

Treating Patient, Not Disease: People-Centered Approach

7th TB Symposium – Ministry of Health of the Kyrgyz Republic
and Médecins Sans Frontières

1-2 March , 2018, BISHKEK , KYRGYZSTAN

Shorter treatment regimens for multi- drug-resistant tuberculosis

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Key strategic directions of action plan for the WHO European Region 2016-2020



1. Complete coverage by rapid DST diagnostics
2. Quick introduction of new drugs
3. Scale-up of patient-oriented approach
4. Shorter and more effective treatment regimens
5. Trials of new diagnostics, drugs and vaccines
6. Cross-sectoral approach to problem solving

Overview of presentation

1. Evaluation of effectiveness of shorter MDR-TB treatment regimen in adult patients.
2. Evaluation of effectiveness of shortening of Intensive Phase of treatment in children with MDR TB.
3. Evaluation of effectiveness of using new anti-tuberculosis drugs for XDR-TB treatment.

The problem of MDR and XDR-TB in the Arkhangelsk region of the Russian Federation

- The prevalence of MDR TB is one of the highest in the world, 33.1% primary and 59.2% acquired
- The percentage of XDR-TB among MDR-TB in the Arkhangelsk region is 11.4%.

Russian TB Society research project, 2016

- **Clinical study** to evaluate pilot *shortened, standardized MDR TB treatment* in Arkhangelsk, Murmansk, and Belgorod regions
- Reduction of Intensive phase with injectable agents to 4 months, and continuation phase to 8 months
- **Primary objective:** to evaluate the possibility of achieving target of **over 75%** MDR TB treatment **success** with the use of short MDR TB treatment regimen **with reduction of standard treatment duration** recommended by WHO **in 2011 to twelve months.**

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

Resumed MDR TB treatment 55 patients

- 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)*
-
- Gaida, A.I., Nikishova, E.I., Maryandyshv, A.O. Long-term treatment outcomes of patients with mlti-drug-resistant tuberculosis who interrupted treatment. Tuberculosis and lung diseases. 2014, №12, с.47-52

Inclusion of patients

	Year 2015 (20 months)	Year 2016 (12 months)
Number of registered patients in civil society	160	144
Pre-XDR-TB	18	14
XDR-TB	13	11
MDR-TB	108	95

		2015r. Standard MDR regimen	2016r. Short course MDR regimen	p
Regimen/drugs		Z Km/Cm Lfx/Mfx Pto Cs	Z Km/Cm Lfx/Mfx Pto Cs	
Duration of treatment		20 months (8/12)	12 months (4/8)	
Number of patients		108	95	
Characteristics	male/female	76 % / 24 %	82 % / 18 %	0,28
	Average age	40,6	40,8	
Treatment Outcomes	Success rate	62 %	74,7 %	0,05
	Still on treatment	-	6,3%	
	Treatment Failure	6,5 %	3,2 %	0,27
	Interrupted treatment	18,5 %	7,4 %	0,02
	Death from tuberculosis	5,6 %	3,2 %	0,41
	Died of causes other than TB	6,5 %	5,3 %	0,71
	Transferred out	0,01%	-	9

Relapse of MDR-TB after 6 months of follow-up

	2015 (n=108)	2016 (n=95)
Relapse	0	0

MDR TB treatment and shorter regimens in children in Arkhangelsk region

- A retrospective cohort study of MDR TB treatment effectiveness 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 EI⁴, Seddon JA⁵, Chappell E⁶, Zolotaya OA¹, Mironuk OM¹, Maryandyshev AO⁴.

