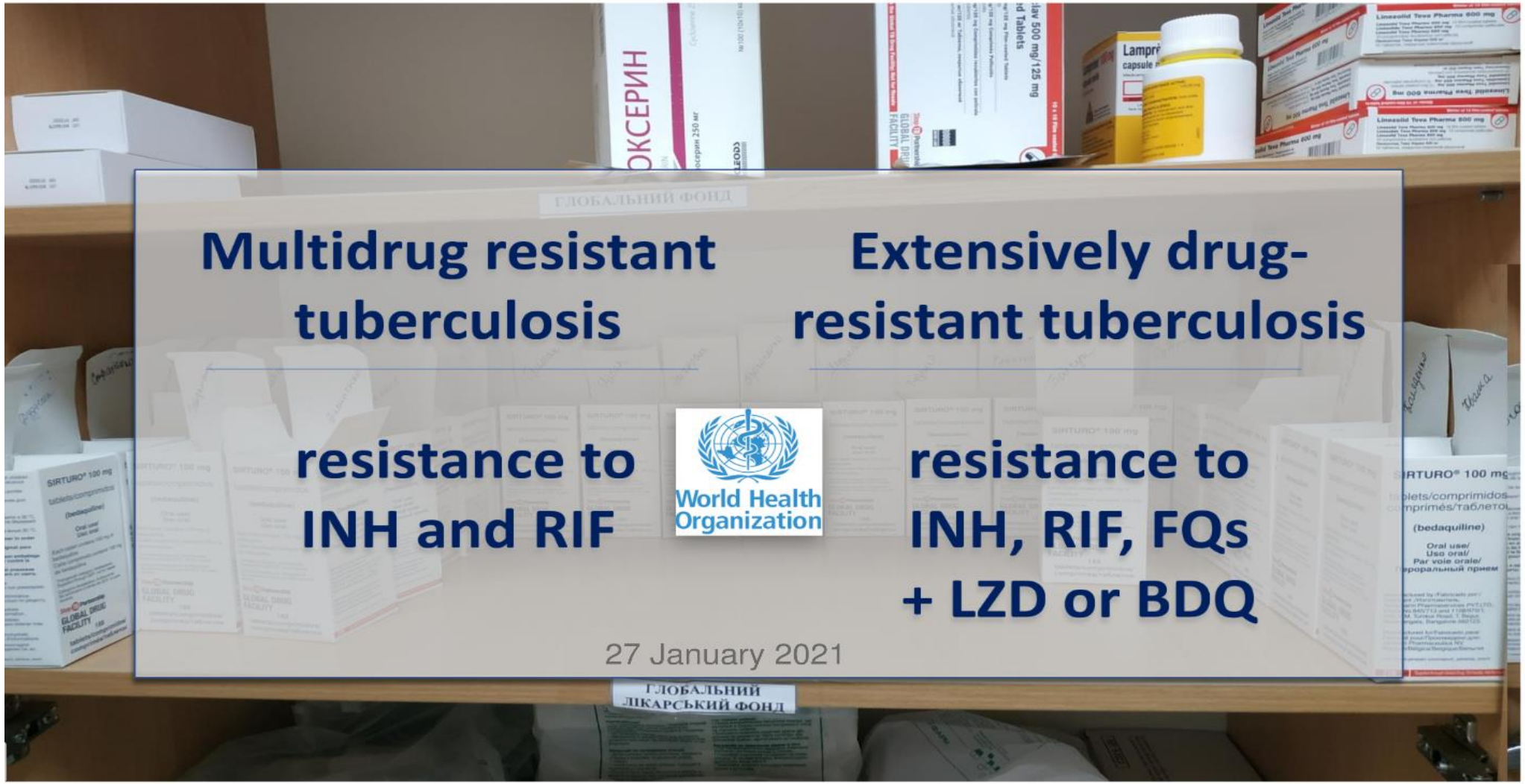
NGO INVOLVEMENT IN TB RESPONSE symposium
Симпозиум **РОЛЬ НПО в ОТВЕТЕ НА ТУБЕРКУЛЕЗ**

