Shorter regimens for multidrug-resistant tuberculosis should also be applicable in Europe

To the Editor:

Since May 2016, the World Health Organization (WHO) has recommended shorter regimens to treat rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB), substantially reducing the treatment duration to 9–12 months [1]. VAN DER WERF *et al.* [2] estimated that only 11% of RR/MDR-TB patients in the European Union (EU)/European Economic Area (EEA) fulfilled the WHO inclusion criteria, which is similar to estimates by LANGE *et al.* [3] and SOTGIU *et al.* [4]. This estimate raises concerns, as that the conventional long-duration regimen has very poor results in the EU/EEA. Health sector crisis, increasing inequality and xenophobia add to the urgency to prevent and manage MDR-TB. The main exclusion criteria are as follows.

1) Previous use of second-line drugs (SLDs). The estimate is clearly too high (55% of RR/MDR-TB cases), as it also excluded previous use of only first-line drugs. A better estimate could be from countries like Latvia where 42% of RR/MDR-TB cases in 2005–2015 were previously treated, 30% of them with SLDs, representing 12% of all RR/MDR-TB cases (V. Riekstina, Centre of Tuberculosis and Lung Diseases, Riga, Latvia; personal communication). In Western Europe, many patients with RR/MDR-TB were born in Asia and Africa, where SLDs have been used far less frequently [5].

2) Resistance to second-line injectable drugs (SLIDs) and/or fluoroquinolones. Such resistance affects 41% of RR/MDR-TB patients in the EU/EEA; 34% in new patients and 48% in previously treated patients (communication with the European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden) (table 1). In patients of Former Soviet Union (FSU) origin, resistance levels are higher (50% in all, 44% in new and 56% in previously treated patients). In patients whose origin was outside the FSU (64% of all cases), the level of resistance was considerably lower (34% overall, 22% in new and 42% in previously treated patients). The proportion in previously treated patients is even lower, if patients treated with SLDs are excluded first (criterion 1). Furthermore, all ofloxacin-resistant cases were also considered to be moxifloxacin-resistant, but only 7% of ofloxacin-resistant strains have been found to be resistant to moxifloxacin [6]. In a study performed in Bangladesh, only high-level fluoroquinolone resistance reduced success, caused by failure [7]. Most of the mutations correlating with this high-level resistance can be identified by the line-probe assay recommended by the WHO [8].

3) Resistance to other drugs in the regimen, particularly ethambutol or pyrazinamide [1]. In the cohort studies performed in Bangladesh [7] and West Africa [9], on which the recommendation for the shorter regimens is based, cases with resistance to isoniazid, ethambutol or pyrazinamide were not excluded and the overall success was high. Moreover, WHO does not recommend that treatment decisions should be based on drug-susceptibility test (DST) results for ethambutol as the test is unreliable [10]. There is no approved rapid test for pyrazinamide resistance and the clinician may decide to use the shorter MDR-TB regimen in its presence [10]. Susceptibility to other drugs, such as clofazimine, is either never tested routinely, or their DST results are notoriously unreliable and their testing is therefore discouraged. In the EU/EEA, DST coverage is fortunately high (fulfilling WHO criteria for exclusion of resistance to SLID and fluoroquinolones), meaning resistance to ethambutol and pyrazinamide would therefore be a major reason for exclusion.

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TABLE 1 Tuberculosis (TB) drug resistance according to each patient's treatment history and place of origin in rifampicin-resistant/multidrug-resistant (RR/MDR)-TB cases registered in European Union/European Economic Area countries, 2010–2014