		Standard Regimen (2001-2013)		Short course Paediatric MDR regimen (>2013)
		Children < 15	Adolescents < 18	
Regimen/drugs		Z (E) Km /CM Ofx /Mfx Pto Cs Pas (Amx/clv, Clr)		Z (E) Cm/Km Mfx Pto Cs
Duration of treatment		20.8 (16.4, 22.8)	22.8 (19.2, 26.4)	12 months 3/9
Duration of intensive phase, months		4.3 (3.0, 6.1)	7.6 (6.2, 9.3)	3
Number of patients		36	16	21
Characteristics	male/female	36 % / 64 %	50 % / 50 %	-
	Average age	7,0	16,6	-
Treatment outcomes	Treatment success	33 (92 %)	2 (88 %)	16 (76%)
	Continue treatment	-	-	3 (14%)
	Unsuccessful treatment	3 (8 %)	2 (12 %)	
	1) Failure of MDR TB	1 (3%)	0	-
	2) Interrupted treatment	1 (3%)	2 (12%)	-
	3) Death from TB	1 (3%)	-	1

Adverse reactions

	Children <15 N 36	Adolescents <18 N 16	Total	p
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 grade 3-4	6 (5)	4 (3)	10 (8)	0.5299 [#]
ALT and/or AST elevation	4	1	5	
Eosinophilia	2	3	5	13

XDR TB treatment regimens 2006 – 2014 (n=81)

Z Km /CM Ofx /Mfx Pto Cs Pas
+ Amx/clv, Clr

Scheme of treatment with new drugs for XDR-TB patients (n=21) after 2014

Scheme of treatment with Dlm	
Dlm Lzd Imp Amx\Cv	3
Dlm Bdq Cfz Amx\Cv	1
Dlm Bdq Lzd Cfz	1
Scheme of treatment with Bdq	
Bdq Lzd Imp Amx\Cv	10
Bdq Imp Amx\Cv Cm Mfx Cz Pto Z	1
Bdq Lzd Cm Cz Pto Z	1
Bdq Cm Pto Pas	1
Bdq Cfz Km Lfx Cz Pto Z	3

DST of patients starting XDR-TB treatment since February 2014 (n=21)

Drug resistance	N=21
H R E Km Ofx	13 (62 %)
H R E Km Cm Ofx	3 (33 %)
H R Km Cm Am Ofx	1 (5 %)
H R E Km Cm Ofx Eto	1 (5 %)
H R E Km Cm Am Ofx	2 (10%)
H R E Cm Ofx Lfx	1 (5 %)

		XDR Regimen (2006-2014)	Treatment Regimen with new drugs (>2014)	p
Regimen/drugs		20	13,2	
Number of patients		81	21	
Characteristics	male/female	75 % / 25 %	71 % / 29 %	<0,05
	Average age	42 года	41 год	
Treatment outcomes	Success rate	25 %	47,6 %	0,32
	Still on treatment	-	14,2 %	
	Treatment failure	-	5 %	
	Interrupted treatment	-	19 %	
	Died of TB	56 %	5 %	<0,05
	Died of causes other than TB	6 %	5 %	0,81
	Transferred out	12%	5 %	0,67

