

Belarus' Early Experience in BPAL(M) Introduction and Scale Up



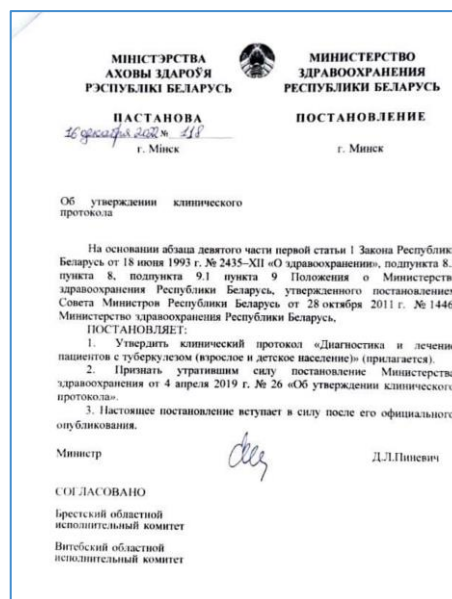
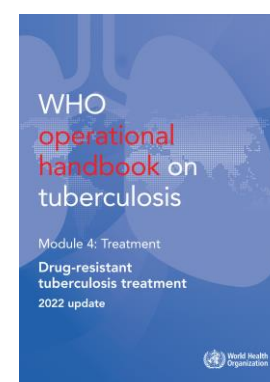
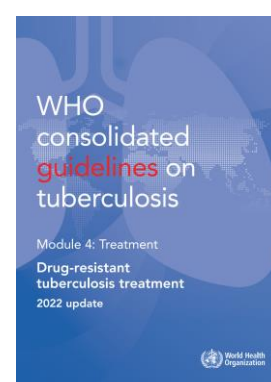
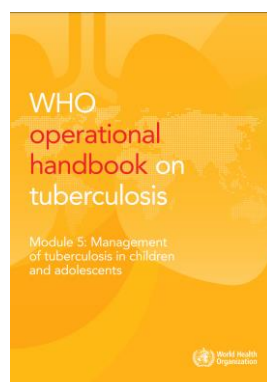
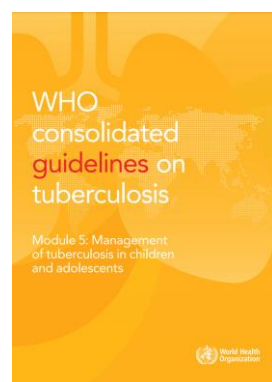
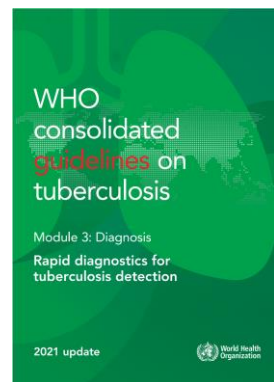
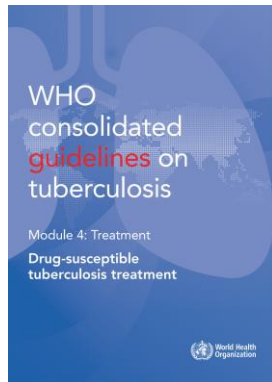
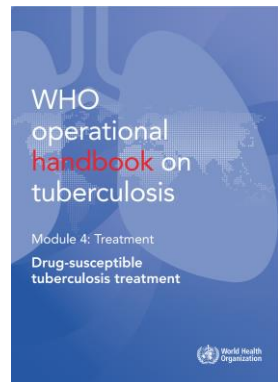
Professor Alena Skrahina

20-th webinar dedicated to 2022 revision of the WHO guidelines on the treatment of DR-TB

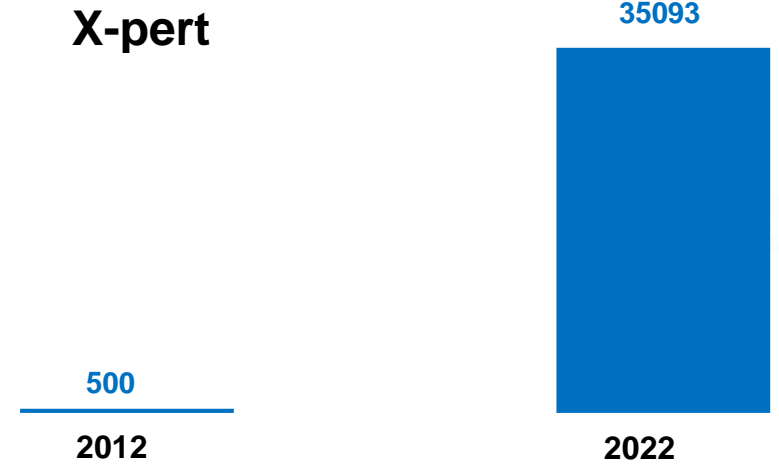
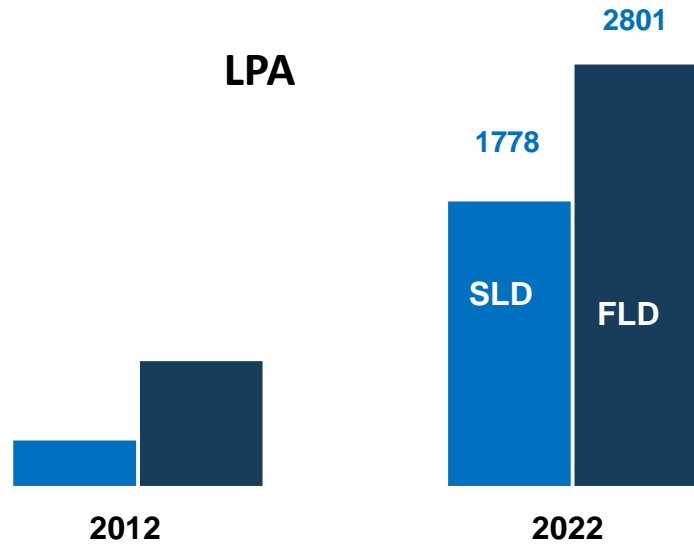
24 February 2023

