Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus,
Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March , 2017, MINSK , BELARUS

Shorter MDR TB treatment regimens – experience of Arkhangelsk region

Andrey Maryandyshev – Chief TB Expert of the Ministry of Health of the RF for the North-Western District

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Andrey Maryandyshev – Chief TB Expert of the Ministry of Health of the RF for the North-Western District

Dmitry Perkhin – Chief TB Doctor of Arkhangelsk Clinical Tuberculosis Dispensary

Миронюк Оксана Михайловна Oksana Mironuk – Medical Deputy Chief Doctor of Arkhangelsk Clinical Tuberculosis Dispensary

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Arkhangelsk region is situated in the North-West of the European part of Russia

Area - 410 700 sq. km – 12th largest region in the country

- **1 117096 population**

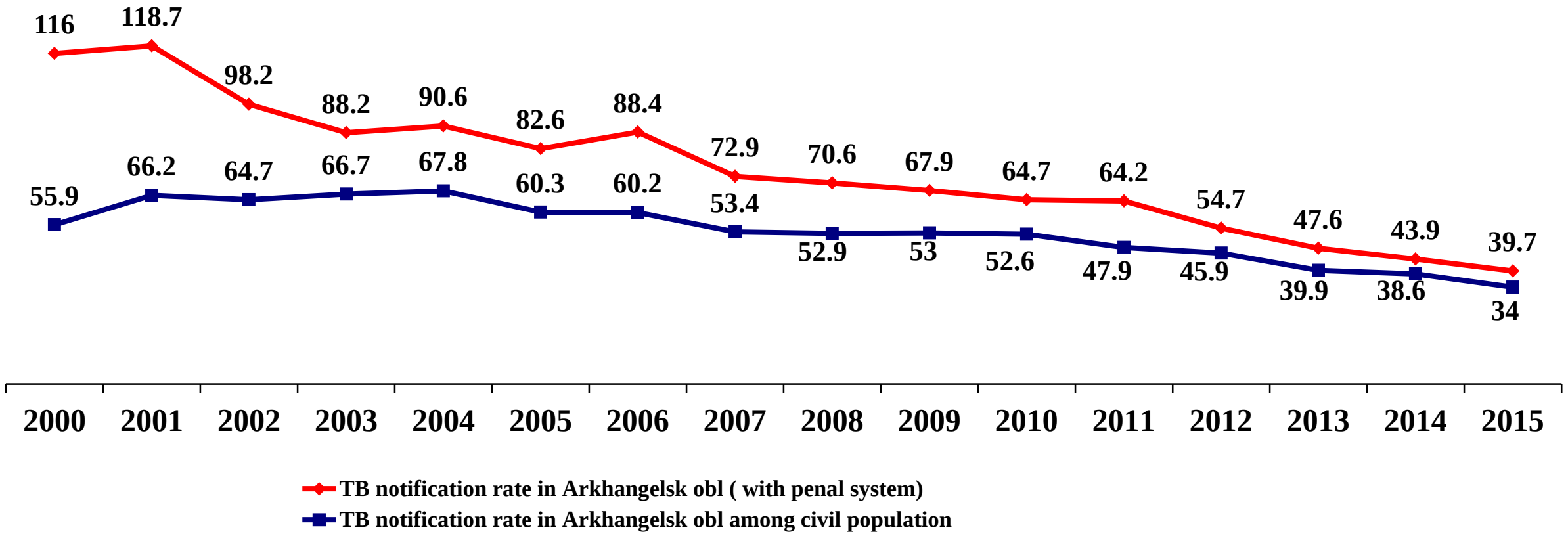
Adults	-	950810
Adolescents	-	33 864
Children	-	186 422

Penitentiary system:

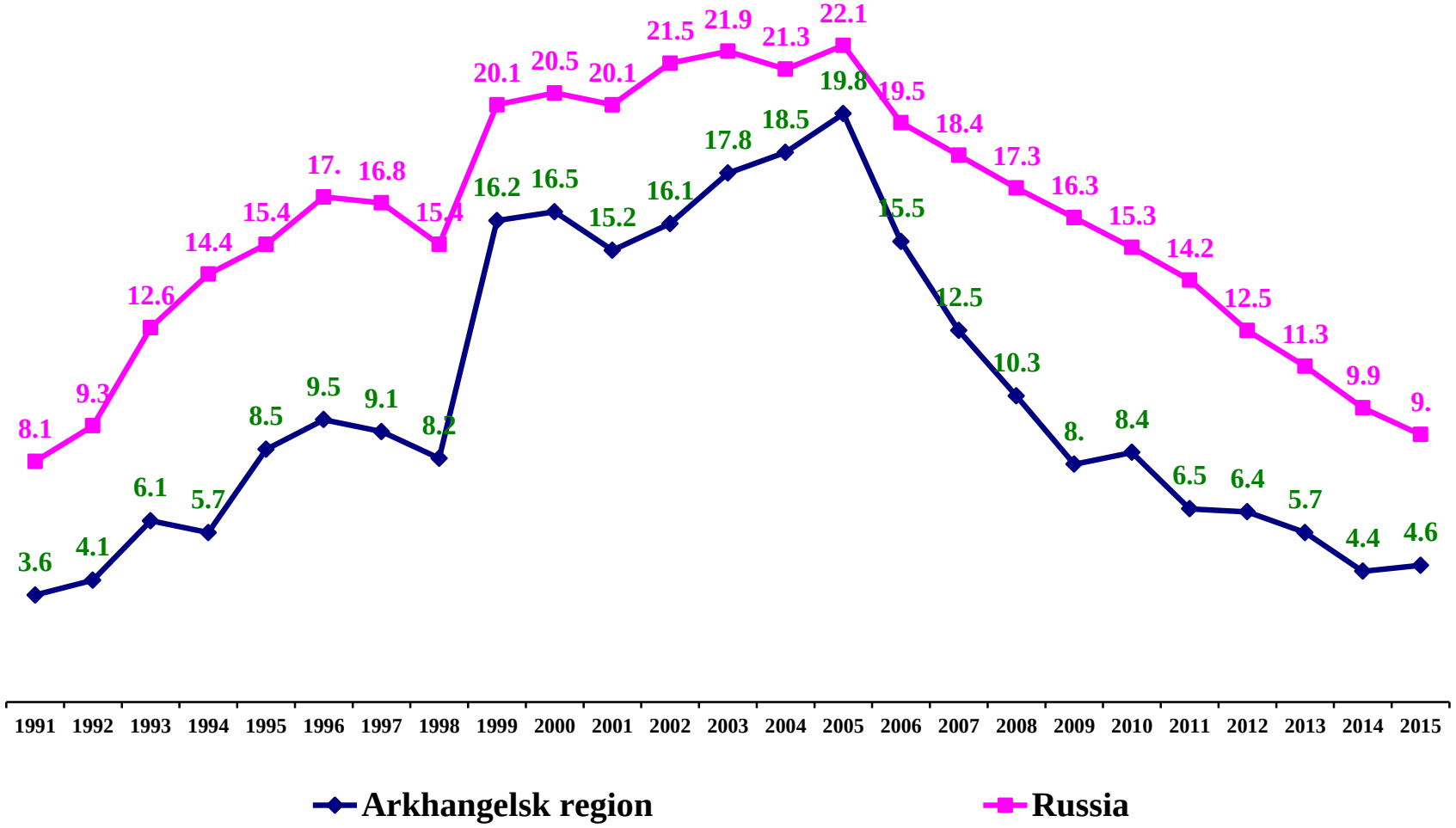
24 institutions

>11000 prisoners and persons under investigation

TB notification rate Arkhagelsk region (new cases and relapses) in 2000-2015 per 100 000 population



