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Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis

To the Editor:

Multidrug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are growing clinical and public health concerns, with an estimated worldwide incidence and mortality of 480 000 and 190 000 cases, respectively (2014) [1]. The World Health Organization (WHO) End TB Strategy reiterates the MDR-/XDR-TB threat and the solutions to control the epidemic [2]. Unfortunately, large proportions of patients with resistant TB do not have access to adequate diagnostics and treatment yet, while treatment success rates remain suboptimal (as demonstrated in the largest retrospective cohort of MDR-TB patients, *i.e.*, TB caused by *Mycobacterium tuberculosis* isolates resistant to at least isoniazid and rifampicin) and decrease further with resistance patterns beyond XDR-TB [3].

Presently, several of the available drugs have limited efficacy, being either toxic or unobtainable or both, and the treatment may take up to 24 months or longer. Although a few, new and repurposed drugs are fortunately available, clinicians often have difficulties in designing effective regimens [4], due to lack of drugs and rapid diagnostics, susceptibility results, comorbidities, drug toxicities and tolerability.

Recently, WHO published new recommendations aimed at speeding up TB second-line drug resistance detection (rapid molecular MTBDRsl test) and improving treatment outcomes of MDR-TB cases (shorter MDR-TB regimen) [5]. This is a demonstration of the efforts urgently being made to provide wider access to diagnosis and treatment in countries with the highest burden of MDR-TB. WHO has highlighted the advantages of the new regimen (consisting of 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol), providing a fact sheet with the necessary explanations. They include its shorter duration (9–11 months), which will improve adherence and its "relatively" low cost (<1000 US dollars per patient), which will ensure sustainability; these features are extremely important in resource-limited settings and in rich countries. It is possible that the antibiotic regimen may be modified: for example kanamycin is likely to be replaced by capreomycin or amikacin and these modifications may increase the overall cost of the regimen [6].

The regimen is recommended for MDR-TB cases not resistant to, and never treated with second-line anti-TB drugs and, therefore, should not be used if there is a documented or suspected resistance or previous use of one of the drugs composing the regimen [5]. The new push towards broader molecular testing at an earlier stage will enable patients to be selected for the shorter MDR-TB regimen more readily

and safely by reducing the window of resistance, laboratory errors and turn-around times. If resistances are present for one or more drugs in the shorter regimen then it could be argued that, possibly, these could be replaced with linezolid, delamanid or bedaquiline and still maintain a shorter treatment duration; however, there is not sufficient evidence presently available to recommend this [5].

Resistance to pyrazinamide, even if determined by reliable drug-susceptibility testing (DST) is not an absolute contraindication for the shorter MDR-TB regimen, unless there are accompanying elements indicating that one or more other agents in the regimen are also ineffective. It is not recommended to base treatment decisions on the DST for ethambutol owing to the unreliable nature of the test. There is no reliable DST available for clofazimine or prothionamide at this stage.

A question clinicians will ask is whether the shorter MDR-TB regimen is likely to work in all settings and especially outside trial conditions. However, the fundamentals of the shorter regimens are practically the same of the previous conventional 24-month regimens. They are using practically the same number of drugs, including a fluoroquinolone, a second-line injectable, and two other companion drugs. The only difference is that the fluoroquinolone should be moxifloxacin (used in many conventional 24-month MDR-TB regimens), and the replacement of cycloserine with clofazimine.

The International Carbapenems Study Group recently carried out a multi-centre, observational, retrospective, cohort study performed in centres specialised in the management of MDR-/XDR-TB cases in 11 countries, out of which eight (72.7%) were in Europe and three (27.3%) were in South America, including 348 patients in total [7–9]. Individuals aged <15 years were excluded. Only adults with a culture-confirmed diagnosis of MDR-TB were enrolled, and evaluated according to meropenem/imipenem-containing and -sparing regimens. The prevalence of resistances to the drugs included in the "shorter MDR-TB regimen" is summarised in table 1. We noted high proportional resistance to ethambutol and pyrazinamide (>60%,) prothionamide (55.4%;), fluoroquinolones (40.8%) and kanamycin (44.4%) (there were no data on clofazimine or high-dose isoniazid). In South America, we noticed higher prevalence of resistance to fluoroquinolones (86.8%) and kanamycin (67.9%), probably due to the selection of complicated cases in reference centres, with higher proportions of retreatment cases compared with the European patients.