New WHO Guidelines, 2021 – 15.12.2022

New National Guideline, 16.12.2022



Rapid Molecular Diagnosis



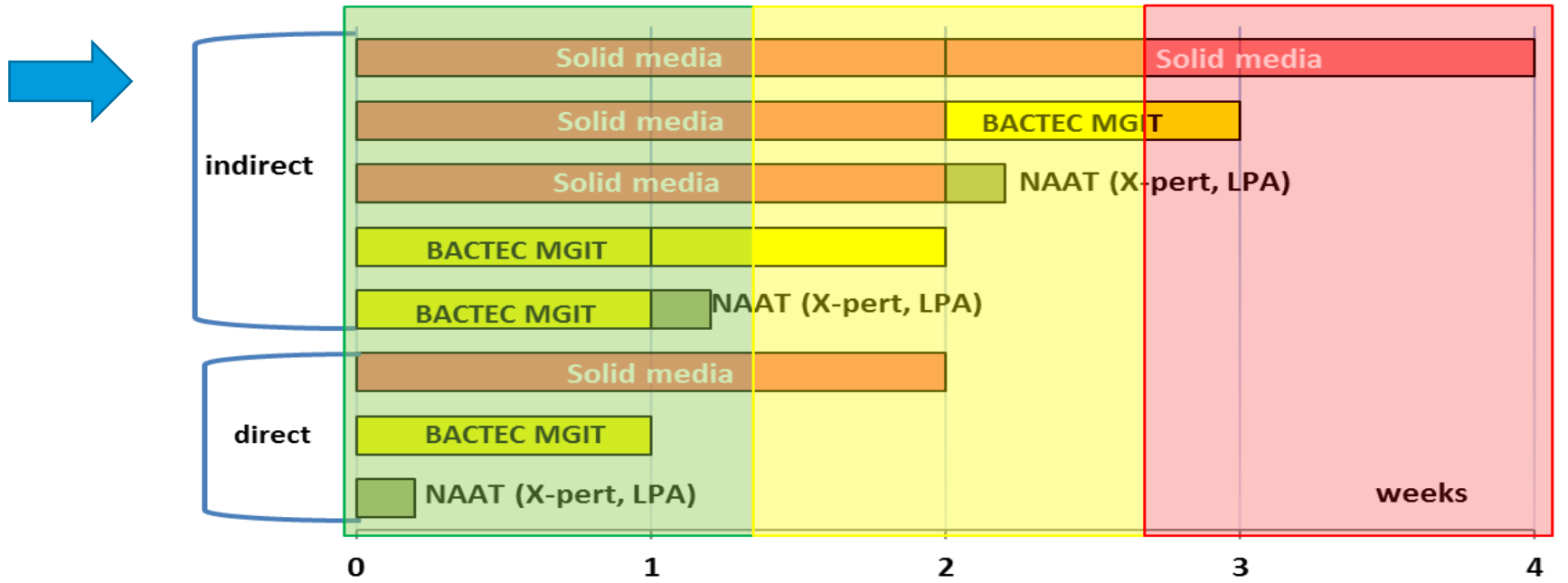
WRD to 1st and 2nd line drugs in > 90% cases

Acceptable time to treatment initiation

1-st and 2-nd line DSTs, incl. Bdq Pa Lzd Cfz Dlm

Sequencing equipment

Collecting MTB strains since 2015



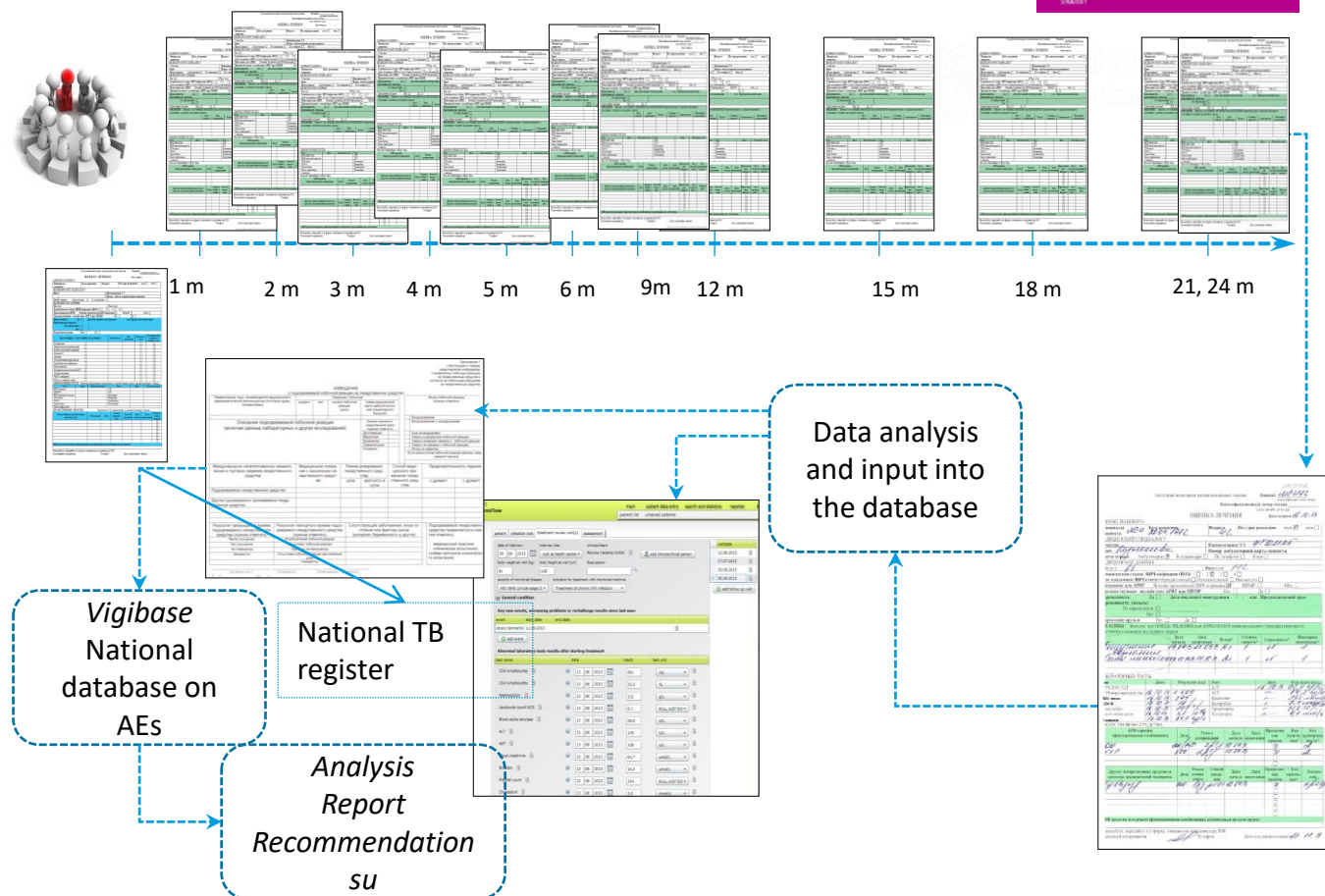
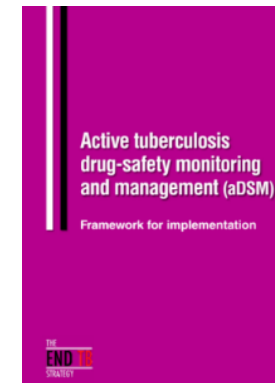
Active Drug Safety Monitoring (aDSM), Interaction With the Pharmacovigilance System

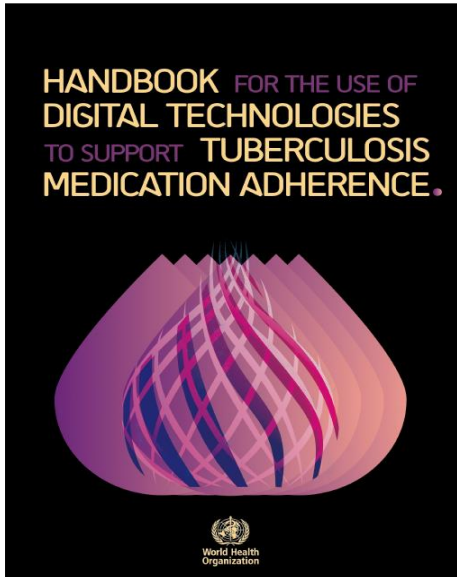
Regulatory framework, NTP capacity

National TB policy based on WHO guidelines
 Laboratory and Diagnostic Capacity
 Drug procurement system
 National TB Registry (PV)
 Recording and reporting, M&E
 Financial resources (including GF, WHO, MSF)

