwide. Such methods enable appropriate clinical care and guidance to the optimal treatment regime.

Bactec MGIT 960 (BD, Sparks, MD, USA) and the absolute concentration method on Löwenstein-Jensen (L-J) medium are important tools in the diagnosis of MDR-TB (4, 5). The former can take from 20 to 35 days until the drug susceptibility test results are obtained and the L- J method takes even longer time.

Molecular Line Probe assays reveal mutations in DNA of *M. tuberculosis* and permit rapid analyses of rifampicin and isoniazid resistance (6-9). Presently the Genotype MTBDRplus assay (Hain Lifescience GmbH Nehren Germany) has become widely used. This assay determines drug resistance in 2 days and is recommended by WHO to detect cases of MDR-TB (10). Numerous studies performed in different settings provide data on good test's performance with high specificity and sensitivity(6-9,19.20,21,22,23), including studies from Russian federation (8) and other Former Soviet Union countries (19) Arkhangelsk region of Russian federation is a hot spot for MDR TB with 23,8% and 25,8% MDR TB among new cases registered in 2008 (2) and 2009 (24). Genotype MTBDRplus assay was introduced in 2009 in this high MDR TB setting for a rapid detection of drug resistant TB cases.

The aim of this study was twofold; to perform epidemiological analyses of tuberculosis (TB) in the Arkhangelsk region with particular focus on multidrug-resistant (MDR) TB and to evaluate the molecular method MTBDRplus assay in this high burden setting.

MATERIALS AND METHODS

Примечание [ПЕ1]: Рецензент 2
пункт 5

Примечание [ПЕ2]: Пункт 1
рецензент 1

The epidemiological analyses were performed at the Regional Clinical Antituberculosis Dispensary in Archangelsk Russia. Specialized tuberculosis control services in Arkhangelsk region consisted of the dispensary as well as out-patient departments in general hospitals and clinics, what meets the principles of TB control in Russian federation (25). Surveillance of TB incidence in the region was performed by statistical department in Regional Clinical Antituberculosis Dispensary. All cases of TB, including pulmonary as well as treatment outcomes, diagnostics results etc., are mandatory registered. Data was collected according to WHO's experts recommendations as well as national law and was presented and reported annually on regional, national and international level (8,9).

Примечание [ПЕ3]: Рецензент 1 3 абзац

All cases were registered as either a new or a relapse case. A new case of TB was defined as patient with newly diagnosed tuberculosis. A relapse case was defined as a patient previously treated for TB who has been declared cured or treatment completed and is diagnosed again bacteriologically with TB according to WHO. Non-pulmonary TB refers to disease in which the initial infection was *not* in the lung (11) and pulmonary TB refers to disease in the lung due to lesions from a pulmonary focus. Age and gender were registered for all patients and whether or not they belonged to the civil sector or the penitentiary system. Concomitant diseases, apart from HIV, were not registered.

Примечание [ПЕ4]: Рецензент 1 пункт 4

After a TB case was registered patients were giving in sputum samples, that could be collected in Central dispensary, if patients were hospitalised, or at the district Tb doctors, where patients were receiving treatment in the outpatient department. Three sputum samples were available for each patient and were sent to the Laboratory of the Regional Clinical Antituberculosis Dispensary for culture, MTBDRplus, cultural DSTs and additional microscopy. Direct microscopy was performed on all three samples. Two of the samples were cultured on L-J medium and one on Bactec MGIT liquid medium, with subsequent cultural DSTs for first line drugs using Bactec MGIT, and second line drugs using method of Absolute concentration on L-J medium. All TB patients were routinely tested for HIV.

Примечание [ПЕ5]: Рецензент 2 пункт 4

Comparison of the two drug-susceptibility testing methods was performed only on samples from patients of the civil sector. Smear-positive samples were analysed for susceptibility patterns by the GenoType MTBDRplus and the Bactec MGIT 960 according to the instructions of the manufacturer. In addition the method of absolute concentrations on L-J medium was used for drug susceptibility testing (DST) in cases of TB when the susceptibility patterns were divergent using the two other methods. One sample was used for GenoType MTBDRplus and the Bactec MGIT 960 culture and subsequent DST simultaneously.

Примечание [ПЕ6]: Reviewer 2 question 2

Примечание [ПЕ7]: Reviewer 1 question 8

Примечание [ПЕ8]: Рецензент 2 пункт 4

RESULTS

In total 812 TB cases were registered in the year 2010 in the Archangelsk region (incidence 65/100000): 661 in the civil sector and 151 in the penitentiary system. The Archangelsk region has a population of 1 254 499 in the civil sector and almost 13 000 in the penitentiary system and the incidence was thus 53/100,000 in the civil sector and 1162/100 000 in the penitentiary system.