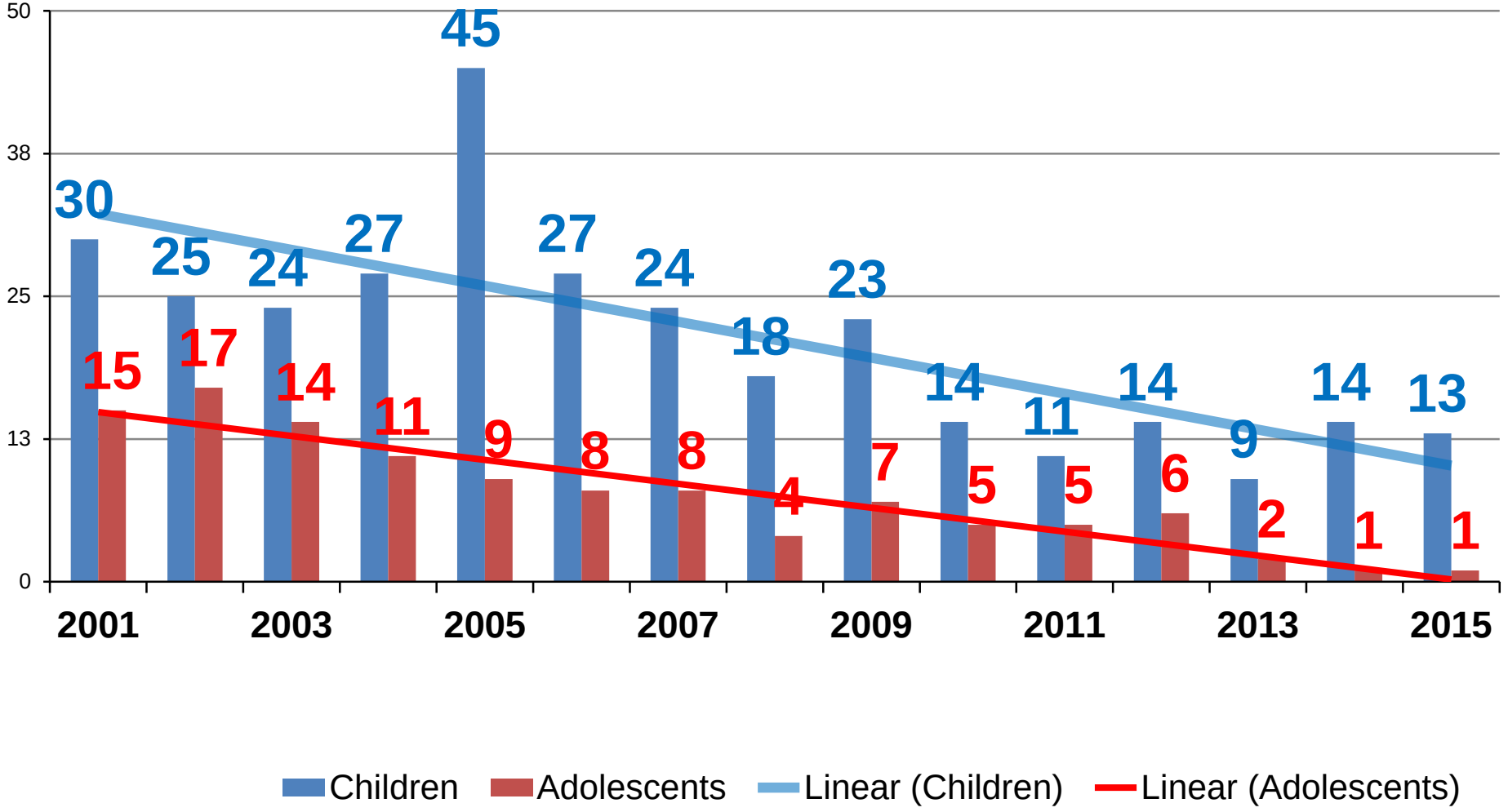
Tuberculosis mortality in Russia and Arkhangelsk region, including penitentiary system. 1991-2015 (per 100 000)