National PV system

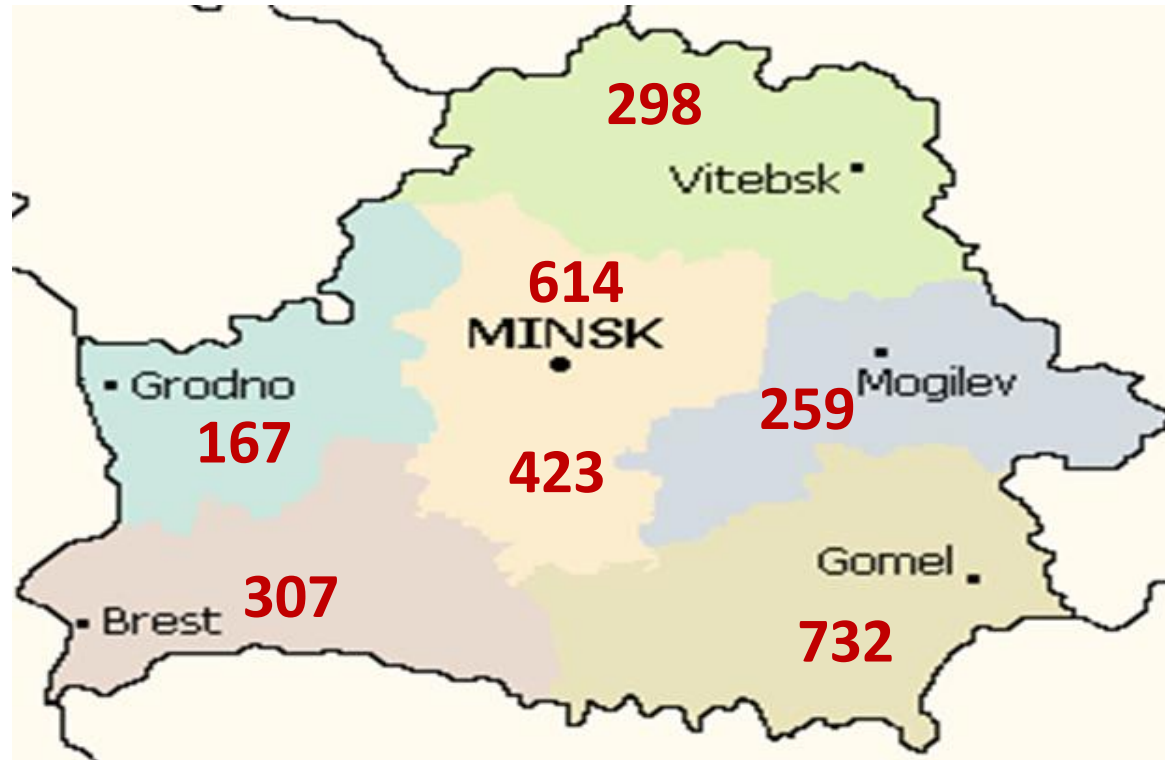
Нац. ФН политика, основанная ВОЗ рек-х
 Spontaneous reporting: 5,4 per 100 000
 KM - HIV, 2012
 KM - HIV M/XDR-TB, 2013
 KM - LZD, 2014
 KM - BDQ, 2015
 KM - DLM, 2016
 KM - BDQ+DLM, 2016
 aDSM - mSTR, 2018





Video-observed treatment 7 days a week

Coverage - 49% of TB patients



ANNEX V. PROGRAMMATIC IMPLEMENTATION OF VOT IN BELARUS

Example of a 5-year timeline¹⁰

Phase	Year	Key Activities			
Phase 1: Planning	Year 1 – 2015	<ul style="list-style-type: none"> Conduct a feasibility assessment – conducted by WHO in January 2015 with support of the European Respiratory Society (ERS) Engage stakeholders to provide input on solution – WHO survey of public views on priority areas in early 2015, WHO/ERS joint technical consultation to develop detailed technical TFP for VOT in February 2015 Develop a costed project proposal – developed by the Global Fund in February 2015 Establish a working group to provide oversight and guidance – established by the Ministry of Health of Belarus in February 2015 Draft detailed technical specifications – drafted by local Belarusian company “BelPromProject” for VOT app in May 2015 Secure in-country ethics committee approval for pilot project – secured through Ministry of Health in September 2015 			
	Phase 2: Development/adaptation	Year 2 – 2016	<ul style="list-style-type: none"> Finalize the software – development finalized by BelPromProject in January 2016 Link solution to current national digital health systems – “VOT module” added to the Ministry of Health of Belarus’ national electronic tuberculosis patient registers in February 2016 Train staff – trained dispensary nurses in January 2016 Distribute hardware and train patients – distributed smartphones and trained patients in January 2016 		
		Phase 3: Roll-out	Years 2 & 3 – 2016-2017	<ul style="list-style-type: none"> Initiate patient enrolment – initiated single-site preliminary pilot in Minsk in January and February 2016 Monitoring and evaluation of pilot study results – monitoring by NIT, Ministry of Health of Belarus from January to October 2016 Publication of preliminary results – pilot findings published in European Respiratory Journal in March 2017 (58) 	
			Phase 4: Mainstream/scale up	Years 3-5 – late 2016-2019	<ul style="list-style-type: none"> Expansion of solution nationwide – expansion to all seven country regions with planned recruitment of 450 patients (150/year) with Belarus Red Cross and the Global Fund from October 2016 to 2019; 231 patients from all regions of the country were on VOT by 1 September 2017

¹⁰ Adapted from Box 4.1 (67)

Video-observed treatment for tuberculosis patients in Belarus: findings from the first programmatic experience

To the Editor:

The treatment of tuberculosis requires daily intake of multiple medications for between 6 months and 2 years, or more [1, 2]. This long duration predisposes to the interruption of medications with the risk of the emergence of drug resistance, death, disease persistence and continued transmission of tuberculosis in the community. Directly observed treatment, together with patient support, has been recommended to improve adherence [3]. However, daily treatment observation presents challenges for both patients and observers, which have limited its implementation [4]. Digital technologies, like video (or virtually)-observed treatment (VOT) can help bridge the gap between patients and health services and promote adherence [5]. VOT usually requires patients to film themselves taking medications on a computer or mobile device and then transmit these images to a remote observer via the internet [6-9]. Video technology has been available for more than a decade, but the increasing availability of smartphones and broadband internet is making VOT practical to implement even in resource-constrained settings.

Belarus, an upper-middle-income country in eastern Europe with a population of 9.5 million reports high levels of multidrug-resistant tuberculosis (resistance to rifampicin and isoniazid), which requires many patients to start long second-line treatment regimens each year: 1949 patients in 2015 alone. These patients need directly observed treatment daily due to the high risk of loss to treatment follow-up [10, 11].