Table 1 shows the epidemiological situation among 812 TB patients in Archangelsk in the year 2010. The new cases represented 668 (82%) and the relapses 144(18%) patients. A majority of the patients in the civil sector were men and the male dominance was particularly high among the relapses. In the penitentiary system all patients were men, but this is due to the fact that women were situated in penitentiary system of different region and only men were situated in Arkhangelsk region. Most patients were in their 30s or 40s; the prisoners being somewhat younger than those in the civil sector. Most patients had pulmonary TB, particularly the relapses. In total 23(2.8%) of the TB patients were HIV infected and most of them were prisoners.

Among all the 812 TB cases 341 (42%) were smear positive and thus contagious. Furthermore 173 (21 %) patients had MDR- strains, and one patient had a strain being resistant to rifampicin but susceptible to isoniazid. Five percent (44 patients) carried strains being resistant to isoniazid but susceptible to rifampicin. Additional drug resistance, including second line drugs is provided in Table X

The number of TB cases being both contagious and MDR-TB was 157 representing 19% of all TB cases and an incidence of 12.5/100000. Among these 157 TB patients being both smear positive and having MDR-TB 94 were new cases representing 14% of all the new cases and 63 were relapses representing 44% of all the 144 relapses.

The MTBDR*plus* assay was implemented in the routine laboratory practice in Archangelsk in 2010. Out of the 297 smear positive pulmonary TB cases diagnosed in the civil sector 211 cases were available for the MTBDR*plus* assay and comparison analyses. Thus, 86 cases were not available for comparison analyses and among them 59 patients were admitted as smear negative according to the preliminary results from other health care facilities. Furthermore, 14 patients were not included since it was primarily not known whether they were new cases or relapses (usually non-local residents), 7 patient died before

Примечание [ПЕ9]: Reviewer 1
question 6

Примечание [ПЕ10]: Reviewer 2
comment 2

definitive diagnosis thus no sample was sent from them to the Laboratory of the Regional Clinical Antituberculosis Dispensary, and 6 patients were residents from a remote area and it was not possible to obtain the requested amount of sputa for the validation procedure.

Примечание [ПЕ11]: Рецензент 2
пункт 4

The results from MTBDR*plus* and Bactec MGIT 960 DST for these 211 cases were compared. However, 7 specimens gave uninterpretable results of the MTBDR*plus* assay due to overall weak signals of the strips and 31 strains did not grow or were contaminated. For 173 patients the results of MTBDR*plus* were compared with DST by Bactec MGIT 960. Thus, the result of 173 cases remained, among which 153 represented new cases and 20 relapses. Median time for result of MTBDR*plus* and Bactec MGIT was 8 and 28 days respectively.

Примечание [ПЕ12]: Reviewer 2
question 7

The result of the comparison is given in Table 2 and 3. As is seen from the tables the results were in concordance but for five cases (3 %). All of the discrepant cases were male and new cases of TB. In three cases out of the five the Bactec MGIT, revealed INH resistance though MTBDR*plus* showed susceptibility which was confirmed by the absolute concentration method. On the other hand, for the other two cases the MTBDR*plus* revealed rifampicin resistance, while both Bactec MGT and L-J showed susceptibility.

The study revealed that the majority of isoniazid resistant isolates (N = 85; 98.8%) had mutations in codon 315 of katG gene including 7 strains in which inhA gene also harboured a mutation. In the majority of rifampicin resistant cases (N = 63; 88.7%) codon 531 of rpoB gene was mutated.

In one case both wild type and mutation probes were registered in katG and rpoB genes simultaneously, in one case only in rpoB gene and in 4 cases only in katG gene. All 6 cases were defined as resistant to drug or drugs according to the mutations revealed by MTBDR*plus*, that was subsequently confirmed by susceptibility testing, i.e. no discrepant results in the two methods were observed in this group.

DISCUSSION

In the present study from Archangelsk Russia we show that an absolute majority of the TB cases had pulmonary TB whereof more than 40% of the cases were contagious i.e. smear positive in a predominately male patient group. The incidence of TB in the penitentiary system was 1223/100 000 i.e. being more than 20 times higher than in the civil sector, which shows that the situation in the prisons is most severe. Incidence figures over 1000 indicate that practically all inmates have been exposed to TB.