Place of origin	Treatment history	Notified cases n	Km or Am		Mfx or Ofx		Km or Am and/or Mfx or Ofx		Ethambutol		Sensitive to all drugs	
			Tested n	% R	Tested n	% R	Tested n	% R	Tested n	% R	Tested n	% S
Outside FSU[#]												
	Total	4859	2475	25.3	1986	21.2	2491	33.6	2443	59.6	1927	44.9
	New	1800	940	14.4	856	13.4	947	21.6	937	49.3	840	51.4
	Previously treated	2866	1439	33.6	1033	28.3	1446	42.3	1410	67.2	994	39.0
	Unknown history	193	96	8.3	97	14.4	98	20.4	96	47.9	93	48.4
FSU[#]												
	Total	2691	2272	37.9	2275	29.6	2277	49.8	2273	70.3	2265	19.3
	New	1303	1128	34.0	1128	20.4	1129	43.8	1127	68.8	1125	22.1
	Previously treated	1253	1070	41.5	1073	39.0	1073	56.0	1073	72.1	1069	16.1
	Unknown history	135	74	43.2	74	32.4	75	52.0	73	67.1	71	22.5
Total												
	Total	7550	4747	31.3	4261	25.7	4768	41.4	4716	64.8	4192	31.1
	New	3103	2068	25.1	1984	17.4	2076	33.7	2064	59.9	1965	34.7
	Previously treated	4119	2509	37.0	2106	33.8	2519	48.2	2483	69.4	2063	27.1
	Unknown history	328	170	23.5	171	22.2	173	34.1	169	56.2	164	37.2

Km: kanamycin; Am: amikacin; Mfx: moxifloxacin; Ofx: Ofloxacin; R: resistant; S: sensitive; FSU: former Soviet Union. [#]: FSU includes Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan. Source: European Centre for Disease Prevention and Control (ECDC).

4) An extrapulmonary site, with exclusion based on lack of data. The rifampicin-based short-course chemotherapy was first developed for pulmonary TB in the 1970s and 1980s [11], and later studies found that it was also effective in extrapulmonary forms (with the exception of TB meningitis) [12]. There is no apparent reason to postulate that the shorter MDR-TB regimen will not work in extrapulmonary TB.

Shortened MDR-TB regimens have been shown to protect against acquired resistance to SLD (one in 515 cases in Bangladesh) [7]. As they do not include new drugs, they will be protected and provide life-saving treatments for patients with resistance or adverse reactions to SLDs. By the end of 2015, bedaquiline had already been used in 70 countries; failures and resistance development has been reported [13].

Specialists may be reluctant to use standardised regimens [14]. When DOTS (directly observed treatment, short course) was introduced globally in the 1990s, standard regimens had already long been adopted in leading European countries without diminishing the role of specialists in providing holistic treatment for their patients. It could and should be analogous with the standardised shorter MDR-TB regimens. Specialists may treat most of the patients with shorter regimens at low cost, leaving more time and funding for the increasing number of patients with resistance to SLID or fluoroquinolones, as well as adverse reactions.

In Norway, the National MDR-TB Technical Group recently included the shorter regimens in the treatment recommendations (unpublished data). WHO criteria are generally interpreted to exclude most patients because of resistance to ethambutol, pyrazinamide or an extrapulmonary site. This forces the patient to be enrolled on the conventional regimen with twice the duration and documented unacceptable results. The shorter regimens should also be eligible for patients with strains resistant to ethambutol or pyrazinamide (not to contradict the latest WHO recommendation) and should be evaluated in patients with an extrapulmonary site (under operational research conditions) in EU/EEA countries, adding much needed evidence about the regimens from another setting.

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From the authors:

In response to our manuscript on the eligibility for shorter treatment of multidrug-resistant tuberculosis (MDR-TB) in the European Union (EU) [1], Heldal and co-workers highlight the limitations of the surveillance data that were used to estimate the proportion of MDR-TB cases eligible for the shorter regimen, and they question the criteria that we used to define eligibility.