New treatments for MDR-TB
Новое лечение для МЛУ-ТБ

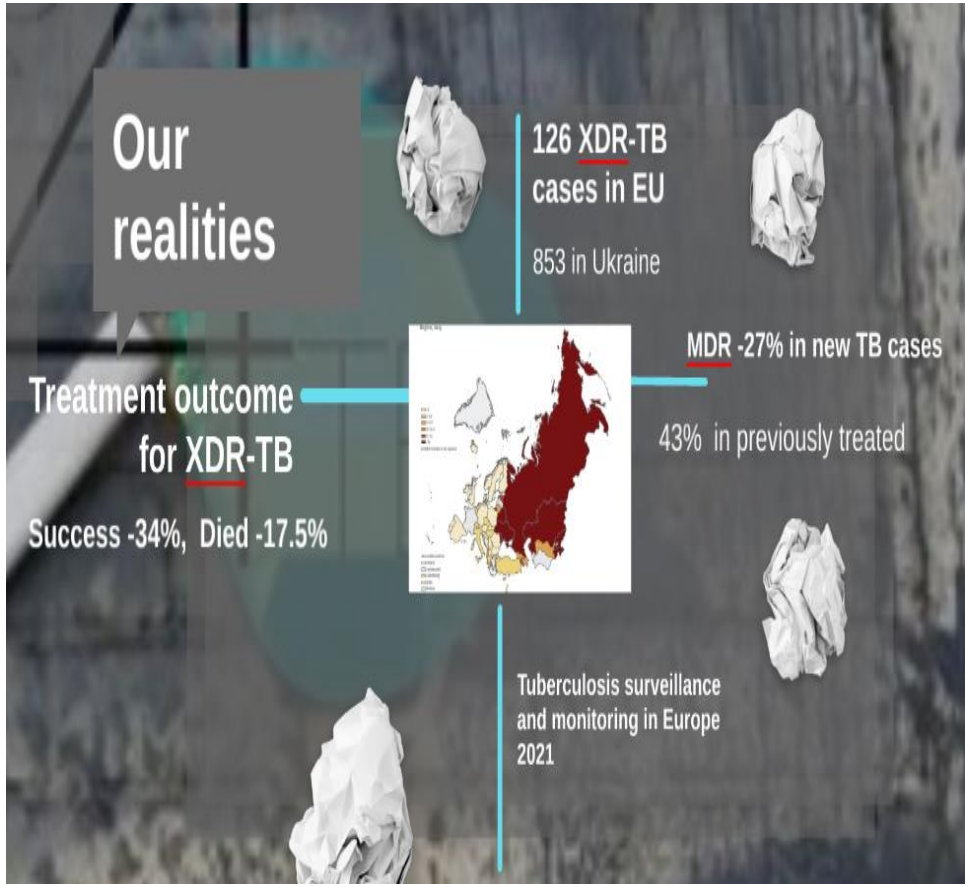
Andrii Dudnyk
Андрей Дудник

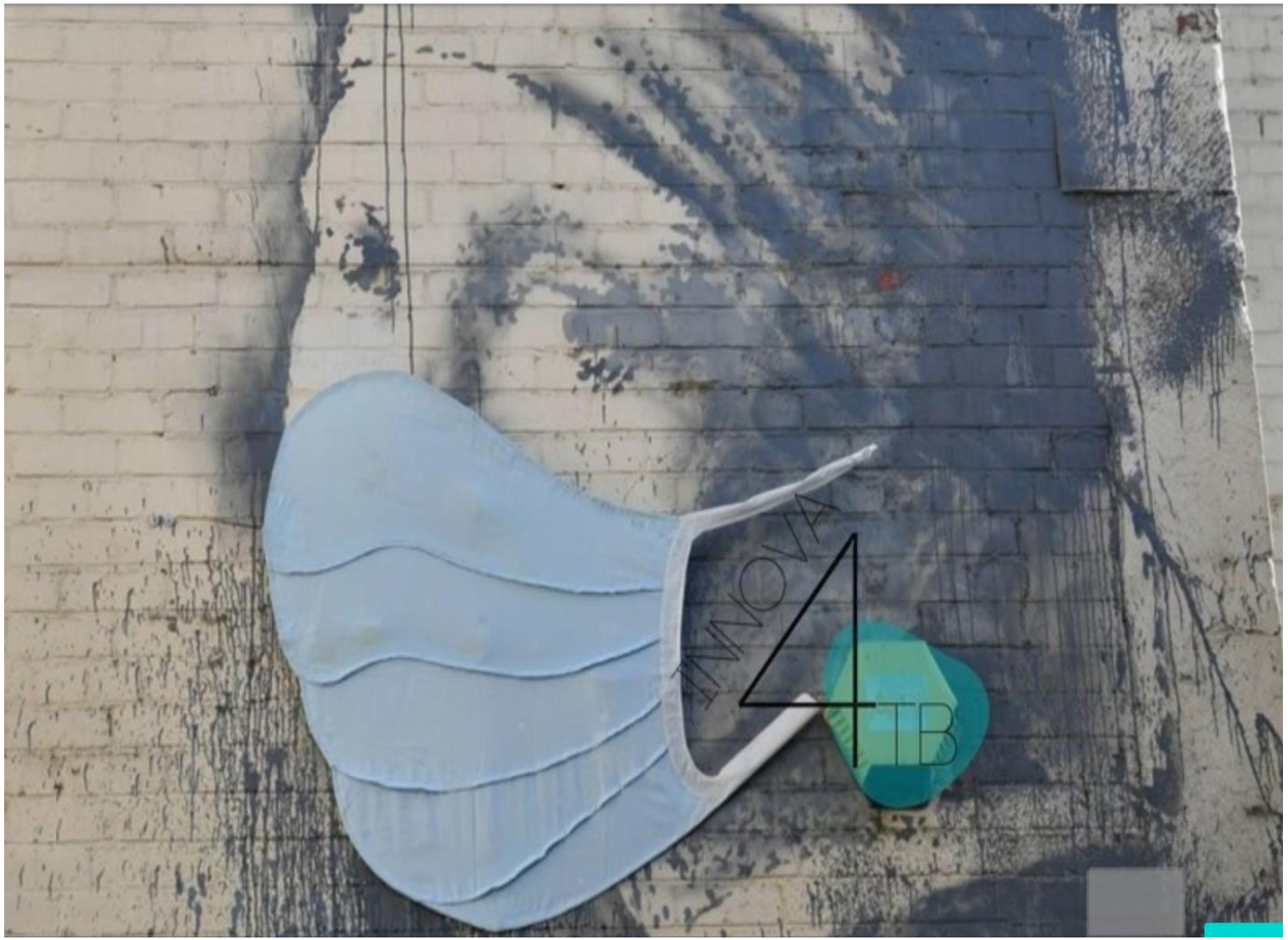
National Pirogov Memorial Medical University, Vinnytsya