As expected HIV positivity was much more common among the inmates, where more than 10% of the TB patients were HIV positive. In contrast less than 1% of the civilian TB patients were HIV positive.

The number of MDR-TB cases was high being 22% of all the cases. Particularly among the civilian relapses the number of MDR cases was dramatically high, being 45% of all these cases. The number of patients being both smear positive i.e. contagious and MDR-TB was 131 representing 16% of all cases (incidence 10/100000). Among all the relapse cases 44% belonged to this group. The large number of contagious MDR cases stresses the necessity of rapid methods for drug susceptibility.

The incidence of tuberculosis declined steadily in Russia until 1990 due to socio-economic improvement and implementation of a strict control program with miniature-chest-X-ray and tuberculin skin testing. Mass BCG-vaccination was performed as well. The TB situation then worsened and the incidence peaked in 2000 being 91/100 000 in Russia and 104/100 000 in Arkhengersk region, but the increase has since then been halted. In the year 2010 the incidence was 77/100000 in Russia and 53/100 000 in Archangelsk (12). The incidence was thus lower in Archangelsk compared to Russia as whole. This may be attributed to several factors e.g. the Archangelsk region is not densely populated (approximately 2,2 men per km²) and the incidence of HIV is low (86 newly diagnosed HIV cases in 2010 with incidence 5.4/100 000). Urbanisation is far less apparent compared to other regions and urbanisation facilitates spread of infectious diseases in particular TB (13). The medical health authorities has furthermore allocated substantial resources for bacteriological diagnosis of TB, supervised treatment of TB cases according to international consensus, and social support to those in need through aid programs (1).

Even if the incidence has decreased there has been a steady increase in MDR-TB cases, not only in relapses, but in new cases as well. The number of MDR-TB cases presented here is strictly based on cases with a positive culture and validated results from a susceptibility test, i.e. the true number of MDR-TB cases is expected to be higher.

The TB patients were usually suffering from pulmonary TB which may be attributed to the dominance of the Beijing strain in this area (14) as well as low TB/HIV coinfection (26). Furthermore a hypothesis of a south-north axis concerning different expressions of TB has been put forward since there are less cases of extrapulmonary TB among the patients born in the Nordic countries compared to those born in Africa (15). Archangelsk is located in the vicinity of the polar circle. In addition extrapulmonary TB may have a less obvious clinical presentation with a possible delay or lack of diagnosis.

Примечание [ПЕ13]: Reviewer1
question 10

Примечание [ПЕ14]: Reviewer 1
question 8

Примечание [ПЕ15]: Reviewer 1
question 3

Prisoners are particularly prone to develop TB during the penal servitude (16) or after release, due to the special risk factors within the prison system including narcotic drug use, low income, high ratio of prisoners per available bed, not having own bed clothes, little time outdoors, smoking (27,28) and their own health conditions. The prison system has unique possibilities to screen risk-groups using chest X-ray for TB and MDR-TB at admission and at least every 6 months during imprisonment. An implementation of rapid molecular biology detection methods for analyses of TB and resistant TB would serve a particular important cause in this setting. In the Archangelsk region there are several penal institutions that may interfere with the civil society from a transmission standpoint, which may partly explain the high percentage of contagious cases and resistant pulmonary TB.

A rapid method for analysing drug susceptibility of *M.tuberculosis* strains is highly cost-effective (2, 10). Appropriate treatment and isolation procedures for MDR-TB can be rapidly implemented and limit transmission to fellow patients and others. In addition the cure rate for MDR-TB cases increases, the number of deaths is reduced and the time of hospitalisation shortens. The present study confirms the value of a rapid drug susceptibility method in a high burden setting such as the Archangelsk region.

As is described in Table 3 the sensitivity and specificity of the assay for the detection of rifampicin, isoniazid and MDR-TB respectively were 96 % or above and correspond to results in other settings (6, 7). The sensitivity rate was similar, though the specificity rate was higher compared to those reported from another Russian study (8). Thus, the results of the MTBDR *plus* assay give a firm basis for therapy decisions in the study setting with its particular prevalence of *M. tuberculosis* genotypes and demographic profile.

A strain being monoresistant to rifampicin was detected in this study and similar findings are described by other authors as well (9, 17). The emergence of resistance is a dynamic procedure and rifampicin monoresistance is an expected biological phenomenon. Monoresistant rifampicin is however relatively uncommon in many settings, why it has been suggested to test only for rifampicin, particularly in low income settings. Since isoniazid is a key drug in TB treatment such suggestions need great cautiousness.