The World Health Organization (WHO) criteria for eligibility state that patients exposed to second-line medicines included in the shorter MDR-TB regimen for ⩾1 month are not eligible. As information on exposure is not available in our surveillance data, we excluded all cases with previous treatment, realising that this was a conservative approach. The data from Latvia (V. Riekstina, Centre of Tuberculosis and Lung Diseases, Riga, Latvia; personal communication) provide an indication that our approach was indeed conservative. Taking this criticism into account, readers are able to ascertain from the data provided in figure 1 in our published study [1], that 524 (16.9%) of the 3103 new cases were eligible for the shorter MDR-TB treatment, given the exclusion of extrapulmonary TB and those resistant to kanamycin/amikacin, moxifloxacin/ofloxacin or ethambutol.

Heldal and colleagues question our decision to consider ofloxacin-resistant cases as moxifloxacin-resistant. They argue that only 7% of ofloxacin-resistant strains have been found to be resistant to moxifloxacin. The data to which they refer are from Azerbaijan, Bangladesh, Belarus (Minsk city), Pakistan and South Africa (Gauteng and Kwazulu Natal). In our EU/European Economic Area (EEA) data, 816 rifampicin-resistant TB cases were tested for both ofloxacin and moxifloxacin. Out of 208 ofloxacin-resistant cases, 169 (81.2%) were also resistant to moxifloxacin. Thus, in our setting, cross-resistance between ofloxacin and moxifloxacin is frequent, supporting our choice of using ofloxacin resistance as a proxy for moxifloxacin resistance to cover missing data (1768 out of 1774 cases were tested for ofloxacin and 386 out of 1774 for moxifloxacin).

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Strict application of criteria shows that 11% of MDR-TB cases are eligible for the shorter MDR-TB regimen in the EU http://ow.ly/p9aq30bt1AI

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The authors also challenge the fact that we considered MDR-TB cases with resistance to ethambutol as ineligible for the shorter MDR-TB regimen. We based our exclusion on the WHO criteria that for patients "who have documented or are likely to have strains resistant to medicines in the [shorter MDR-TB] regimen" [2] the new regimen should not be used [3]. As ethambutol is part of the shorter regimen, cases with reported resistance to ethambutol were considered ineligible in our analysis. It is questioned by Heldal and co-workers whether ethambutol resistance should be an exclusion criterion since the test for ethambutol resistance is unreliable, according to the WHO. In the EU/EEA, the growth-based (liquid) drug-susceptibility test (DST) methods (*e.g.* the mycobacteria growth indicator tube system) are widely used, especially in high-income countries. These methods have been found to be reliable for most of the anti-TB drugs [4]. Discrepancies amongst DST results obtained using the growth-based tests have been reported for ethambutol, in comparison with proportion methods (*e.g.* agar proportion) and *emb*B mutation analysis. Proportion methods and *emb*B mutation analysis more frequently indicate ethambutol resistance compared with growth-based methods [5]. Thus, ethambutol resistance may be underdiagnosed in the EU/EEA due to the preferred use of growth-based methods. Therefore, we believe that we were conservative in considering ethambutol-resistant MDR-TB cases ineligible. If ethambutol resistance had not been an exclusion criterion, 602 of the 1774 MDR-TB cases who only had additional resistance to ethambutol would have been eligible for the shorter MDR-TB regimen.

The authors also remark on the reliability of pyrazinamide resistance. However, information on pyrazinamide resistance is not available in our database and was therefore not considered.

We agree with Heldal and colleagues that the shorter MDR-TB regimen is also likely to be effective in extrapulmonary TB cases. However, as discussed, we followed the WHO eligibility criteria and therefore excluded extrapulmonary TB cases. It is hoped that data will soon be available to support the use of the shorter regimen in extrapulmonary MDR-TB cases.

We applaud the fact that Norway included the shorter regimens in their MDR-TB treatment options and we would welcome data from operational research in a European setting on the effectiveness of the shorter regimen in patients who are currently excluded.

Several papers have recently been published on this topic [6–11]. This is an indication of the increased interest in shorter MDR-TB treatment regimens. It is hoped that this interest will result in further studies that might provide evidence for the revised criteria, meaning more MDR-TB patients will be eligible for the shorter regimen.

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