New treatments for MDR-TB



New treatments for MDR-TB





New treatments for MDR-TB

2021 – top harmful alternative treatment

Gryllotalpa

Lesser wax moth

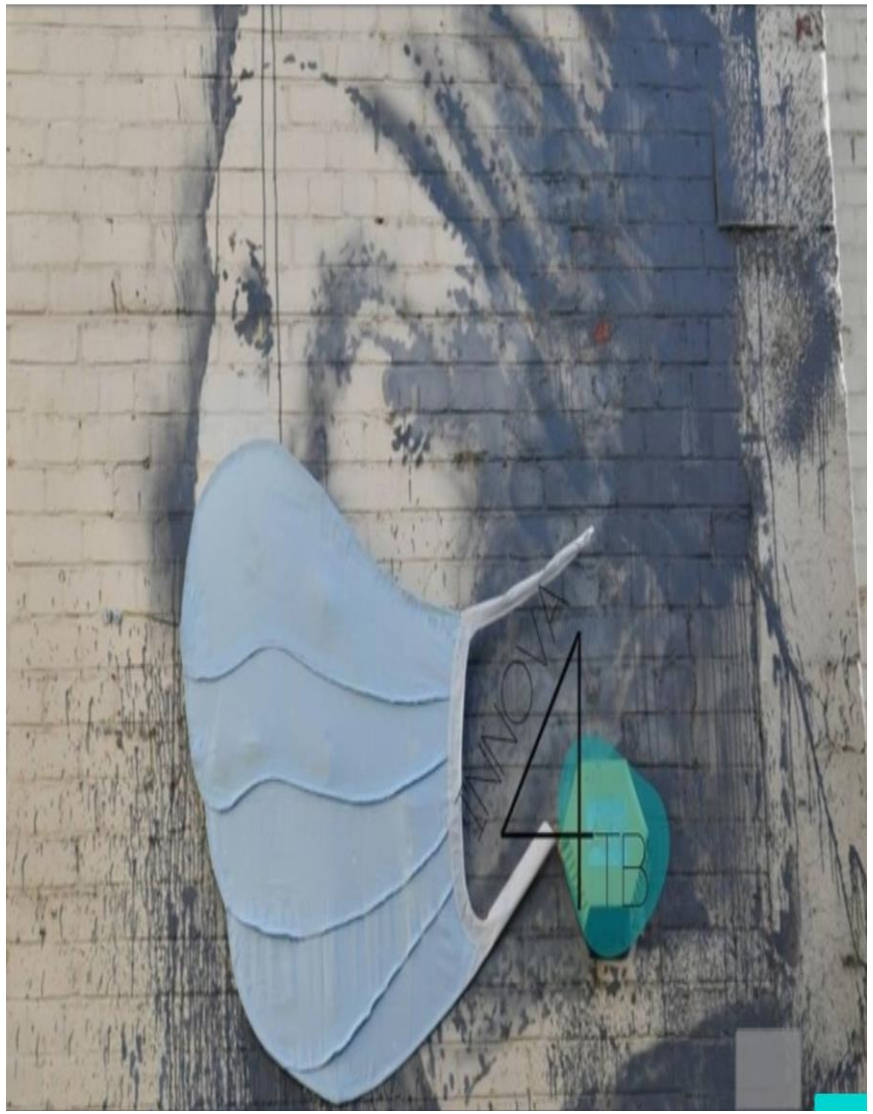
Horse immunomodulator

Prezi

New treatments for MDR-TB

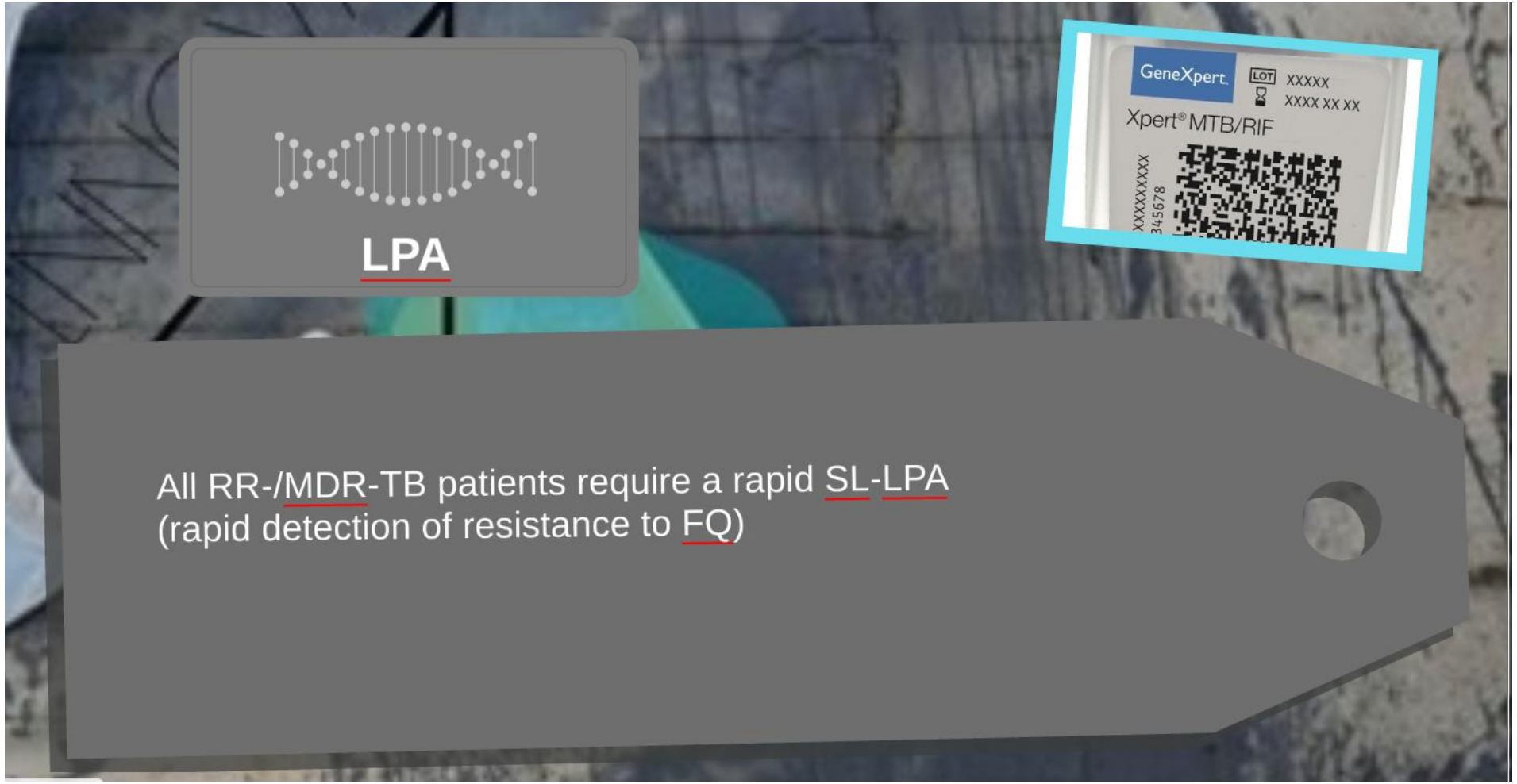
New landscape for MDR-TB treatment

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS



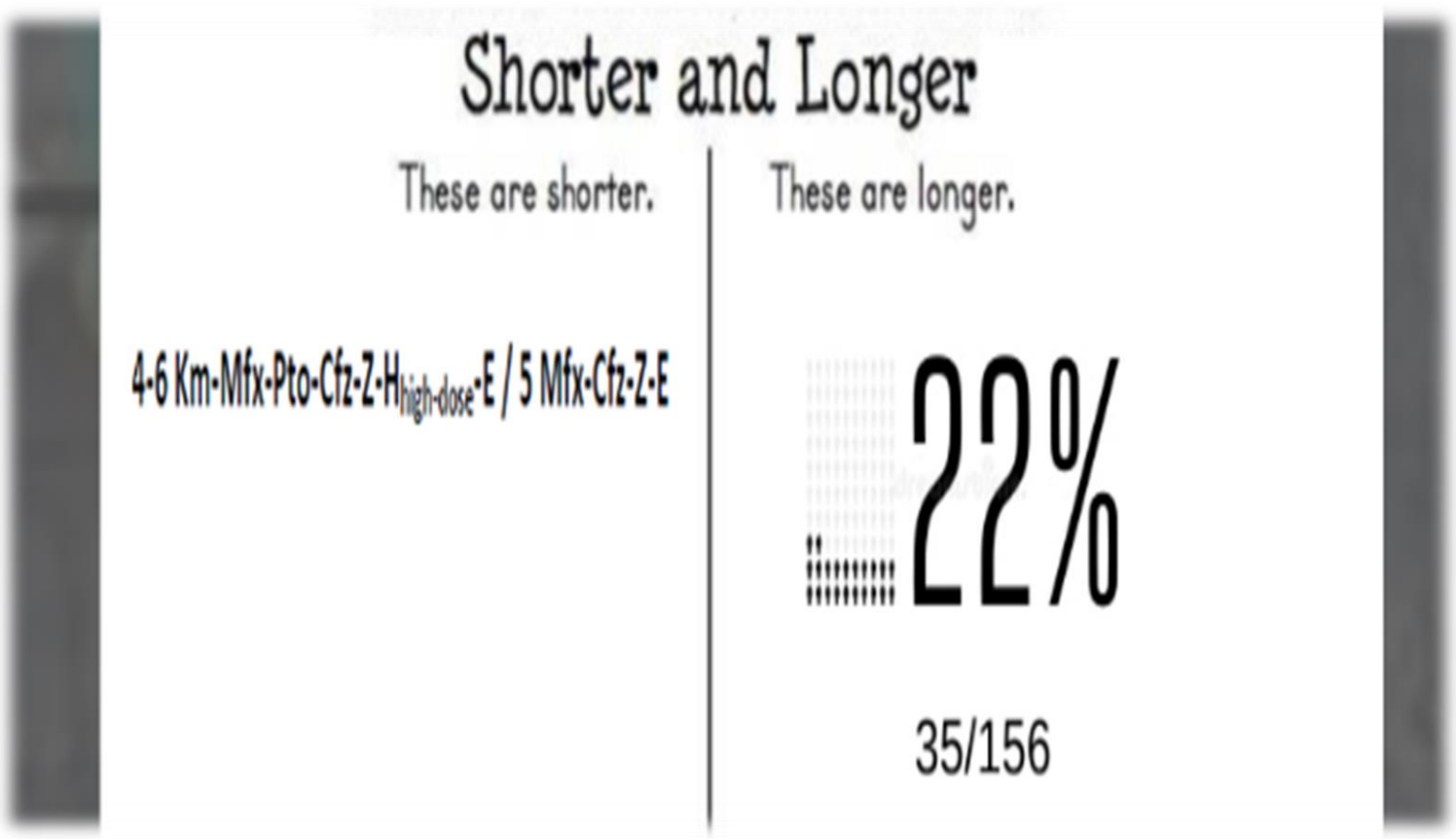
New treatments for MDR-TB

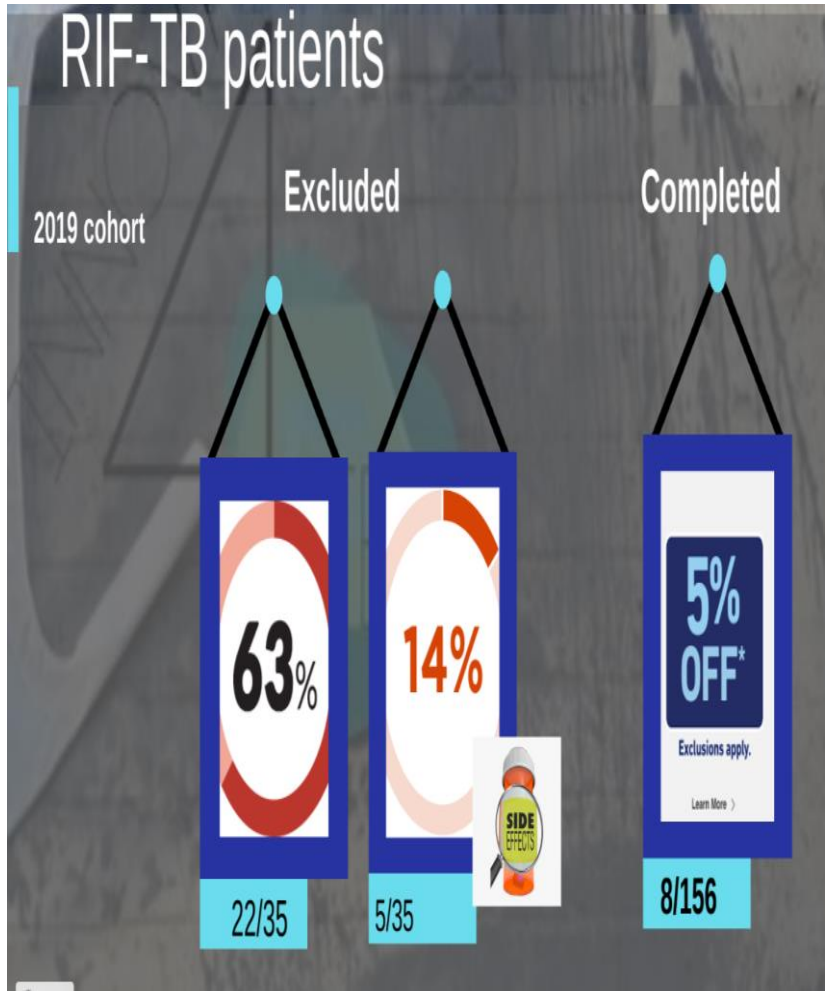
New treatments for MDR-TB



WHO consolidated guidelines on tuberculosis: drug-resistant tuberculosis treatment, 2020

