Multidrug-resistant TB in Eastern region of the EU: is the shorter regimen an exception or a rule?

WHO recently recommended the use of a shorter multidrug-resistant TB (MDR-TB) regimen under programmatic conditions. We assessed eligibility for this regimen in a cohort of 737 adult patients with MDR-TB from Latvia, Lithuania, Estonia and Bucharest city recruited in 2007 and 2009. Only 4.2% of the patients were eligible for this regimen. Ethambutol (64%), pyrazinamide resistance (58%) and previous exposure to second-line TB drugs were major reasons for non-eligibility. High-level resistance to isoniazid is expected due to widespread prevalence of *katG* mutations. In Eastern Europe, the use of the shorter regimen might be an exception rather than a rule.

In May 2016, WHO recommended the use of a shorter multidrug-resistant TB (MDR-TB) regimen under programmatic conditions. The 9–12 months regimen consists of treatment with kanamycin, moxifloxacin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol followed by moxifloxacin, clofazimine, pyrazinamide and ethambutol. It is recommended for patients without previous exposure to second-line drugs (SLDs) and TB strains susceptible to fluoroquinolones and second-line injectable agents. It is not recommended for pregnant women and patients with extrapulmonary TB.[1] This recommendation is based on observational studies[2–4] as well as on the STREAM (Evaluation of a Standardised Treatment Regimen of Antituberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) trial performed in Asia and Africa.[5]

WHO estimates that in 2015 about 480 000 new MDR-TB cases occurred worldwide with 73 000 cases registered in the WHO European Region, where MDR-TB prevalence rates in new cases range between 10% and 34%.[6] However, there were no studies on the potential use of the shorter regimen in the European Region to inform the guidelines. A recent retrospective investigation of a cohort of 1140 patients with MDR-TB in Western Europe showed that only 7.8% of patients with MDR-TB would have been eligible for this regimen.[7]

We aimed to assess the proportion of patients with MDR-TB that would be eligible for the shorter regimen in the Eastern European settings, where the rate of drug resistance is highest.

We revisited the data from 737 adult pulmonary MDR-TB cases in our cohort recruited in 2007 and 2009 and followed-up to 2012 across Latvia, Lithuania, Estonia and Bucharest city within the European Union-funded project 'TB-PAN-NET'.[8] Drug susceptibility testing (DST) for first-line drugs (FLD) and SLD was performed using solid or automated liquid culture media systems (BACTEC MGIT 960, Becton Dickinson, Sparks, Maryland, USA) according to standard procedures.[9] High and low levels of isoniazid resistance were not distinguished phenotypically.

Fluoroquinolone resistance was defined based on resistance to ofloxacin or moxifloxacin; DST to ethionamide or prothionamide was equivalent. Clofazimine DST was not routinely conducted. Eligibility for the shorter regimen was defined as susceptibility to kanamycin, moxifloxacin/ofloxacin, ethionamide/prothionamide, pyrazinamide and ethambutol with no history of previous treatment. Non-eligibility was defined when at least one of the exclusion criteria was valid irrespective of the overall information completeness per case. Descriptive statistical analyses stratified by eligibility were performed using Stata V.14 (StataCorp, College Station, Texas, USA).

Among 737 patients with MDR-TB, 610 (83%) had sufficient DST information for the evaluation. Among these, 38 (6.2%) were eligible for the shorter regimen and 572 (94%) were non-eligible. Drug resistance to ethambutol (64%) or pyrazinamide (58%) was the most common reason for exclusion; however, concerns regarding DST reliability might question the findings. Considering both DST and information on previous treatment, 687 (93%) had sufficient information for the evaluation. Among these, only 29 (4.2%) were eligible and 658 (96%) non-eligible (table 1). The eligibility was largely similar across different patient groups. However, none of the patients with TB living with HIV or using recreational drugs was eligible (table 2).