In this study wild type and mutation probes simultaneously were revealed in five TB-cases. This may be due to the co-existence of two or more strains in the same sample and poses important clinical questions such as which therapy regime should be used. The corresponding finding has been reported in another Russian setting as well (8). There were discrepant results between the methods in 12 cases which can be explained by errors that might occur during the performance of the methods, a current progressive development of

Примечание [ПЕ16]: Review 1 question 12

Примечание [ПЕ17]: Review 1 question 13

resistance and by simultaneous presence of susceptible and resistant strains of *M. tuberculosis* as well as the possible coexistence of non-tuberculous mycobacteria.

In the prospect of further development of rapid molecular biology detection methods for detection of TB, MDR-TB and extended drug resistant TB the conventional methods may in the future be used for divergent and unclear cases.

The disadvantage of molecular biological techniques such as the present one is mainly the need of a well equipped laboratory and a skilled laboratory staff. A more robust method for use in field like conditions is thus a priority development goal. The methods are costly, but a wider use of rapid drug susceptibility testing is nevertheless considered the most cost-effective by WHO (18).

Conclusion The present study from Archangelsk Russia shows an alarming TB situation with a high number of contagious MDR-TB cases. The Archangelsk Regional Clinical Antituberculosis Dispensary was among the first laboratories in Russia that implemented in routine clinical practice the Genotype MTBDR_{plus} assay which was shown to be of major value in this high burden setting.

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Table 1 Epidemiological characteristic of the 812 TB patients

	Civil sector		Penitentiary system	
Number of TB cases	661		151	
	New cases	Relapse cases	New cases	Relapse cases
Number	574	87	94	57
Male (%)	385 (67)	70 (82)	94 (100)	57 (100)
Age years median (SD)	42 (14)	46 (12)	34 (10)	38 (10)
Pulmonary TB(%)	512 (89)	83 (95)	90 (96)	57 (100)
HIVinfected (%)	7(1)	0	9 (10)	7 (12)
Smearpositivity (%)	252 (49)	45 (54)	26 (28)	18 (32)
MDR (%)	109 (19)	39 (45)	13 (14)	15 (26)

Table 2. Comparison of Bactec MGIT and MTBDRplus: the number of resistant strains is given

	New cases		Relapses	
Total number of strains	153		20	
	Bactec MGIT	MTBDRplus	Bactec MGIT	MTBDRplus
Isoniazid	73 (48 %)	70 (46 %)	16 (80 %)	16 (80 %)
Rifampicin	55 (36 %)	57 (37 %)	14 (70 %)	14 (70 %)
MDR	55 (36 %)	57 (37 %)	14 (70 %)	14 (70 %)

Table 3. Sensitivity, specificity of MTBDRplus assay and rate of matching results

	Matching results (%)	Sensitivity (%)	Specificity (%)
Isoniazid	98.3	96.6 (95 CI 89.8 – 99.1)	100.0 (95 CI 94.6-100.0)
Rifampicin	98.8	100.0 (95 CI 93.4-100,0)	98.1 (95 CI 92.5-99.7)
MDR	98.8	100.0 (95 CI 92.5 – 99.7)	98.1 (95 CI 92.5 – 99.7)

Table X. Drug susceptibility testing results in Arkhangelsk region in 2010

Примечание [ПЕ18]: Reviewer 2 comment 2

	Civil sector				Penitentiary system			
	New cases		relapses		New cases		relapses	
	Number	%	Number	%	Number	%	Number	%
Total number of patients with DST results	307		55		35		21	
No drug resistance detected	121	39,4	7	12,7	10	28,6	4	19
Drug resistance detected	186	60,6	48	87,3	25	71,4	17	81
H	140	45,6	43	78,2	18	51,4	16	76
R	108	35,2	38	69,1	13	37,1	15	71
S	165	53,7	43	78,2	23	65,7	17	81
E	94	30,6	32	58,2	11	31,4	10	48
Z	24	7,8	8	14,5	1	2,9		0
Km	14	4,6	5	9,1	6	17,1	4	19
Cm	9	2,9	3	5,5	1	2,9		0
Ofx	3	1,0	3	5,5	2	5,7		0
Pto	25	8,1	18	32,7	1	2,9		0
PAS	24	7,8	3	5,5	5	14,3	3	14
Cs	6	2,0		0,0	2	5,7	1	5