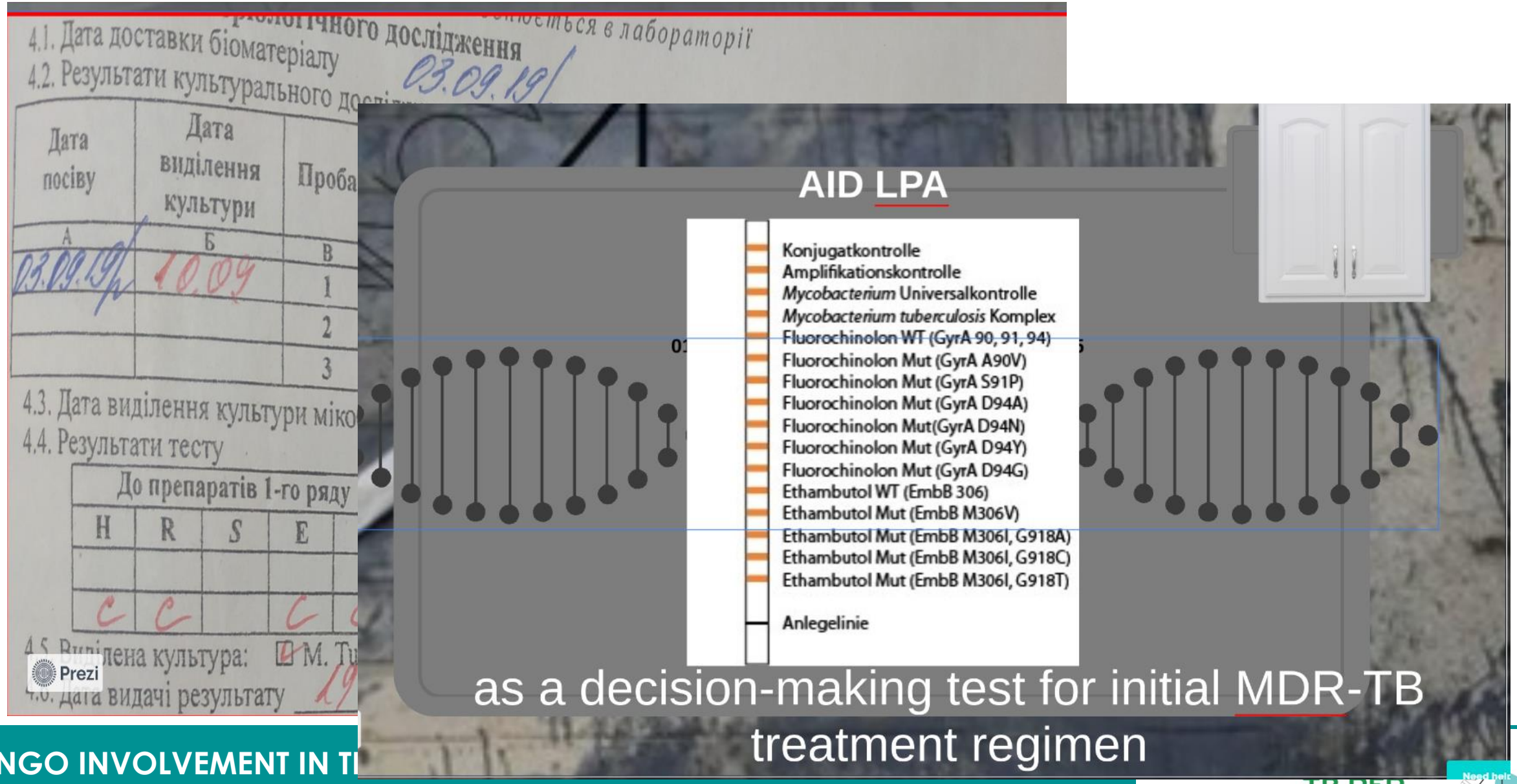
New treatments for MDR-TB



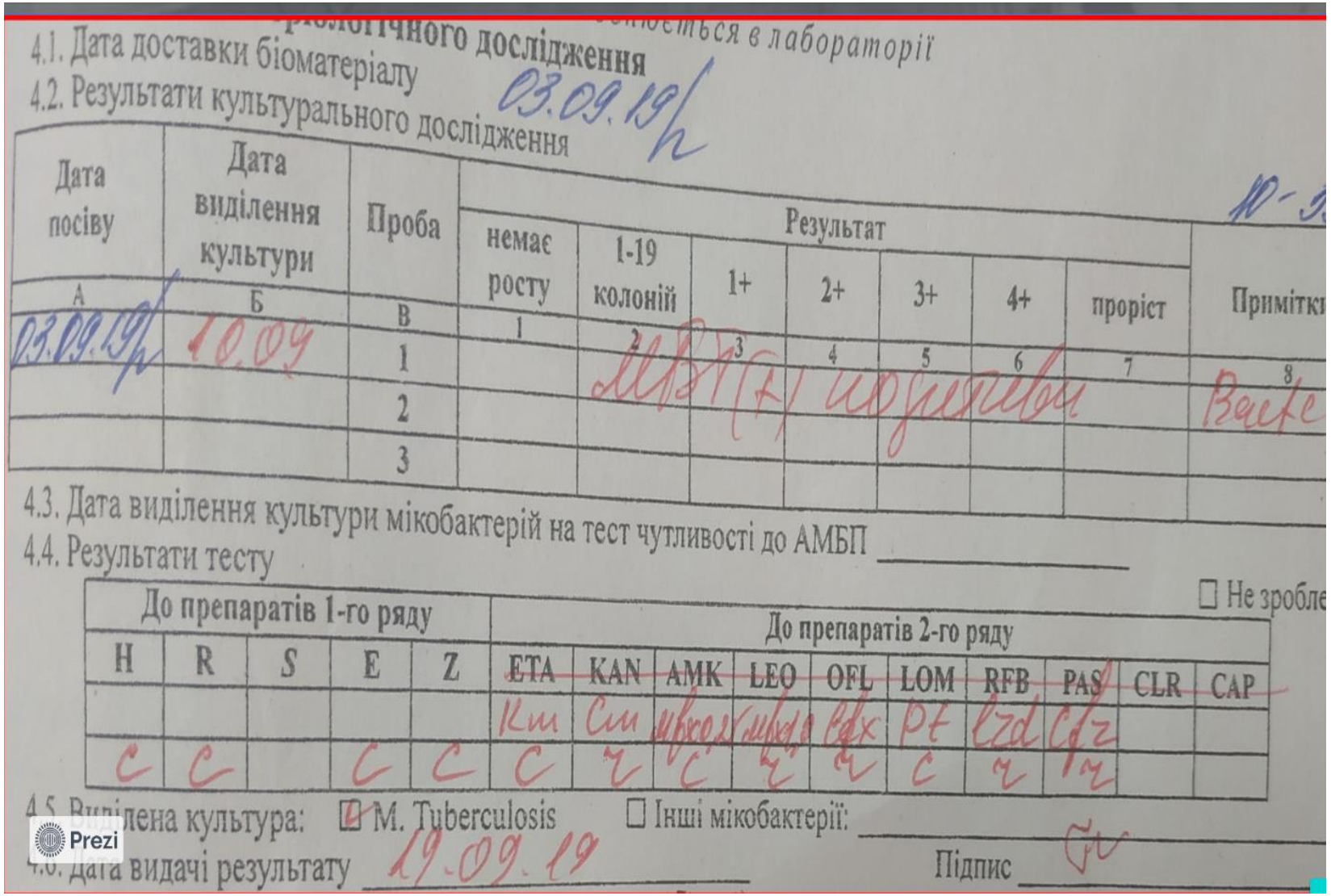


Dudnyk A et al. Why Ukraine is not Bangladesh, 2021

New treatments for MDR-TB



New treatments for MDR-TB



4.1. Дата доставки біоматеріалу 03.09.19

4.2. Результати культурального дослідження

Дата посіву	Дата виділення культури	Проба	Результат: немає росту	1-19 колоній	1+	2+	3+	4+	проріст	Примітки
А	Б	В	1	2	3	4	5	6	7	8
03.09.19	10.09	1		МБТ(+)						Бакте
		2								
		3								