These results are largely in line with published data for other regions; the proportion of 6.2% eligible patients was slightly higher than in pooled findings from the European and Latin American settings (4.0%)[10] and slightly lower than in a Western European cohort (7.8%).[7] Of note, even in the context of settings with a well-developed quality controlled DST, many DST profiles were not complete.

The study was limited to the information available for the cohort that was based on routine management data. Complete information on the level of isoniazid resistance, pregnancy and drug intolerance was missing. However, over 90% of all isoniazid-resistant strains (mainly of the Beijing family) isolated in many Eastern European countries are known to harbour mutations in *katG* gene associated with high levels of isoniazid resistance.[11 12]

Previous studies have demonstrated that the epidemic in the former Union of Soviet Socialist Republics countries including the Baltic countries is likely to be associated with a fairly homogenous 'East European' subtype of the Beijing lineage.[13] We therefore hypothesise that the findings might be applicable to the countries beyond the study settings.

Table 1 Eligibility of patients with MDR-TB for the shorter regimen in an Eastern European MDR-TB cohort (N=737)

Criteria	Evaluable			Not evaluable
	Eligible*	Non-eligible	Total	
DST results				
Kanamycin susceptibility	462/701 (66%)	239/701 (34%)	701 (95%)	36 (4.9%)
Ofloxacin /moxifloxacin susceptibility	581/705 (82%)	124/705 (18%)	705 (96%)	32 (4.3%)
Ethionamide/prothionamide susceptibility	361/519 (70%)	158/519 (30%)	519 (70%)	218 (30%)
Pyrazinamide susceptibility	245/586 (42%)	341/586 (58%)	586 (80%)	151 (20%)
Ethambutol susceptibility	255/710 (36%)	455/710 (64%)	710 (96%)	27 (3.7%)
Full susceptibility	38/610 (6.2%)	572/610 (94%)	610 (83%)	127 (17%)
Pretreatment information				
Not previously treated	336/737 (46%)	401 (54%)	737 (100%)	0 (0%)
Combined information				
Eligibility for shorter regimen	29/687 (4.2%)	658/687 (96%)	687 (93%)	50 (6.8%)

*Eligibility was determined based on the information on the DST profile and a history of previous treatment. Non-eligibility was defined when at least one of the exclusion criteria was valid irrespective of the information completeness per case, that is, a history of previous treatment rendered the case as non-eligible even in the absence of the full DST profile.
DST, drug susceptibility testing; MDR-TB, multidrug-resistant TB.

Table 2 Patient characteristics and eligibility of patients with MDR-TB for the shorter regimen (according to DST criteria) in an Eastern European MDR-TB cohort (N=737)