Adverse reactions to new drugs

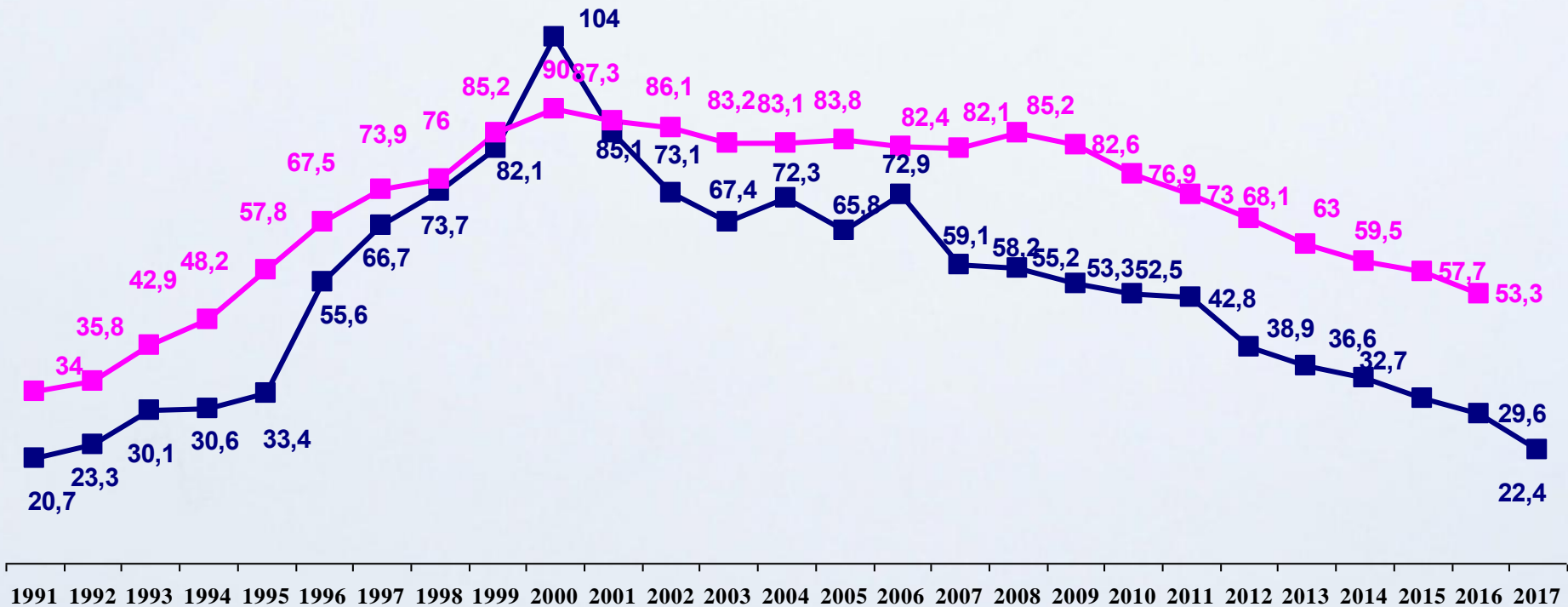
Adverse reaction	Drug	Number of patients (%)
Allergic dermatitis	Lzd Imp Cfz	1 (5%)
Anaemia	Lzd	9 (43%)
Arthralgia	Bdq	1 (5%)
Gastritis	Lzd Imp	2 (10%)
Hepatotoxicity	Lzd Bdq Imp Amx	6 (29%)
Hypokalaemia	Lzd Imp Dlm	3 (14%)
Disbiosis	Lzd Imp Amx Dlm	4 (19%)
Optic neuritis	Lzd	2 (10%)
Renal toxicity	Lzd Imp	4 (19%)
Arrhythmia	Bdq Dlm Cfz	2 (10%)
Polyneuropathy	Lzd Imp	8 (38%)
Nausea and vomiting	Imp Bdq	2 (10%)
Eosinophilia	Imp	1 (5%)

Conclusions

- The global target of 75% treatment success has been achieved through short courses chemotherapy (74,5%), higher than standardized treatment regimen
- It's necessary to continue long-term follow up after MDR-TB treatment.
- Using new drugs for XDR-TB treatment increased effectiveness of treatment (to 47,6%) and decreased mortality rate to 4,7%.
- It's necessary to continue research on effectiveness of new drugs and to design an optimal XDR-TB treatment regimen.