TABLE 1 Profile of tuberculosis patients in the pilot video-observed therapy (VOT) programme in Minsk, Belarus (2016)

Age-group years	Sex	Tuberculosis resistance pattern	VOT episodes (by May 12, 2016)	Video recording of insufficient quality
20-29	Male	MDR-TB	99	7 (7)
30-39	Male	Isoniazid-monoresistant	102	5 (5)
20-29	Female	Drug-susceptible	99	1 (1)
<20	Female	MDR-TB	91	1 (1)
40-49	Male	Drug-susceptible	82	1 (1)
20-29	Male	Drug-susceptible	43	1 (2)
30-39	Male	MDR-TB	28	2 (7)
30-39	Female	MDR-TB	22	0 (0)
20-29	Female	MDR-TB	14	0 (0)
30-39	Female	Drug-susceptible	15	0 (0)

Data are presented as n or n (%). MDR-TB: multidrug-resistant tuberculosis.

Regions	N=2800
Minsk city	614
Minsk	423
Gomel	732
Mogilev	259
Vitebsk	298
Brest	307
Grodno	167

Drug Supply

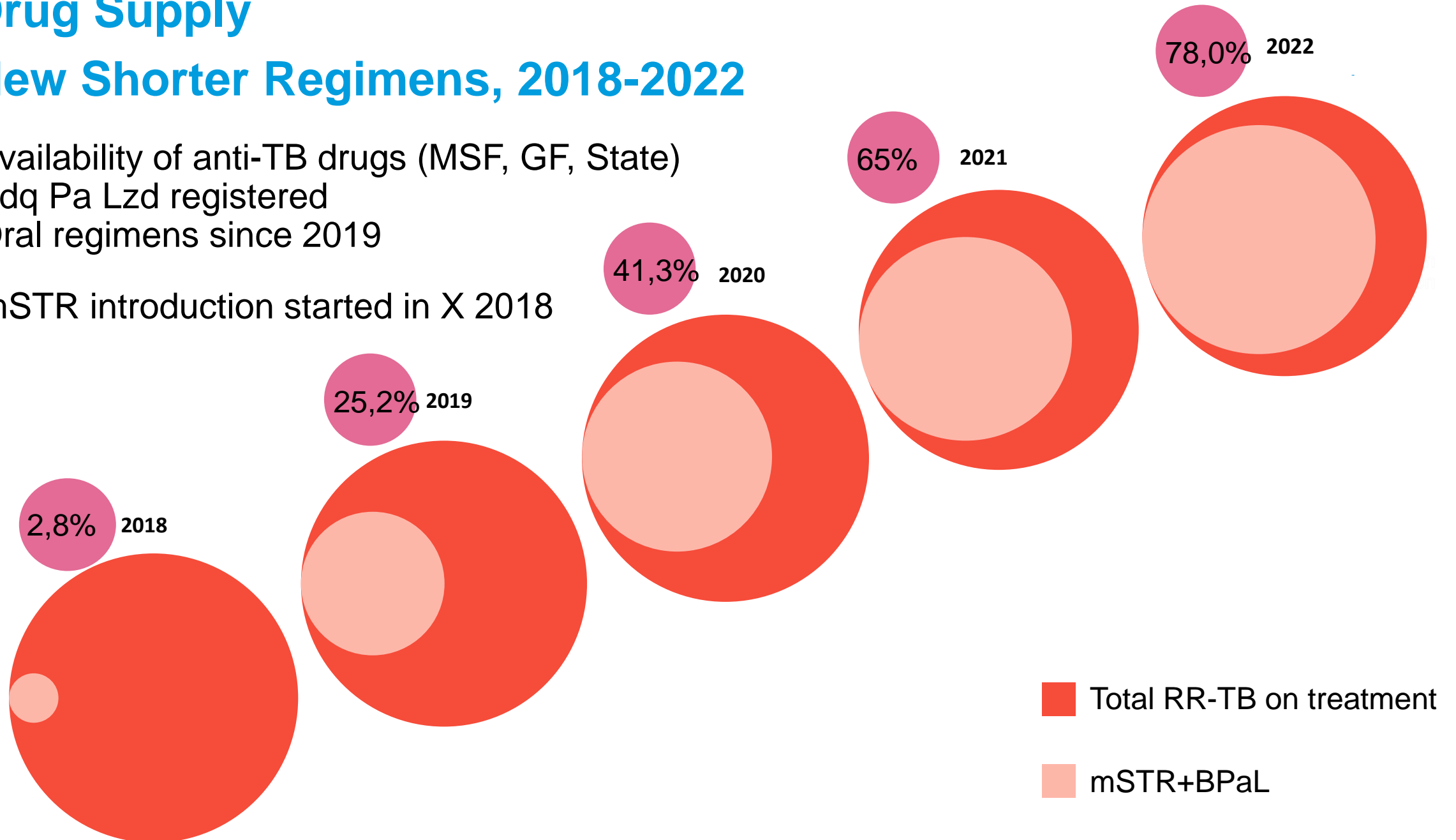
New Shorter Regimens, 2018-2022

Availability of anti-TB drugs (MSF, GF, State)