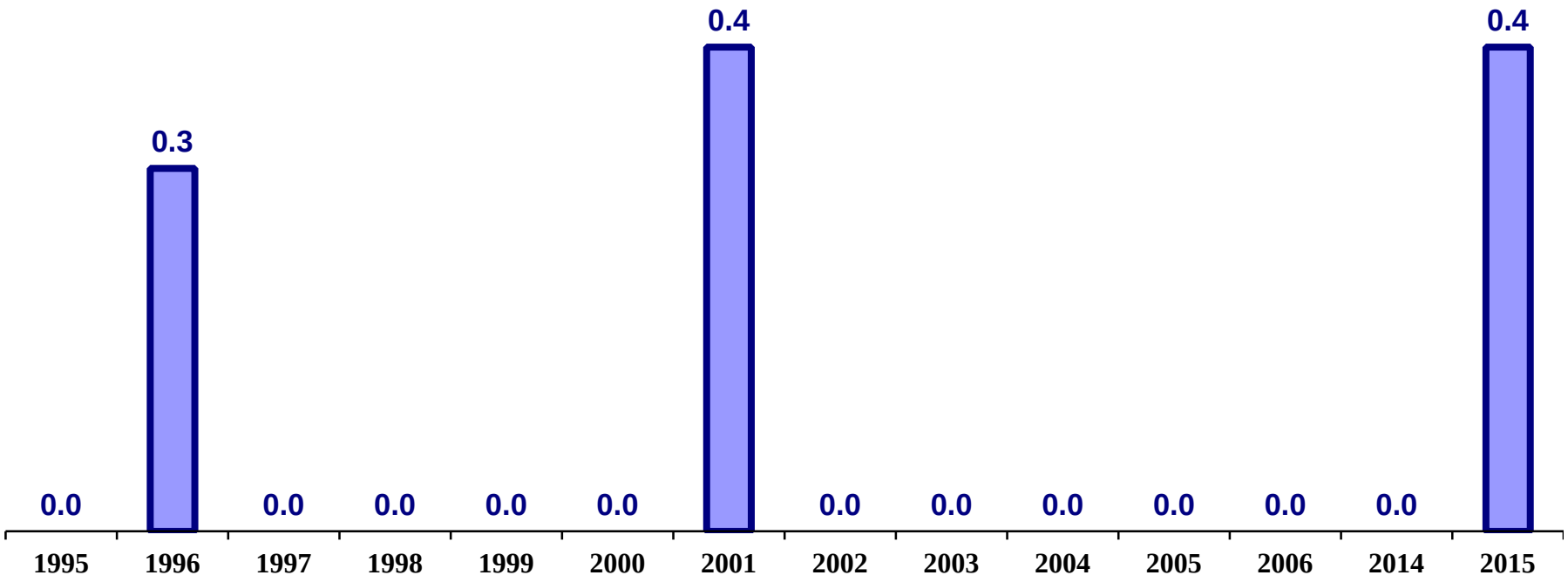
Drug sensitivity of MTB in 2015

Drug sensitivity pattern	New cases	Relapses	Treatment after default	Treatment after failure
Total # registered	329	58	1	2
AFB+ patients	228	46	1	2
# and % with DST done	222 (97,4%)	46 (100%)	1	2
DS	52,3%	26,1%	-	100%
Resistance to H+	8,6%	-	-	-
Resistance to R/H R	29,3%	56,5%	100%	-
Resistance to H R Fq	4,1%	6,5%	-	-
Resistance to H R Km/Am/Cm	3,2%	2,2%	-	-
Resistance to H R Fq Km/Am/Cm	3,6%	6,5%	-	-

Tuberculosis incidence in children and adolescents, 2011-2015



Tuberculosis mortality in children and adolescents in Arkhangelsk region in 1995-2015 per 100000 population



MDR TB treatment and shorter regimens in children in Arkhangelsk region

- Prevalence of MDR TB is among the highest in the RF: 40% of new cases and 70.2% of previously treated cases
- Retrospective cohort study of MDR TB treatment efficiency in children was conducted
- First paediatric case of MDR TB was registered in 2001
- 52 children treated for MDR TB from 01.01.2011 to 31.12.2012

Eur Respir J. 2016 Nov;48(5):1496-1499. doi: 10.1183/13993003.00354-2016. Epub 2016 Sep 1.

Multidrug-resistant tuberculosis in children in northwest Russia: an observational cohort study.