Thank you for your
attention

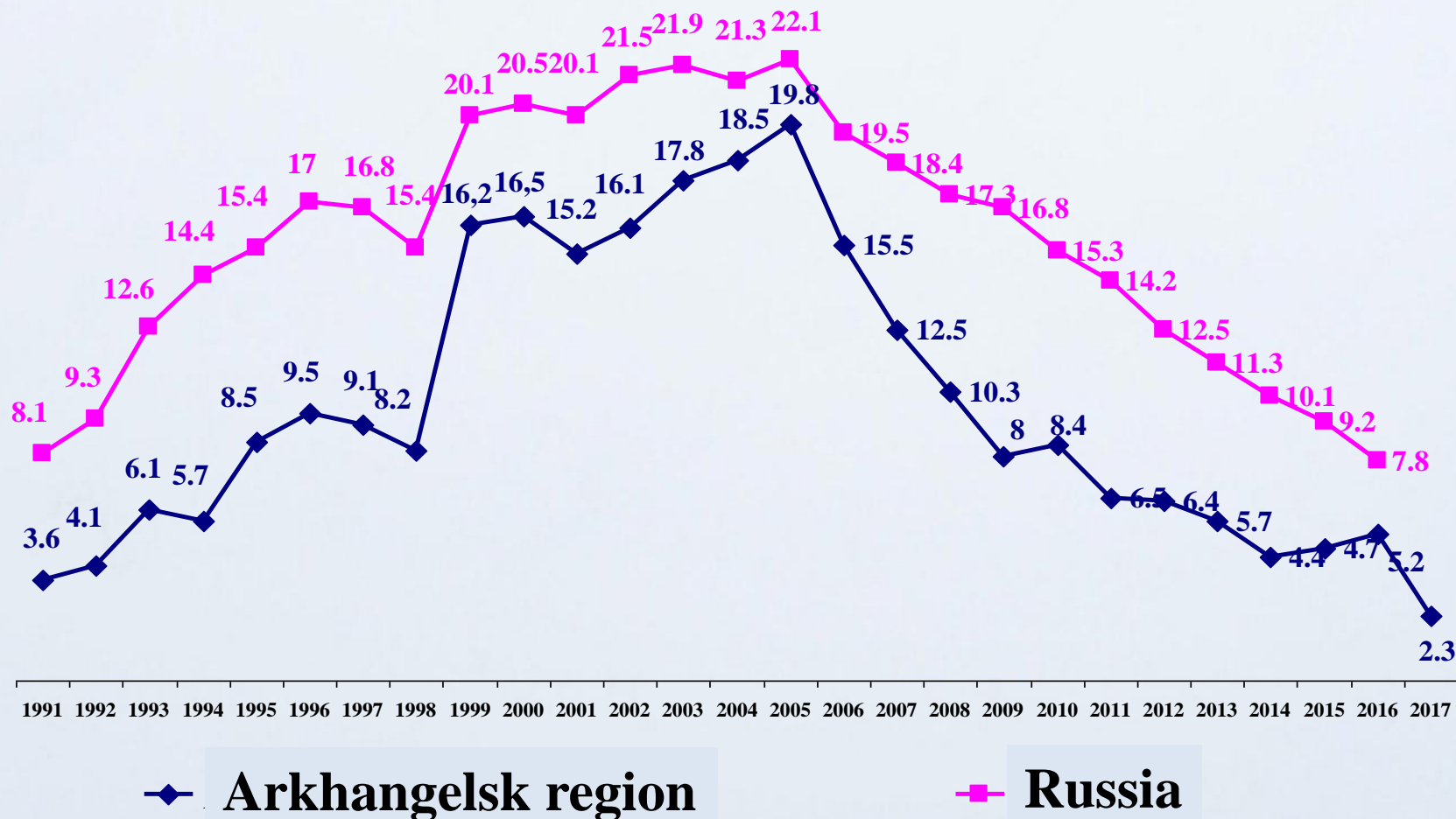
Tuberculosis incidence (new cases and relapses) in Arkhangelsk region in 2000-2016 per 100 000 population)



■ Arkhangelsk region

■ Russia

Tuberculosis mortality in Russia and Arkhangelsk region, including penitentiary system. 1991-2016 (per 100 000 population)



Лечить пациента, а не болезнь: ориентированный на человека подход

7й симпозиум по вопросам лечения туберкулеза –
 Министерство здравоохранения Кыргызской Республики и
 "Врачи без границ"/ Médecins Sans Frontières