Bdq Pa Lzd registered

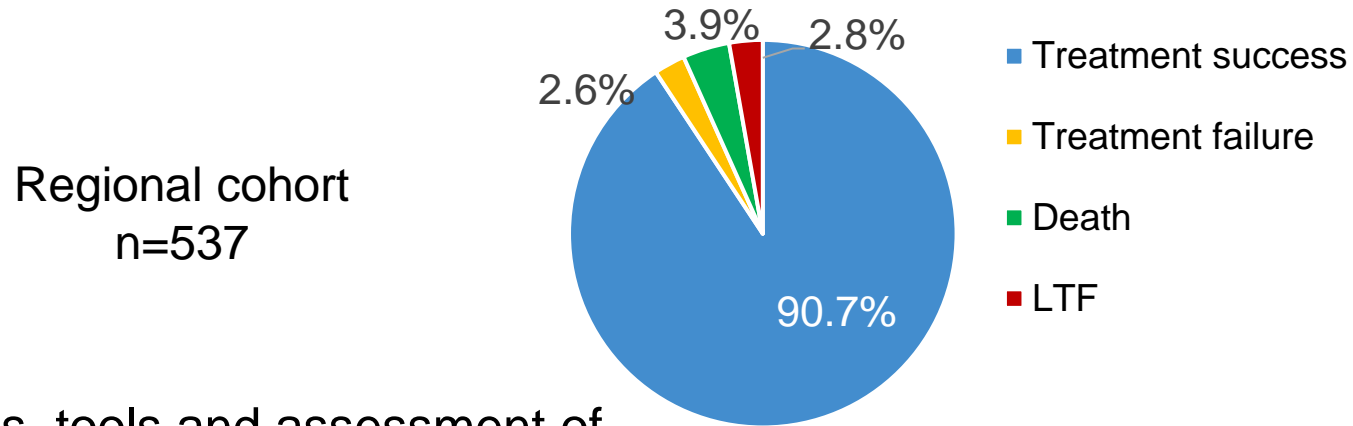
Oral regimens since 2019

mSTR introduction started in X 2018

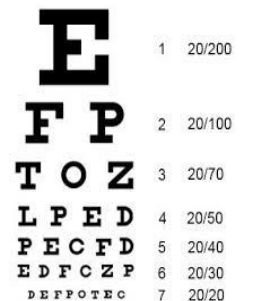
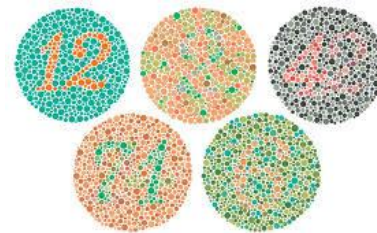
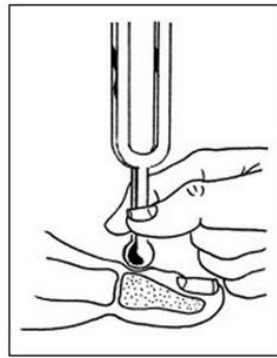
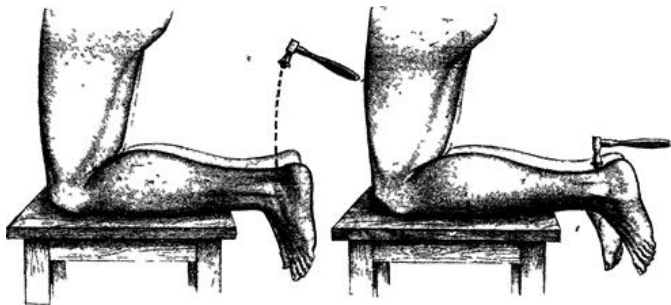


RR-TB Concilium. Experience In the implementation of mSTR OR

- RR-TB Concilium - since 2010, online - III 2020
- Regular monitoring visits



- aDSM skills, tools and assessment of neurological status, visual acuity and colour perception
- Quality assurance 'Monitoring template'



BPaL(M) Experience: Clinical Trial (CT) and Operational Research (OR)

1st patient CT



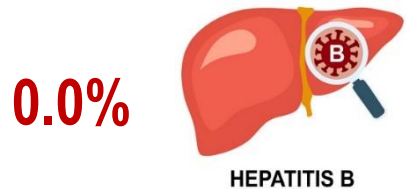
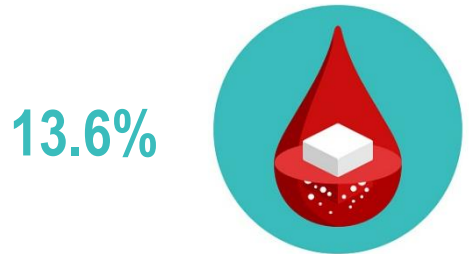
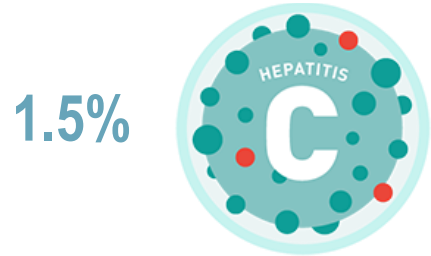
End of CT



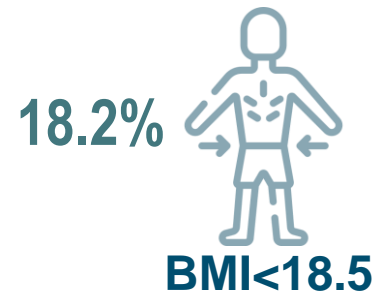
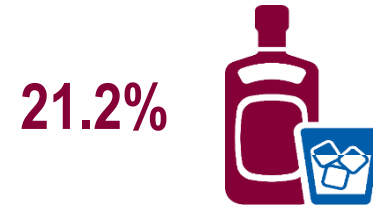
1st patient OR

TB-Practecal BPaL/M/C Clinical Trial

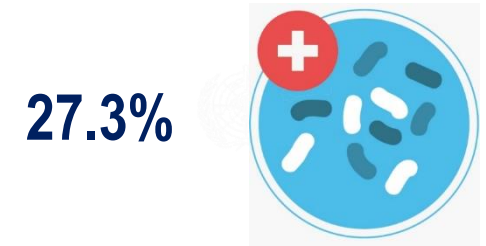
Concomitant diseases



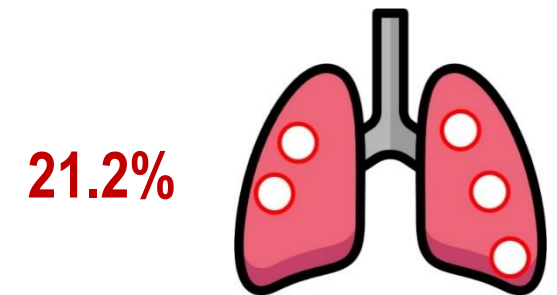
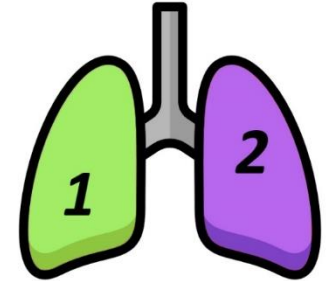
Risk factors



Characteristics of TB



62.2%
unilateral
37.8%
bilateral



Outcome	n	%
Treatment success	60	85.7
Excluded from the study	10	14.3

BRaLM Treatment Monitoring

	Исследование/Обследование	Исходная оценка и скрининг	Фаза лечения (N=Неделя)						Последующее наблюдение (M=Месяц)	
			N л 4	N л 8	N л 12	N л 16	N л 20	N л 24	M п 6	M п 12
Клиническая оценка	Письменное информированное согласие	X								
	Анкетные данные, анамнез	X								
	Клинический осмотр ¹	X	X	X	X	X	X	X	X	X
	Соблюдение лечения	X	X	X	X	X	X	X	X	X
	Сопутствующая терапия	X	X	X	X	X	X	X	X	X
	Нежелательные явления	X	X	X	X	X	X	X	X	X
Бактериологические исследования	Мазок мокроты	X (2)	X	X	X	X (2)	X	X (2)	X	X
	Посев мокроты	X	X	X	X	X	X	X	X	X
	mWRDT (GeneXpert) ²	X								
	Экспресс-тест на устойчивость к FQ ³	X								
	ТЛЧ (R/FQ +/- Bdq +/- Lzd) ⁴	X					(X)	(X)	(X)	(X)
	Количество гемоглобина/тромбоцитов/лейкоцитов	X	X	X	X	X	X	X	X	X
Лабораторные исследования	Креатинин сыворотки крови (на момент включения в исследование и при наличии клинических показаний или отклонений на ЭКГ)	X								
	Сывороточный калий (на момент включения в исследование и при наличии клинических показаний или отклонений на ЭКГ)	X								
	Липаза сыворотки крови (по клиническим показаниям)	X								
	Ферменты печени в сыворотке крови	X	X	X	X	X	X	X	X	X
	Тест на беременность (для женщин) ⁵	X								
	Анализ на ВИЧ и анализ на гепатит ⁶	X								
Другие исследования	Глюкоза в крови /HbA1c ⁷	X	X	X	X	X	X	X	X	X
	Рентгенография грудной клетки ⁸	X								X
	ЭКГ ⁹	X	X	X	X	X	X	X	X	X
	Скрининг на остроту зрения и обследование с использованием краткого скрининга периферической нейропатии (КСПН) ¹	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

REDCap Six-Month All-Oral Regimens for Rifampicin-Resistant Tuberculosis Treatment - Belarus

Record Home Page

Legend for status icons:

- Incomplete (Yellow)
- Completed (Green)
- Unverified (Grey)
- Many statuses (Blue)

Идентификационный номер пациента / Patient study number: 2022-01-001 (0)

Y1	Y2	Y3	Y4	Y5	Y6
●	●	●	●	●	●

Severity grading scale
version 5.0, 06/14 Nov 2016. Main version: 04/01 Nov 2007 and CTCAE v4.03 14 Jun 2007

For parameters not included in the table, the general definition of severity as displayed under the tabulation 'introduction' applies.