Smimova PA[1,2], Turkova A[3,2], Nikishova EI[4], Seddon JA[5], Chappell E[6], Zolotaya OA[1], Mironuk OM[1], Maryandyshev AO[4].

Paediatric MDR TB: Background

	Children <15 n 36	Adolescents <1816	Total
Age	7,0 (4,1-10,9)	16,6 (15,9-17,2)	10,6 (5,0-15,9)
Boys	13 (36%)	8 (50%)	
Diagnostic method:			
Contact	25 (69%)	8 (50%)	33 (63%)
Screening TST 2 TU	6 (17%)	3 (19%)	9 (17%)
Radiological screening		3 (19%)	(19%)
Self-presenting	5 (14%)	2 (13%)	7 (13%)
Pulmonary TB	5 (14%)	12 (75%)	17 (33%)
Extrapulmonary TB	21 (58%)	3 (19%)	24 (46%)
PTB and EP TB	10 (28%)	1 (6%)	11 (21%)
Bacteriological confirmation			

Paediatric MDR TB treatment regimen

- Z (E) Km (CM) Ofx (Mfx) Pto Cs Pas (Amx/clv, Clr)

Treatment duration, months	20.8 (16.4, 22.8)	22.8 (19.2, 26.4)	21.7 (17.0, 24.0)	0.1268
Duration of injectable phase, months	4.3 (3.0, 6.1)	7.6 (6.2, 9.3)	5.9 (3.3, 7.4)	0.0002
Adverse reactions				
Severity grade 1-2	33 (20)	1 (1)	33 (21)	0.0082#
Hypothyroidism	14	0	14	
ALT and/or AST elevation	6	0	6	
Nausea/vomiting	4	1	5	
Arthralgia	4	0	4	
Depressed state	2	0	2	
Increased creatinine	1	0	1	
Eosinophilia	1	0	1	
Loss of hearing	1	0	1	
Severity grade3-4	6 (5)	4 (3)	10 (8)	0.5299#
ALT and/or AST elevation	4	1	5	
Eosinophilia	2	3	5	

Treatment outcome				0.6374^
Treatment success	33 (92%)	14 (88%)	47 (90%)	
Cured	9	7	16	
Treatment completed	24	7	31	
Treatment failed	3 (8%)	2 (13%)	5 (10%)	
Retreatment Relapse of MDR TB	1	0	1	
Interrupted treatment	1	2	3	
Failure, death	1	0	1	

Shorter MDR TB treatment regimens for children since 2013

- 3 Z (E) Cm(Km) Mfx Pto Cs (PAS) intensive phase of treatment
- 9 Z (E) Mfx Pto Cs (PAS) continuation phase

Russian TB Physicians Society's Research Project

Assessment of efficacy and safety of shortened standardized treatment regimen for multiple drug-resistant tuberculosis (SCMDR)

Background

- Clinical study to evaluate pilot *shortened standardised MDR TB treatment* in Arkhangelsk, Murmansk, and Belgorod regions
- Since 2007 patients in these regions have been treated following the WHO Guidelines for the programmatic management of drug-resistant tuberculosis and RTPS clinical recommendations
- Intensive phase with injectable agent reduced to 4 months, and continuation phase to 8 months

Relevance and justification

- Reduction of continuation phase was informed by previous studies conducted in Arkhangelsk region which indicate that there is no statistically significant difference in treatment outcomes of MDR-TB patients who *received the full course of treatment* (600 to 720 daily doses) and those who *interrupted the treatment* but have completed at least 300 daily doses of medication (i.e., 300 to 600 doses).

Follow-up data for 211 MDR TB patients who interrupted treatment

- Resumed MDR TB treatment
- 26 (35%) – less than 100 doses
- 20 (33%) –100 to 200 doses
- 5 (15%) –200 300 doses
- 4 (10%) more than 300 but less than 720 doses (380 doses on average)

- Гайда А.И., Никишова Е.И., Марьяндышев А.О. Отдаленные результаты лечения больных с множественной лекарственной устойчивостью микобактерий туберкулеза, прервавших курс химиотерапии. Туберкулез и болезни легких. 2014, №12, с.47-52

- **Study design:** prospective and retrospective cohort study

- **Studied condition:** Multiple drug-resistant tuberculosis (MDR TB) *diagnosed using molecular methods* from direct sputum, other biological fluids or *Mycobacterium tuberculosis* culture isolated on liquid or solid media.