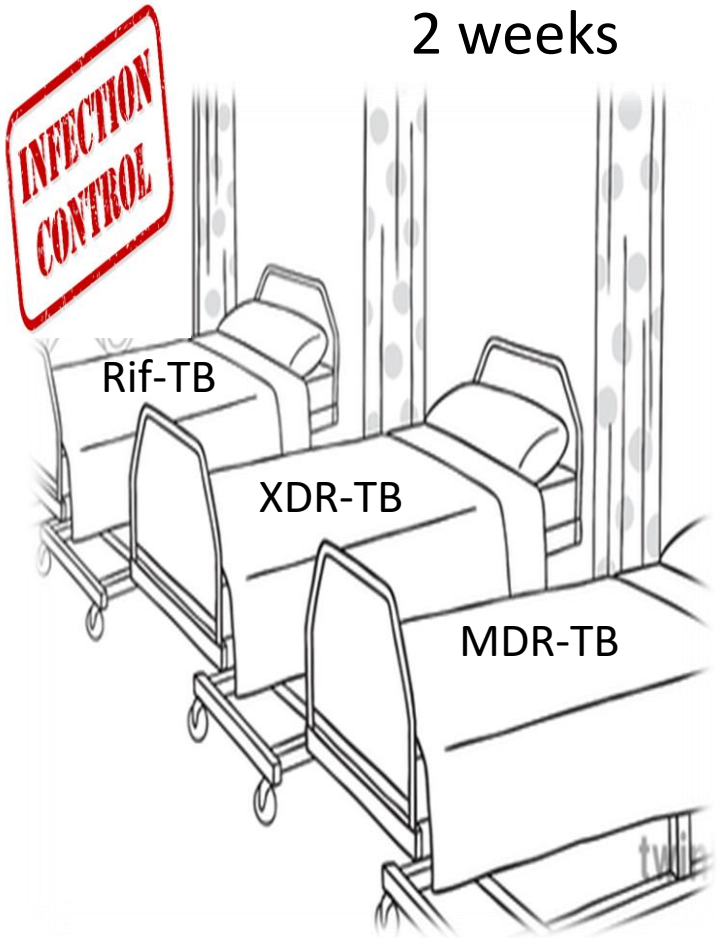
4.3. Дата виділення культури мікобактерій на тест чутливості до АМБП _____

4.4. Результати тесту ☐ Не зробле

До препаратів 1-го ряду					До препаратів 2-го ряду									
H	R	S	E	Z	ETA	KAN	AMK	LEO	OFL	LOM	RFB	PAS	CLR	CAP
					Km	Cm	[illegible]	[illegible]	Lfx	Pt	Lzd	Cfz		
C	C		C	C	C	r	C	r	r	C	r	r		

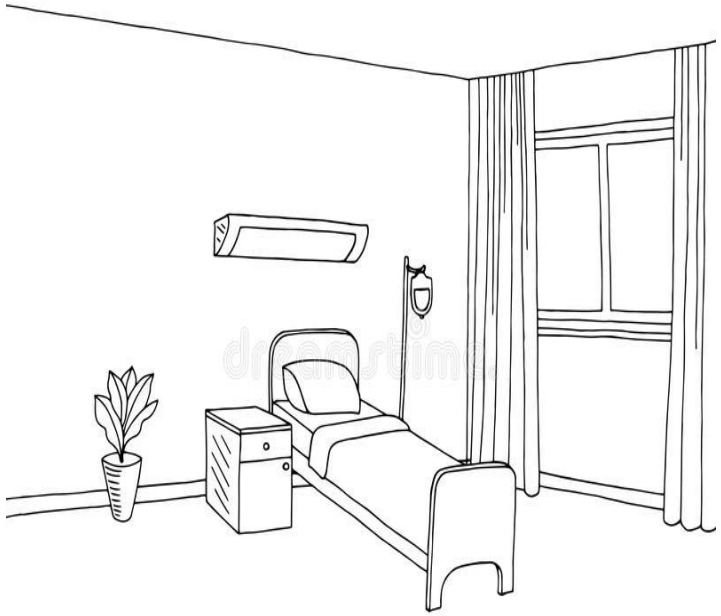
4.5. Виділена культура: ☒ M. Tuberculosis ☐ Інші мікобактерії: _____

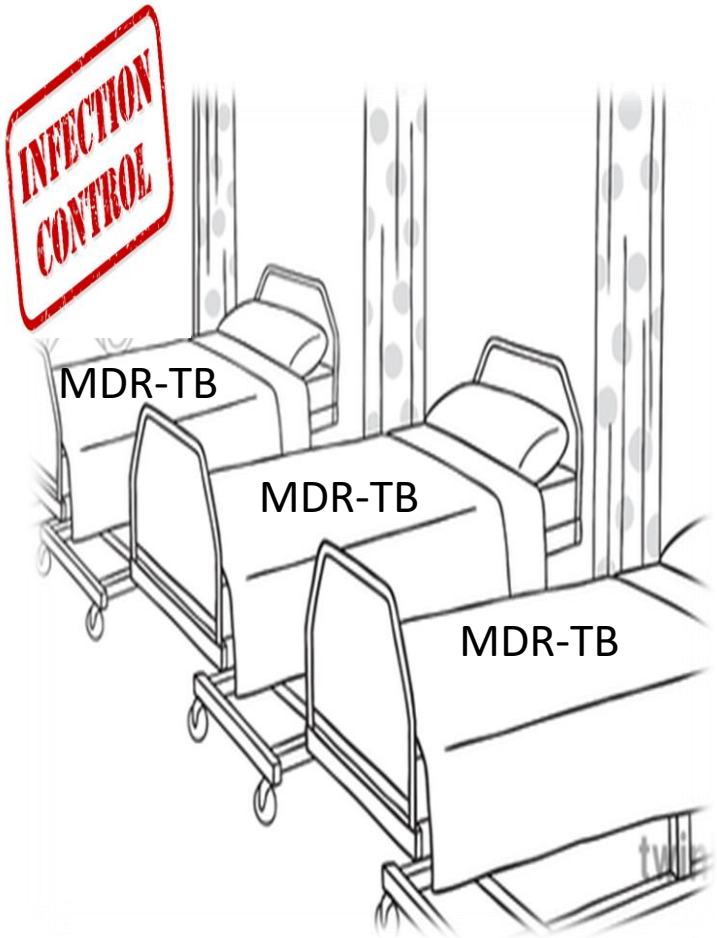
4.6. Дата видачі результату 19.09.19 Підпис _____