Source	Body system	Condition term	Grade 1	Grade 2	Grade 3	Grade 4	Definition
CTCAE	Hematology	Fibrin Split Product	>240 mg/dl	>412 mg/dl	>560 mg/dl	>700 mg/dl	Presence of fibrin degradation products.
CTCAE	Hematology	Haptoglobin Decreased	<0.1 g/L	N/A	N/A	N/A	A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.
CTCAE	Hematology	Hemoglobin Increased	Increase in >0 - 2 g/L (>20 - 40 g/L) above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/L (>20 - 40 g/L) above ULN or above baseline if baseline is above ULN	Increase in >4 g/L (>40 g/L) above ULN or above baseline if baseline is above ULN	N/A	A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.
CTCAE	Hematology	Hemolysis	Laboratory evidence of hemolysis only (e.g. direct antiglobulin test, DAT, Coombs), schistocytes, increased haptoglobin)	Evidence of hemolysis and >2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g. steroids)	Life threatening consequences; urgent intervention indicated	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.
DMDD	Hematology	High Fibrinogen	High: 400-600 mg/L	High: >600 mg/L	N/A	N/A	Fibrinogen associated with disseminated coagulation
CTCAE	Hematology	International Normalized Ratio Increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	N/A	A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.
CTCAE	Hematology	Leukocytosis	N/A	N/A	>100,000/mm ³ (>100 x 10 ⁹ /L) (>100 x 10 ⁹ /L)	N/A	Clinical manifestations of leukostasis; urgent intervention indicated

endTB

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Search

July 27, 2016

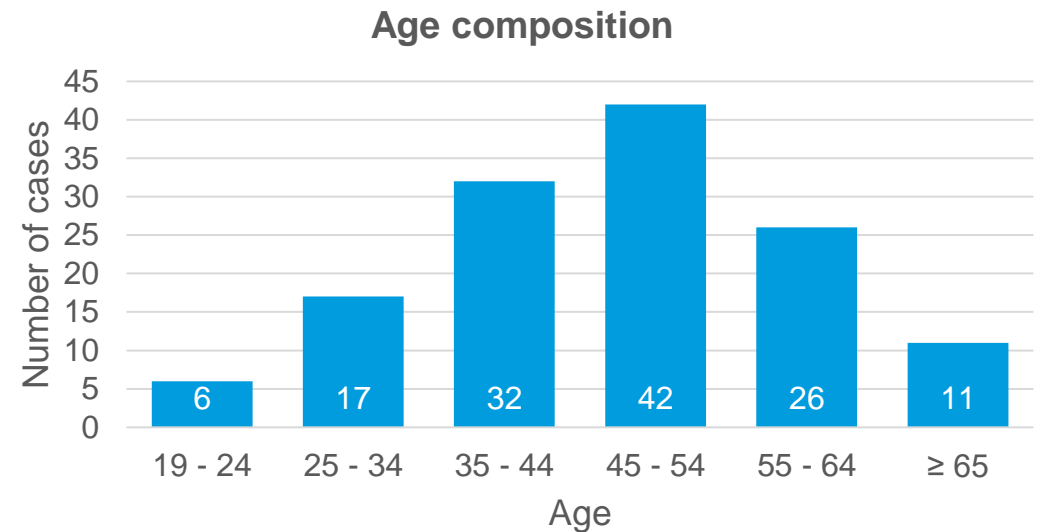
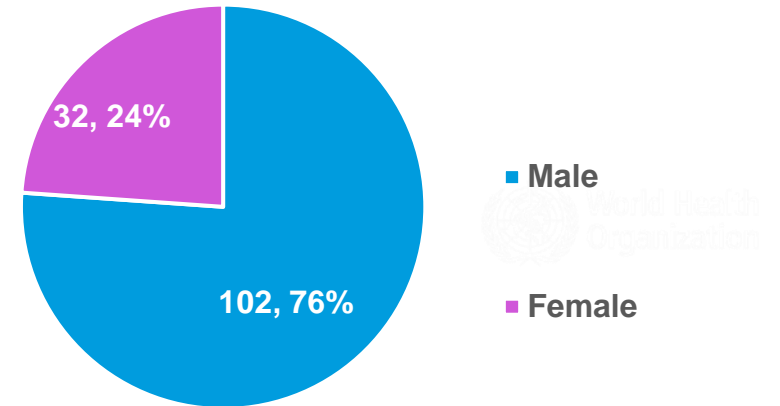
Pharmacovigilance forms and other resources for staff on endTB sites:

- PV178-003 - Causality assessment Aide Memoire.pdf (209.27 KB)
- PV178-D01 - SAE report form completion guidelines.pdf (763.95 KB)
- PV178-001 - SAE report form.pdf (877.14 KB)
- PV178-002 - Pregnancy report form completion guidelines.pdf (770.54 KB)
- PV178-D12 - TB Severity Grading Scale, print out version, 14Nov2016.doc (2813 KB)
- PV178-D12 - TB Severity Grading Scale, version 5.0, 14Nov2016.doc (2123 KB)
- RUSSIAN - PV178-D01 - SAE report form completion guidelines.pdf (1.02 MB)
- RUSSIAN - PV178-D02 - Pregnancy report form completion guidelines.pdf (969.89 KB)
- RUSSIAN - PV178-P01 - SAE report form.pdf (71.14 KB)
- RUSSIAN - PV178-P02 - Pregnancy report form.pdf (673.48 KB)
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- RUSSIAN - PV178-D12 - TB Severity Grading Scale, v.5.0 Updated, 15Oct2018.doc (1.2 MB)
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- SPANISH - Pregnancy report form completion guidelines.pdf (754.46 KB)
- SPANISH - Pregnancy report form.pdf (607.22 KB)
- SPANISH - SAE report form completion guidelines.pdf (854.28 KB)
- SPANISH - SAE report form.pdf (671.39 KB)
- SPANISH - TB Severity Grading Scale, print out version, 14Nov2016.pdf (2813 KB)
- SPANISH - TB Severity Grading Scale, version 5.0, 14Nov2016.pdf (188 KB)