Objectives

Primary objective

- Evaluate the possibility to realise the global target of over 75 per cent MDR TB treatment success with the use of short MDR TB treatment regimen with reduction of WHO-recommended standard treatment duration to twelve months.

Secondary objectives

- 1) Compare the efficacy of standardised 12-months MDR TB treatment regimen with the results from previous cohorts of standard 20-months MDR TB treatment in Arkhangelsk region, Russia.
- 2) Evaluate relapse rate among MDR TB patients successfully treated with shortened MDR TB treatment regimen for 12 months in Arkhangelsk region.
- 3) Compare safety of 20 and 12-months treatment course for MDR TB.

Proposed treatment regimen

Intensive phase

- Pyrazinamide, kanamycin/capreomycin, levofloxacin /moxifloxacin, protionamide, cycloserine (ethambutol sensitivity MGIT, Hain Test)
- Daily for four months

Фаза продолжения

- Pyrazinamide, levofloxacin /moxifloxacin, protionamide, cycloserine (ethambutol sensitivity MGIT)
- Daily for next 8 months

Intensive phase extension

- For two months till sputum smear conversion, if it has not occurred after 4 months, but no longer than 6 months.
- Till at least one negative culture result on liquid and solid media
- Failure as per SCMDR protocol can be registered after 6 months in patients without smear microscopy conversion and with insufficient clinical response to treatment –› switch to standard-length treatment regimen, repeat DST, MIRU VNTR genotyping of MTB

Daily doses of TB drugs

Drug	Weight range	
	30 kg – 50 kg	**> 50 kg**
Moxifloxacin	400 mg	400 mg
Levofloxacin	500 mg	750 mg
Ethambutol	1200 mg	1600 mg
Pyrazinamide	1500 mg	2000 mg
Cycloserine	500 mg	750 mg
Prothionamide	500 mg	750 mg
Kanamycin†	15 mg per kg of body weight (1 g maximum)	

† For adults over 59 years old dosage should be reduced to 10 mg/kg (maximum dosage 750 mg)

Patient management

- Principle of directly observed treatment (DOT) should be strictly followed over the whole course of treatment by a trained person not directly related to the patient.

Benefits

- Shorter treatment duration
- Easier to use for patients
- Decrease in interruption rate
- Fewer and less intense side reactions to drugs
- Costs reduction

Follow-up period

- Patients with favourable outcomes (i.e. cured and treatment completed) will be followed up for 24 months after treatment completion to evaluate for possible relapse of tuberculosis
- Biannual visits for bacteriological test and X-ray

MDR TB case detection

- With molecular methods (GenoType MTBDRplus, BIOCHIP, Xpert MTB / RIF test)
- Patients with high risk of rifampicin resistance can be started on MDR-TB treatment before rifampicin resistance is bacteriologically confirmed.
- Patients with pre-XDR and XDR are started on individualized treatment regimens and excluded from short regimen MDR-TB cohort.

Inclusion criteria

Patient can be included into the study if:

- Patient is willing and able to give an informed consent
- Patient has positive smear microscopy or culture or is diagnosed with pulmonary rifampicin-resistant tuberculosis on GeneXpert, Hain at baseline.
- Patient is not infected with a strain with high probability of resistance to fluoroquinolones or injectable agents
- Patient has no history of treatment with second-line drugs for over one month, if not tested for sensitivity to second-line drugs
- Ready to adhere to the schedule of procedures.
- Full cohort of all MDR TB patients in Arkhangelsk, Murmansk and Belgorod regions since 1 January 2016

Limitations

- Monitoring for relapses for two years (final results expected in 2019)
- Contribution of inpatient treatment to relapse rate through nosocomial transmission

Thank you for your attention