Our results suggest that a shorter MDR-TB regimen in our cohort would have an impact on only a minority of patients and may have limited use in these settings where patients have more resistant forms of TB and are more treatment experienced (like in reference centres); only 14 (4.0%) out of 348 new and retreated patients were susceptible to all the shorter MDR-TB regimen drugs (high-dose isoniazid and clofazimine resistance is unknown as both not routinely tested).

The lack of susceptibility to the new regimen was replicated even in the new patients' subgroup in our cohort (145 patients). Our study has a number of limitations given that it is retrospective, our cohort is super selected with a large representation of resistant cases with few therapeutic options, and is by definition not representative of the European and Latin America settings.

The study supporting the WHO recommendation is solid, being based on a multi-centre study including 1200 patients. The WHO analysis provides a strong evidence-based backbone to the implementation of this innovative regimen. It will favour an improvement of patient adherence and of drug safety and tolerability profile. However, a cautious decision-making approach, based on DST, is necessary, particularly in "hot spots" for MDR-/XDR-TB (*e.g.*, former Soviet Union Countries) in new and previously treated cases. The "shorter MDR-TB regimen" will be a useful tool in the fight against MDR-/XDR-TB if properly utilised.

Critics are concerned that the programmatic management of MDR-TB with a shorter MDR-TB regimen may in turn lead to the selection of XDR-TB cases; however, at present, there is no evidence to substantiate for this, as shorter regimens have produced excellent outcomes under operational research conditions in some settings [10–12]. The opposite may be true, as the availability of a shorter MDR-TB regimen will allow for more patients to be treated and increase the chances of completing treatment, and this ultimately will reduce numbers of MDR-TB patients and the prevalence of XDR-TB patients over time. Currently the strongest risk factor for a bacteriologically unfavourable outcome with the shorter MDR-TB regimen consists of high-level fluoroquinolone resistance, particularly when compounded by initial pyrazinamide resistance [12]. If local epidemiology is known and rapid MTBDRsl testing used to ensure susceptibility for the key drugs composing the regimen, the shorter MDR-TB regimen could be very important for some patients as treatment duration is significantly reduced. To further safeguard the regimen, drug exposure may be evaluated. This will reduce the chance of development of drug resistance. Nowadays, simple tools are available which limit the use of therapeutic drug monitoring not only to the reference centre [13]. Apart from the selection of treatment based on DST it will then be up to the clinician to tailor the regimen based on the extensiveness of the disease, its location, monitoring of

TABLE 1 Proportional prevalence of anti-tuberculosis drug-resistance in the International Carbapenems Study Group cohort

Cohort	Fluoroquinolones	Clofazimine	Ethambutol	Pyrazinamide	Prothionamide	Kanamycin
International Carbapenems Study Group						
New cases[#]	30/140		90/140	81/130	60/137	19/84
	21.4% (14.6–28.2)		64.3% (56.4–72.2)	62.3% (53.9–70.6)	43.8% (35.5–52.1)	22.6% (13.7–31.5)
Previously-treated tuberculosis cases	107/195		140/197	113/169	113/176	80/140
	54.9% (47.9–61.9)		71.1% (64.8–77.4)	66.9% (59.8–74.0)	64.2% (57.1–71.3)	57.1% (48.9–65.3)
All cases	137/336		232/339	195/300	174/314	100/225
	40.8% (35.6–46.1)		68.4% (63.5–73.4)	65.0% (59.6–70.4)	55.4% (49.9–60.9)	44.4% (37.9–50.9)
Stratification by geographical region						
International Carbapenems Study Group Europe						
Previously-treated tuberculosis cases	61/142		103/142	83/124	89/141	44/87
	43.0% (34.9–51.1)		72.5% (65.2–79.8)	66.9% (58.6–75.2)	63.1% (55.1–71.1)	50.6% (40.1–61.1)
All cases	91/283		195/284	165/255	150/279	64/172
	32.2% (26.8–37.6)		68.7% (63.3–74.1)	64.7% (58.8–70.6)	53.8% (48.0–59.7)	37.2% (30.0–44.4)
International Carbapenems Study Group South America						
Previously-treated tuberculosis cases	46/53		37/55	30/45	24/35	36/53
	86.8% (77.7–95.9)		67.3% (54.9–79.7)	66.7% (52.9–80.5)	68.6% (53.2–84.0)	67.9% (55.3–80.5)
All cases	46/53		37/55	30/45	24/35	36/53
	86.8% (77.7–95.9)		67.3% (54.9–79.7)	66.7% (52.9–80.5)	68.6% (53.2–84.0)	67.9% (55.3–80.5)
Control						
International Carbapenems Study Group control group						
New cases (108/168)	15/105		61/105	53/96	35/103	7/56
	14.3% (7.6–21.0)		58.1% (48.7–67.5)	55.2% (45.3–65.1)	34.0% (24.9–43.1)	12.5% (3.8–21.2)
Previously-treated tuberculosis cases (59/168)	12/56		30/58	20/45	28/56	9/32
	21.4% (10.7–32.1)		51.7% (38.9–64.6)	44.4% (29.9–58.9)	50.0% (36.9–63.1)	28.1% (12.5–43.7)
All cases	27/161		92/164	73/141	63/159	16/88
	16.8% (11.0–22.6)		56.1% (48.5–63.7)	51.8% (43.6–60.0)	39.6% (32.0–47.2)	18.2% (10.1–26.3)