Experience with the Use of BPaLM

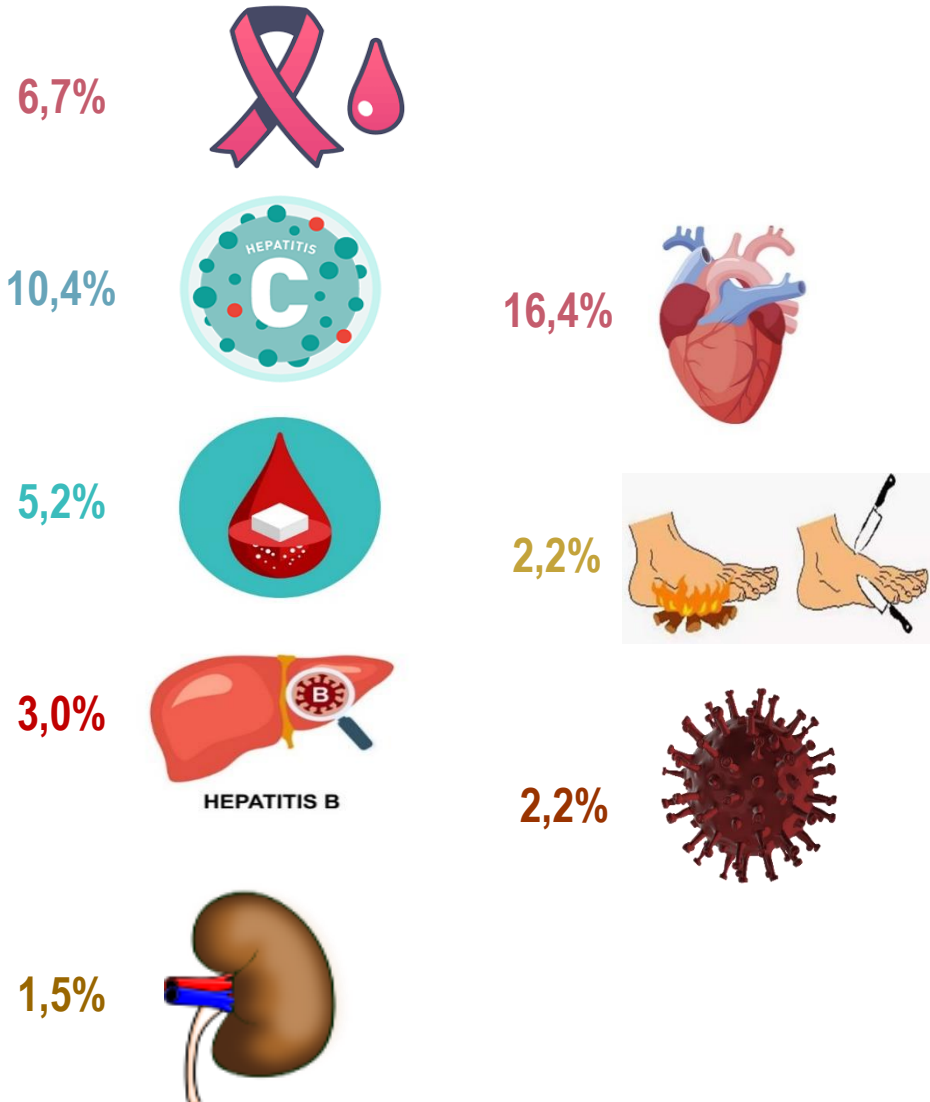
02.03.2022 – enrollment of the first patient,
Total number enrolled – 197 patients,
Of them 134 – completed treatment

History of TB - 31 out of 134 (23,1%)