New treatments for MDR-TB

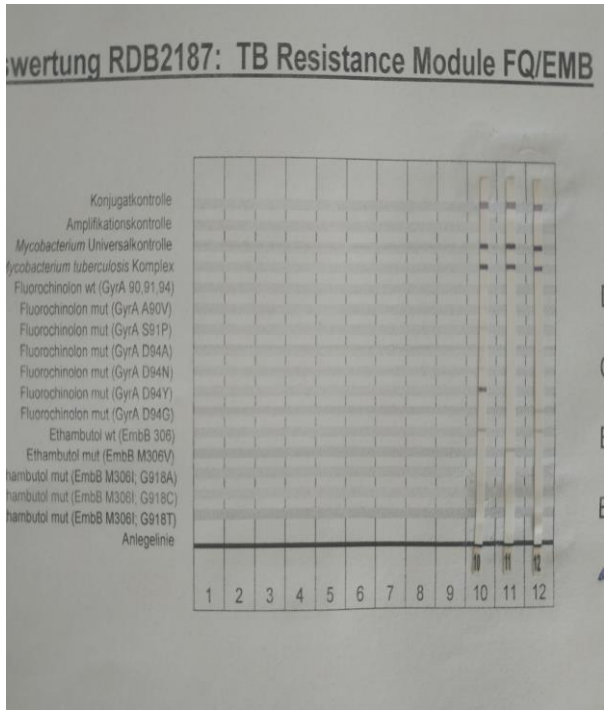
2 weeks
pending DST result

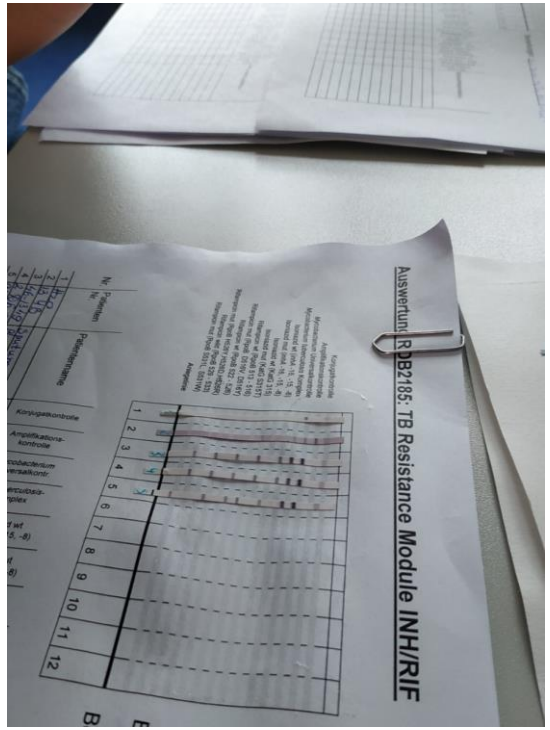


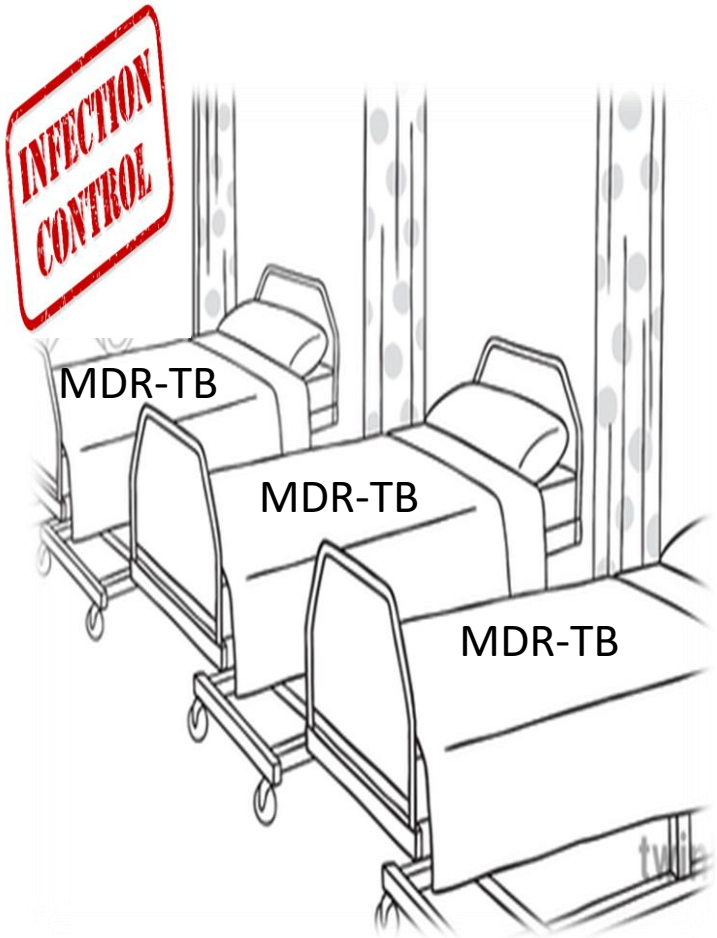


New treatments for MDR-TB

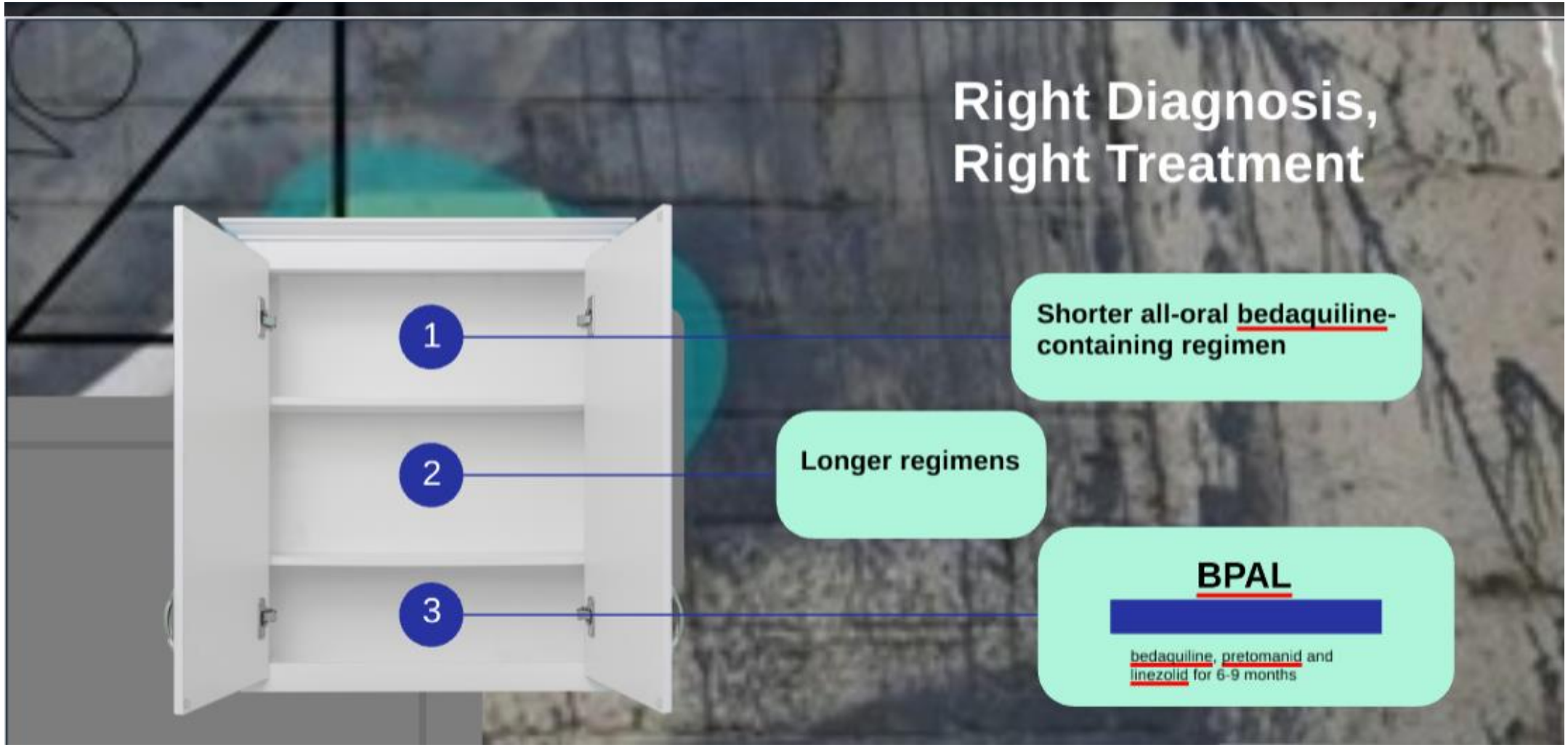
1 working day







New treatments for MDR-TB



Treatment regimens under investigation

World Health Organization
REGIONAL OFFICE FOR Europe

In this study, three all-oral shorter RR-TB treatment regimens are proposed, based on knowledge of their safety and efficacy as of 2020.

For adult patients:

Regimen 1: 39 weeks Lfx + Bdq + Lzd + Cfz + Cs

Regimen 2: 39 weeks Lfx + Bdq + Lzd + Cfz + Dlm

Treatment regimen 1 is preferred in adults as it includes all Group A and Group B anti-TB drugs. In patients with suspected resistance or intolerance of Cs, regimen 2 should be considered as primary choice of therapy.

For children:

Regimen 3: 39 weeks Lfx + Dlm + Lzd + Cfz

Non-invasive exclusion criteria for mSTR

World Health Organization
REGIONAL OFFICE FOR Europe

- Did patient ever receive drugs included in mSTR for one month or more?
- Is the patient unable to take oral medication?
- Is the patient taking any medications contraindicated with the medications in the mSTR?
- Does the patient have TB meningitis, miliary TB or TB osteomyelitis?
- Does the patient have a known allergy to any medication in the mSTR?
- Is the patient in a very severe clinical condition (Karnofski scale <40 or ECOG ≥4)?