Patient characteristics	Eligible	Non-eligible	Not evaluable
Demographic factors			
Age (years) (N=737)			
Median (IQR)	46 (31–57)	45 (34–54)	46 (35–56)
Gender (N=737)			
Male (n=156)	28 (4.8%)	450 (78%)	103 (18%)
Female (n=581)	10 (6.4%)	122 (77%)	24 (15%)
Living settings (N=737)			
Urban (n=499)	17 (3.4%)	384 (77%)	98 (20%)
Rural (n=238)	21 (8.8%)	188 (79%)	29 (12%)
Social factors			
Employment (n=736)			
Unemployed (n=481)	21 (4.4%)	371 (77%)	89 (19%)
Retired (n=71)	7 (10%)	60 (85%)	4 (5.6%)
Employed (n=184)	10 (5.4%)	141 (77%)	33 (18%)
Homelessness (N=737)			
Homeless (n=54)	3 (5.6%)	49 (91%)	2 (3.7%)
Have home (n=683)	35 (5.1%)	523 (77%)	125 (18%)
Prison (N=422)			
In prison (n=59)	1 (1.7%)	57 (97%)	1 (1.7%)
Not in prison (n=363)	31 (8.5%)	265 (73%)	67 (18%)
*Substance abuse**			
Smoking (N=570)			
Yes (n=434)	15 (3.5%)	324 (75%)	95 (22%)
No (n=136)	10 (7.3%)	101 (74%)	25 (18%)
Alcohol abuse (N=731)			
Yes (n=421)	15 (3.6%)	337 (80%)	69 (16%)
No (n=310)	23 (7.4%)	232 (75%)	55 (18%)
Recreational drugs (N=719)			
Yes (n=37)	1 (2.7%)	32 (86%)	4 (11%)
No (n=682)	37 (5.4%)	531 (78%)	114 (17%)
Comorbidities†			
HIV (N=737)			
Negative (n=510)	31 (6.1%)	393 (77%)	86 (17%)
Positive (n=20)	0 (0%)	19 (95%)	1 (5.0%)
Not tested (n=297)	7 (3.4%)	160 (77%)	40 (19%)
Condition other than HIV† (N=737)			
Yes (n=37)	4 (4.9%)	28 (78%)	5 (17%)
No (n=700)	34 (11%)	544 (76%)	122 (14%)
Disease characteristics			
Site of disease (N=737)			
Pulmonary only (n=705)	38 (5.4%)	545 (77%)	122 (17%)
Pulmonary and extrapulmonary (n=32)	0 (0%)	27 (84%)	5 (16%)
Presence of cavities (N=732)			
Yes (n=456)	27 (5.9%)	352 (77%)	77 (17%)
No (n=276)	11 (4.0%)	216 (78%)	49 (18%)
Smear positivity at diagnosis (N=737)			
Yes (n=573)	26 (4.5%)	429 (75%)	118 (21%)
No (n=164)	12 (7.3%)	143 (87%)	9 (5.5%)

*Alcohol excess and recreational drug use were determined by physicians and reported as stated in patients' case histories according to nationally accepted breakdown categorisation.
†Including hepatitis B, hepatitis C, chronic liver condition, other immunocompromised conditions (including autoimmune disorders), cancer.
MDR-TB, multidrug-resistant TB.

In conclusion, in many Eastern European countries, only an extremely small proportion of patients with MDR-TB would be eligible for the shorter regimen. Given complex drug-resistance patterns and the expected significant prevalence of high-level resistance to isoniazid, the shorter regimen should be applied with great caution. It is crucial to consider all exclusion criteria before its administration. Reliable and comprehensive DST must be available before considering the new regimen for programmatic use. Meanwhile, available molecular assays, specifically those detecting mutations in genes associated with isoniazid, fluoroquinolones and aminoglycoside resistance can support the adequate design of drug regimens. Further larger research in different geographic settings is critically needed to assess benefits of the shorter regimen. The impact of the new regimen on adherence improvement should be evaluated. Should the shorter regimen be proved to be applicable at least for a proportion of patients, costs saved due to the shortened treatment duration could be invested in measures targeted to improve adherence.

Overall, in spite of the demonstrated success of the shorter MDR-TB regimen in Africa and Asia, its use in Eastern Europe might be an exception rather than a rule. The continuous availability of all required drugs in the regimen needs to be addressed in settings with limited resources. Further options for shorter regimens are still urgently needed for most patients with MDR-TB.

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Funding The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement FP7–223681. LF received a

research grant from the not-for profit organisations Oskar-Helene-Heim and Günther Labes. The funders had no role in the design or analysis of the study.

Competing interests None declared.

Ethics approval The 'TB-PAN-NET' project was reviewed and approved by the Ethics Review Committees of the University of Tartu and Riga Stradins University and received a waiver of informed consent as anonymised data were used. Local Ethics Committees exempted the study from an ethics review in Lithuania and Romania. The study was approved by Queen Mary College Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We agree to share the data from this research.

To cite Balabanova Y, Fiebig L, Ignatyeva O, *et al*. *Thorax* 2017;**72**:850–852.

Received 9 December 2016
Revised 4 January 2017
Accepted 23 January 2017
Published Online First 16 February 2017

► http://dx.doi.org/10.1136/thoraxjnl-2017-210163

Thorax 2017;**72**:850–852.
doi:10.1136/thoraxjnl-2016-209841

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