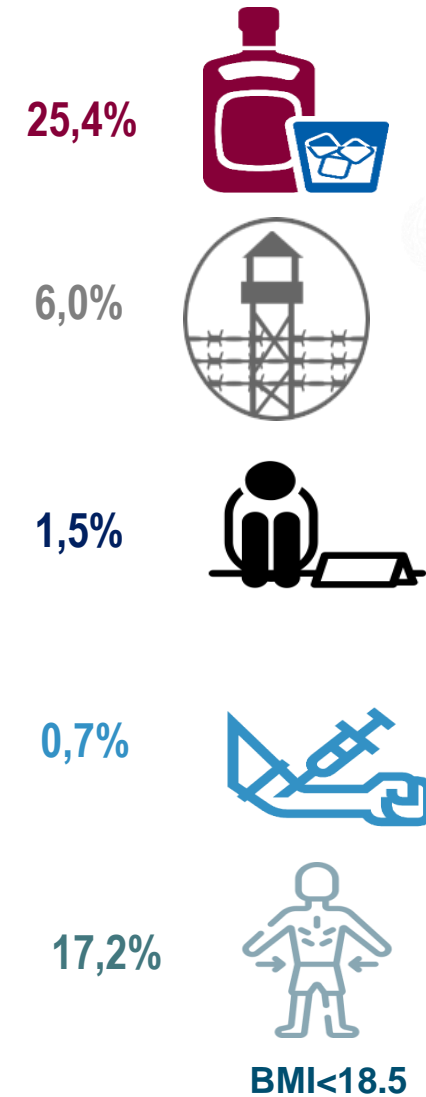


BPaLM, patients' characteristics, n=134

Concomitant diseases



Risk factors

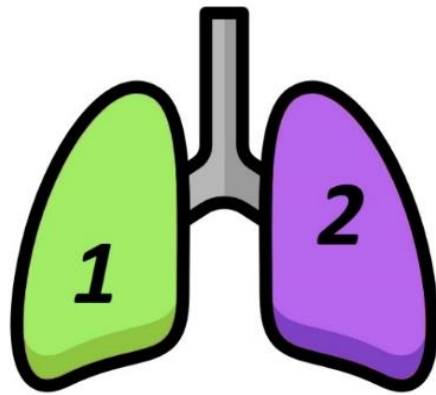


BPaLM, characteristics of TB, n=134

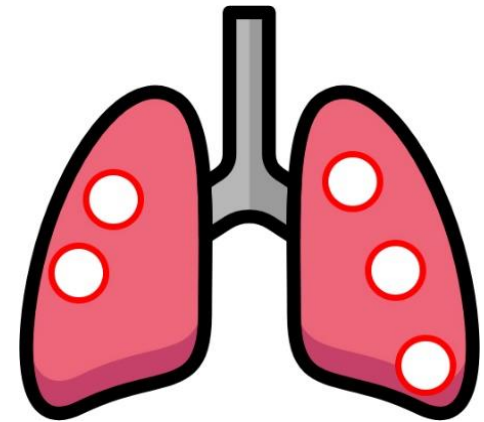
30,6%



64,9%
unilateral
32,8%
bilateral
2,2%
Extrapulmonary TB



40,3%
with cavities
22,4%
unilateral
17,9%
bilateral

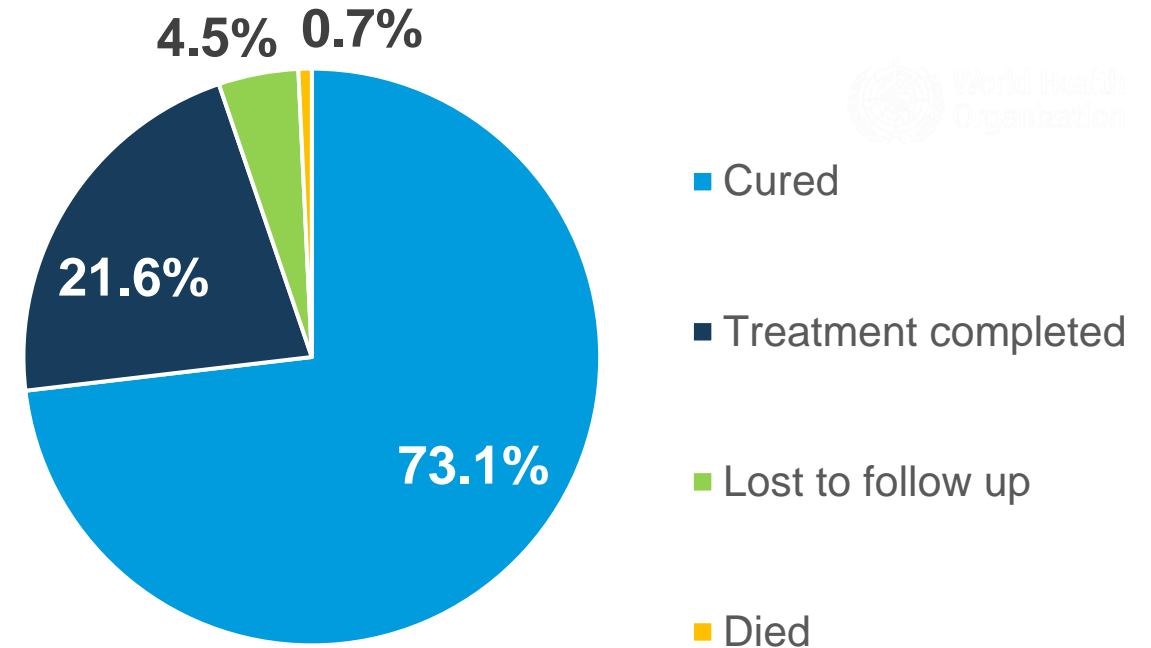
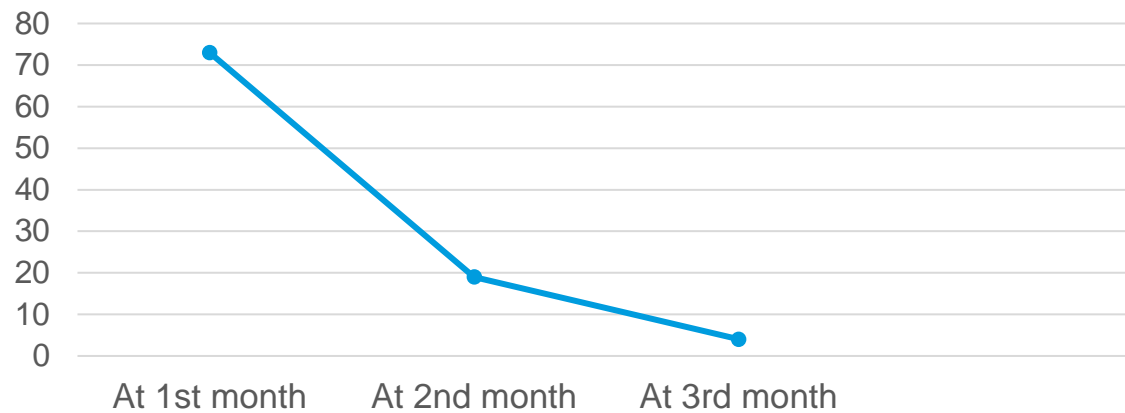


Evaluation of the effectiveness of BPaLM treatment, n=134

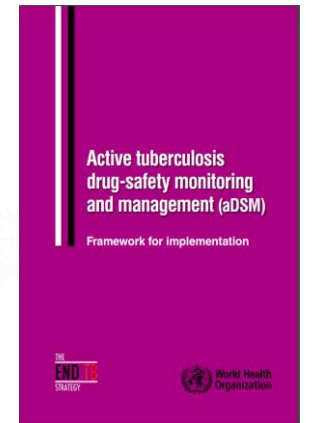
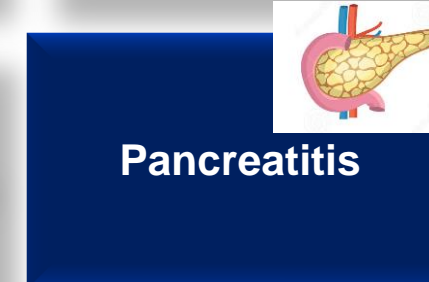
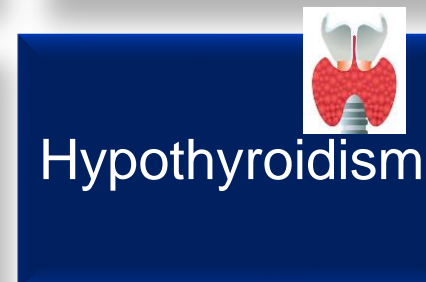
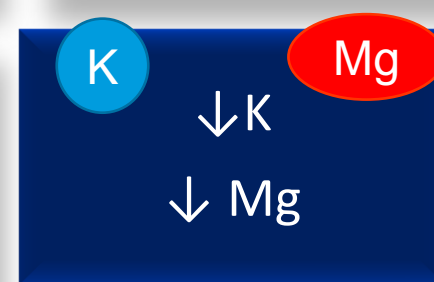
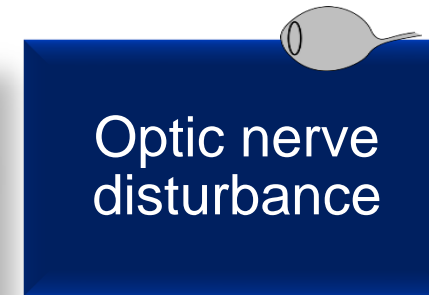
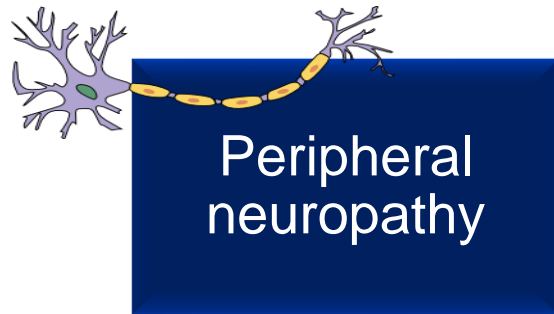
Treatment success—
94.8%



Culture conversion



Active Drug Safety Monitoring and Management (aDSM), BPaLM n=134



«Intermediate package»:

Serious adverse events - 11 in 9 patients

Adverse events of special interest - 0

Introduction of BPaL/M in Belarus - 2023

BPaL/M – 75%

mSTR*
5%

Longer regimens**
20%

* mSTR - 5%: children < 14 years old, pregnant, lactating women

** Longer regimens - 20%:

- severe extrapulmonary TB (CNS, military, bone and joint)
- drug resistance to Bdq, Lzd, Pa, Lfx, Cfz, Dlm
- treatment failure due to lack of conversion, clinical response, additional resistance
- loss to follow-up
- intolerance of BPaL or mSTR component drugs
- conditions that require a personalized approach