Invasive exclusion criteria

World Health Organization
REGIONAL OFFICE FOR Europe

- Does the patient have documented resistance to a fluoroquinolones?
- Does the patient have a heart rate-corrected QT (QTc Fridericia correction) interval of ≥500 msec on ECG at screening?
- Does the patient have AST or ALT > 3 times the upper limit of normal?
- Does the patient have a creatinine clearance of less than 30 ml/min per 1.73 m2 of body surface area?

New treatments for MDR-TB

GDF estimated prices* for new MDR-TB Regimens

Regimen	Regimen Price Estimate
New All Oral Longer Regimen (20 months, includes BDQ for 6 months at $400)	
With Moxifloxacin (6 or 12 Months linezolid)	
6 Mfx Bdq Lzd Cs Cfz / 14 Mfx Cs Cfz	$1,861
6 Mfx Bdq Lzd Cs Cfz / 6 Mfx Lzd Cs Cfz / 8 Mfx Cs Cfz	$2,105
With Levofloxacin (6 or 12 Months linezolid)	
6 Lfx Bdq Lzd Cs Cfz / 14 Lfx Cs Cfz	$1,611
6 Lfx Bdq Lzd Cs Cfz / 6 Lfx Lzd Cs Cfz / 8 Lfx Cs Cfz	$1,854
New Shorter Regimen	
4 Am Cfz E H Mfx Pto Z / 5 Cfz E Mfx Z	$621
STR with BDQ instead of Injectable**	$852

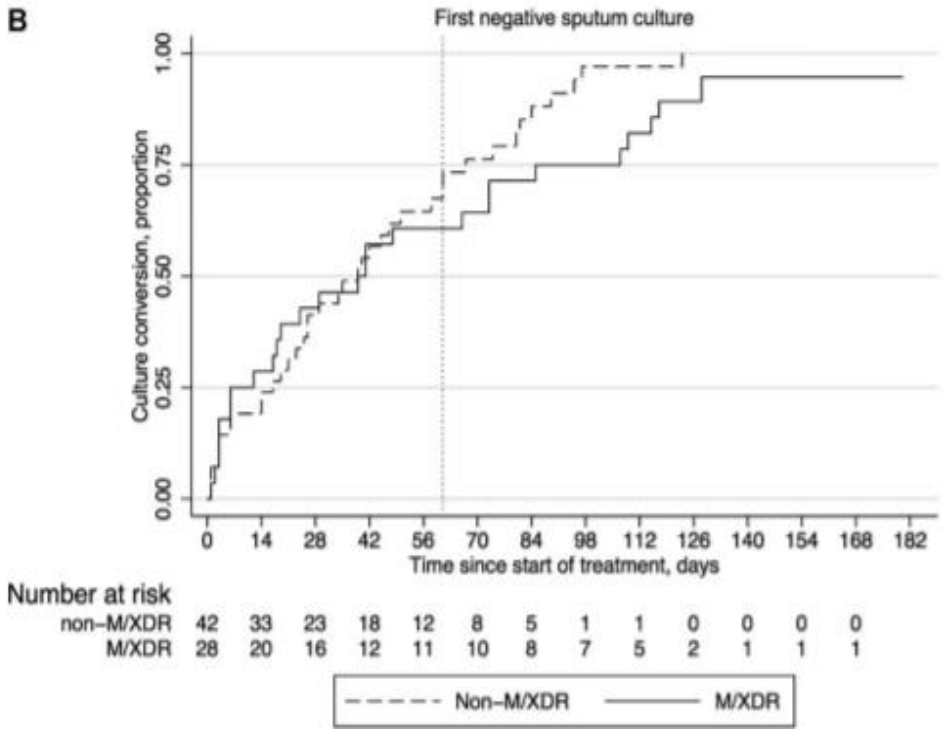
New treatments for MDR-TB

Table 3.2. Relative risk for treatment failure or relapse, and death (versus treatment success), 2018 IPD meta-analysis for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[a]

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
A	Levofloxacin *or* moxifloxacin	3143	0.3 (0.1–0.5)	3551	0.2 (0.1–0.3)
	Bedaquiline	1391	0.3 (0.2–0.4)	1480	0.2 (0.2–0.3)
	Linezolid	1216	0.3 (0.2–0.5)	1286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1096	0.4 (0.3–0.6)
	Cycloserine *or* terizidone	5483	0.6 (0.4–0.9)	6160	0.6 (0.5–0.8)
C	Ethambutol	1163	0.4 (0.1–1.0)	1245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)[b]	290	1.2 (0.5–3.0)[b]
	Pyrazinamide	1248	2.7 (0.7–10.9)	1272	1.2 (0.1–15.7)
	Imipenem–cilastatin *or* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *or* prothionamide	2582	1.6 (0.5–5.5)	2750	2.0 (0.8–5.3)
	P-aminosalicylic acid	1564	3.1 (1.1–8.9)	1609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2946	1.9 (1.0–3.4)	3269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

WHO consolidated guidelines on tuberculosis: drug-resistant tuberculosis treatment, 2020

Monitoring patient response to MDR-TB treatment and treatment duration



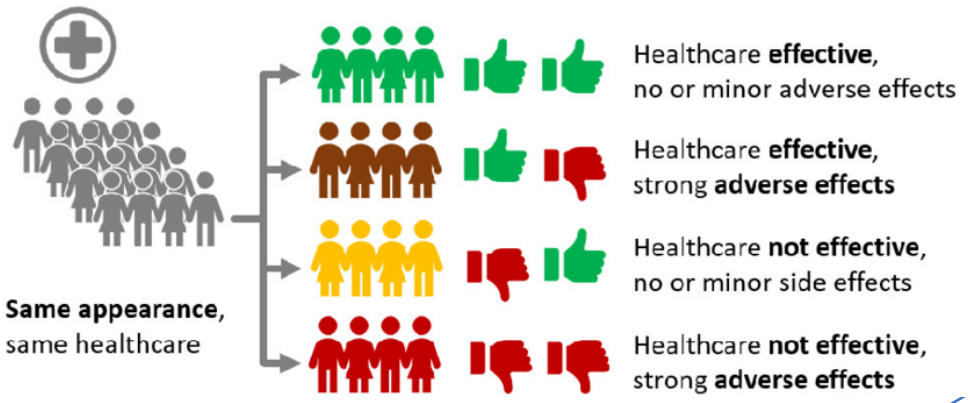
INT J TUBERC LUNG DIS 22(4):399-406

http://dx.doi.org/10.5588/ijtld.17.0741

Treatment responses in multidrug-resistant tuberculosis in Germany

J. Heyckendorf,*†‡ F. van Leth,§ K. Avsar,¶ G. Glattki,# G. Günther,*†‡** B. Kalsdorf,*†‡ M. Müller,†† I. D. Olaru,*† T. Rolling,†‡‡§§ H. J. F. Salzer,*†‡ M. Schuhmann,¶¶ E. Terhalle,*†‡ C. Lange*†‡##

New treatments for MDR-TB



Personalized therapy durations

MDR	XDR
HIV -	HIV +
Nodular	Milliary
Asymptomatic	Severe symptoms
Early sputum conversion	Complications/ comorbidities