Data are presented as number of resistant cases for a specific drug/total number of cases tested for a specific drug and % proportional resistance (95% CI). [#]: Out of 145 total new cases, 144 cases were from Europe. Susceptibility to all drugs in the International Carbapenems Study Group was found only in the control group: 14 cases were susceptible to all six drugs out of 168 controls. No data were available for clofazimine.

toxicities and psychological wellbeing and compliance of the patient, taking into account what WHO recommends to keep the MDR-TB regimen "shorter" [5, 14]. The importance of cohort discussion and "consilia" for the evaluation of MDR-TB patients could be a useful decisional tool in determining the appropriateness of the shorter MDR-TB regimen and in ensuring its maximum effectiveness [15].

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Evaluation of drug resistances is needed to identify candidates for the shorter regimen in MDR-TB hot spots http://ow.ly/wZV33022VXt

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Variation in vitamin D deficiency among tuberculosis patients by ethnic group and geographical region of birth: evidence from a diverse south London population

To the Editor:

Numerous studies have demonstrated an important association of vitamin D deficiency with tuberculosis (TB) [1, 2]. Vitamin D is important for immune function and an appropriate host response to *Mycobacterium tuberculosis* [3, 4]; 25-hydroxyvitamin D (25(OH)D) is the primary circulating form of vitamin D and is used to measure deficiency.

We have previously demonstrated that, although vitamin D deficiency is common in south-east London, patients with TB have significantly lower serum 25(OH)D than healthy controls matched for age, sex, ethnicity, diet and geographical location [1], with particularly low levels found in TB patients of certain Asian and African ethnicities [2]. Trials of vitamin D supplementation during TB therapy have produced mixed results, particularly with certain vitamin D receptor (VDR) polymorphisms [5, 6].

In this study, we aimed to investigate the effect of both ethnicity and region of birth on the 25(OH)D levels of TB patients living in the UK.

Patients diagnosed with TB between January 2001 and September 2012 at two large south London hospitals were identified retrospectively from the London TB Register and in-house databases. Demographic data, country of birth, year of entry into the UK, TB site (pulmonary or extrapulmonary), treatment dates, 25(OH)D levels and HIV status were extracted.

Patients were included if they had a 25(OH)D level recorded within 6 months before, or 1 month after, starting treatment. Patients with chronic kidney disease on dialysis were excluded.

Country of birth was categorised as Africa (excluding the Horn of Africa); Horn of Africa (Eritrea, Ethiopia, Kenya, Somalia, Sudan); Americas (North and South); Asia (excluding the Indian subcontinent); Indian subcontinent (Bangladesh, India, Pakistan, Sri Lanka); Caribbean; and Europe (including the UK).

Ethnicity was reported by the patient and categories used for analysis were: white, including Irish, European and Latin American; black, including black African, black Other and black Caribbean; Indian Asian for Bangladeshi, Indian and Pakistani; Asian, including Asian, Chinese and Vietnamese; and Other. Patients with missing ethnicity data were recorded as missing.