Expression level of 9 genes

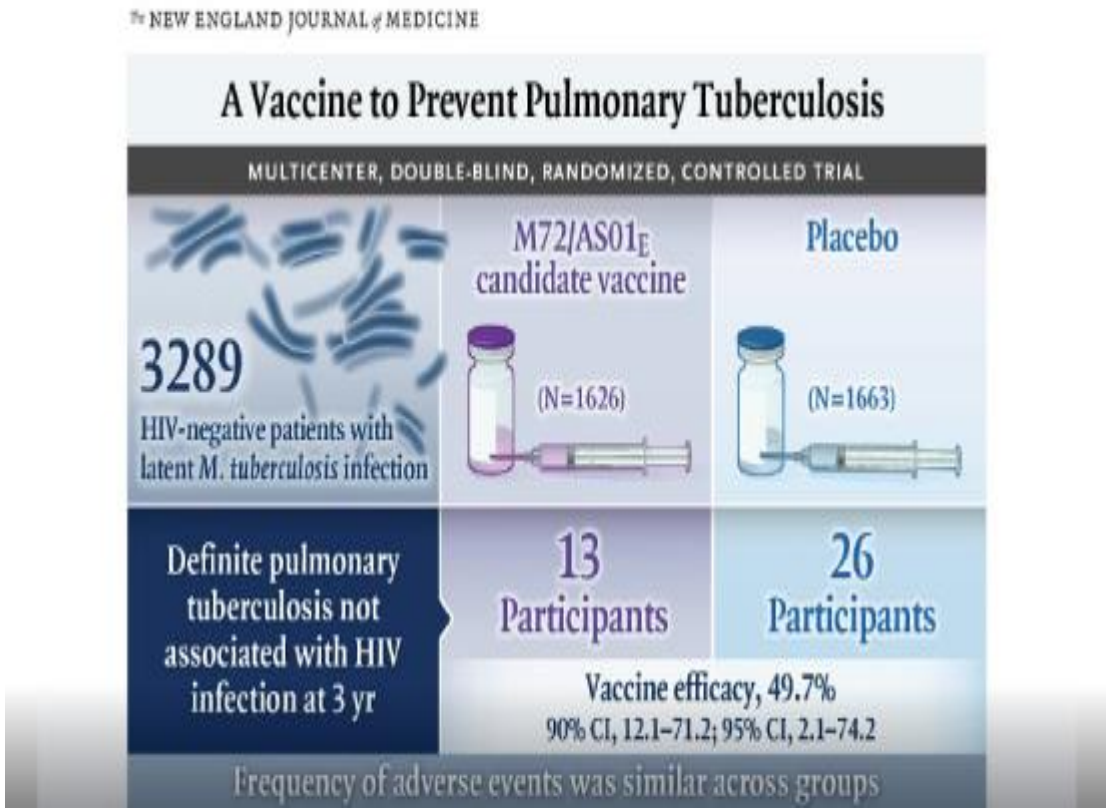
Blood RNA-based model for individualizing treatment in multidrug-resistant tuberculosis

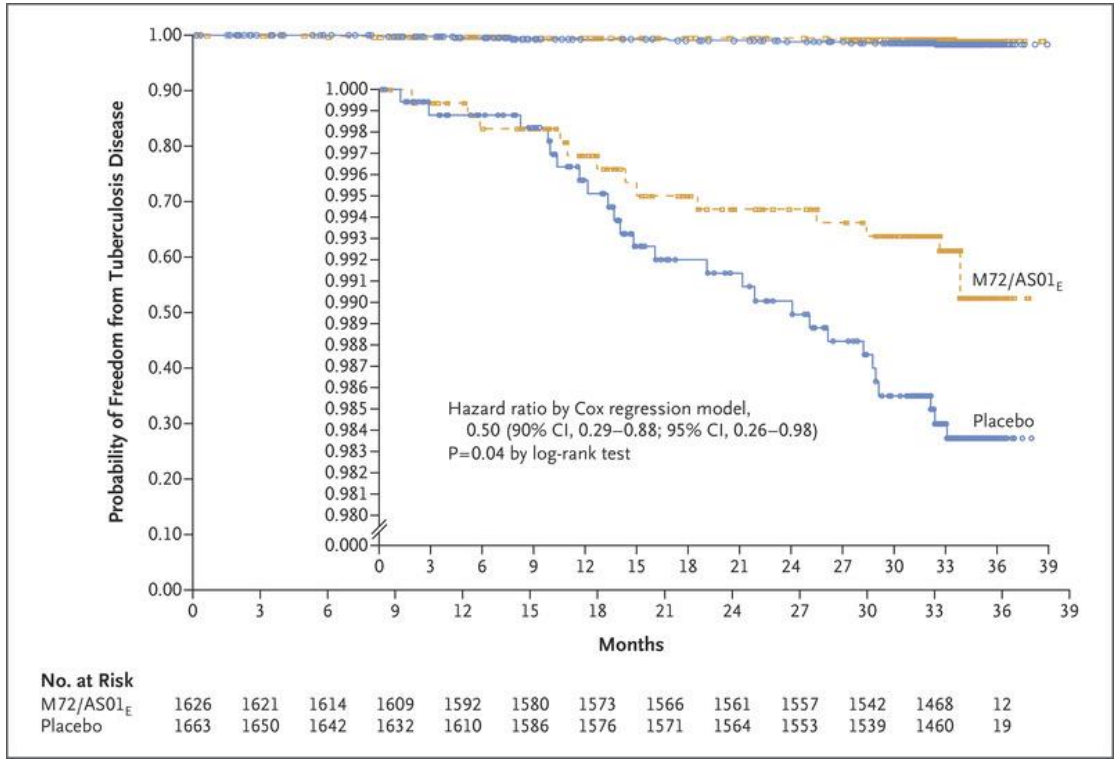
disease severity score

predicted remaining days of therapy

PredictEndTB signature

New treatments for MDR-TB





New treatments for MDR-TB

ORIGINAL ARTICLE

Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates

Pei-Chun Chan,[1,2,3] Chin-Hui Yang,[1] Luan-Yin Chang,[3] Kwei-Feng Wang,[1] Yi-Chen Kuo,[4] Chou-Jui Lin,[5] Shih-Wei Lee,[5] Po-Ren Hsueh,[6,7] Chi-Tai Fang,[2,7] Li-Min Huang[3]

Thorax 2013 Mar;68(3):263-8.

Table 3 Summary statistics for results of QuantiFERON-TB Gold In-tube

Stratification	Number of persons	Cut-off for positivity (%)	Cut-off for positivity (%)
	2416	LTBI (QFT-IT ≥0.35 IU/ml)	Recent LTBI (QFT-IT ≥0.7 IU/ml)
Age (years)		N (%)	
18–24	178	15 (8)	12 (7)
25–34	955	141 (15)	98 (10)
35–44	753	205 (27)	161 (21)
45–54	389	163 (42)	130 (33)
55–64	105	50 (48)	41 (39)
≥65	36	20 (56)	18 (50)
χ^2 p Value		<0.001	<0.001
Age (years)			
18–34	1133	156 (14)	110 (10)
35–54	1142	368 (32)	291 (25)
≥55	141	70 (50)	59 (42)
		<0.001*	<0.001*
BCG scar number	2406	N (%)	
No inoculation	216	102 (47)	86 (40)
Inoculation once	1062	271 (26)	216 (20)
Booster	1128	218 (19)	155 (14)
		<0.001*	<0.001*
Controlling for age		<0.001†	<0.001†
18–34 years		N (%)	
No inoculation	65	12 (18)	10 (15)
Inoculation once	563	93 (17)	66 (12)
Booster	504	51 (10)	34 (7)
		p=0.002*	p=0.002*
35–54 years			

The Journal of Infectious Diseases
1 January 2020 Volume 221 Number 1
IDSA hivma

Table 4: Crude and adjusted ORs for the association of LTBI and years since BCG vaccination, by age of vaccination.

Age at BCG	Years since BCG	Proportion with LTBI *(%)*	Crude OR *(95% CI)*	p value*	Adjusted OR** *(95% CI)*	p value*
≤2 years	No BCG	142/453 *(31.4)*	1		1	
(n=1867)	≤10	-	-		-	
	11-20	27/160 *(16.9)*	0.44 *(0.28-0.70)*		0.55 *(0.33-0.90)*	
	>20	423/1254 *(33.7)*	1.11 *(0.89-1.40)*	<0.001	0.78 *(0.60-1.00)*	0.026
>2 years	No BCG	142/453 *(31.4)*	1		1	
(n=1236)	≤10	12/106 *(11.3)*	0.28 *(0.15-0.53)*		0.31 *(0.15-0.63)*	
	11-20	51/243 *(21.1)*	0.58 *(0.40-0.84)*		0.73 *(0.48-1.10)*	
	>20	92/434 *(21.2)*	0.59 *(0.43-0.80)*	<0.001	0.67 *(0.46-0.98)*	0.0014

* Likelihood ratio test p value

BCG and M. tuberculosis Infection • jid 2019:XX

Treatment of LTBI in MDR-TB contacts		
V-QUIN	Six months of daily oral levofloxacin	50kg and above 750mg
TB-CHAMP	levofloxacin taken daily for six months	Children less than 5 years old
PHOENIX	26 weeks of delamanid (DLM) versus 26 weeks of isoniazid (INH) for prevention	high-risk household contacts of adults with MDR-TB
G.J. Fox et al. / Clinical Microbiology and Infection 23 (2017) 147e153		

New treatments for MDR-TB

THE LONGER
YOU WAIT
FOR THE FUTURE

THE SHORTER
IT WILL BE