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Availability of anti-tuberculosis drugs in Europe

To the Editors:

The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) represents a major threat to TB control globally and, specifically, in Europe [1–3]. MDR-/XDR-TB is at large due to clinical mismanagement of drug-susceptible and drug-resistant TB cases as well as to transmission of resistant strains [1–3]. Continuous availability of quality-controlled drugs is a prerequisite to ensure correct clinical management of TB patients [2, 4].

Comprehensive and updated information on the availability and registration procedures of first-line (FLD) and second-line (SLD) anti-TB drugs is not available, neither in Europe nor elsewhere. Anecdotal evidence suggested that in most European Union (EU) countries, where TB has a low incidence, procurement procedures are decentralised (not through Global Drug Facility, GDF), and with no specific responsibility for TB drug procurement available at the ministerial level. Despite high costs of SLD, registration procedures are strong enough to potentially prevent marketing and prescription of poor quality drugs. FLD and SLD are usually available (with mechanisms to prevent stock-outs), although the low number of drug doses sold can create challenges in assuring their continuous availability [5].

In EU countries with TB incidence >20 per 100,000 people, high MDR-TB prevalence and intermediate income, drug-procurement procedures are centralised (through GDF), drug

costs are lower, and FLD (but not necessarily all SLD) are available. In these countries procurement relies on the Green Light Committee mechanism (GLC, a technical body from the World Health Organization (WHO) and partners providing assistance for developing national capacity to manage SLD) and on the Global Fund (GF). To optimise the use of SLD for the treatment of MDR-/XDR-TB, several countries have introduced national ''consilia'' or groups to advise on the different aspects of MDR-/XDR-TB management, some of which also supervise the drug procurement process.

Here we present the results of a survey to describe drug-procurement practices, anti-TB drug-availability and drug costs within the EU/EEA. This study was part of a larger assessment of clinical management of MDR-/XDR-TB cases in national reference centres [6–9].

A questionnaire was developed to collect the key variables required for a comprehensive and detailed assessment of the availability of FLD and SLD in 2010; it was validated by country representatives, and discussed and finalised by the survey teams during the visits to selected reference centres [6–9]. Five MDR-TB reference centres were identified in five countries representing four different TB epidemiological settings in the EU/EEA. These were one country each from the former Soviet Union (intermediate TB incidence, high MDR-TB prevalence), one northern and one southern European country (low TB incidence, low MDR-TB prevalence), southern Europe (intermediate TB incidence, low MDR-TB prevalence) and central Europe (intermediate TB incidence, low MDR-TB prevalence).

The questionnaire included the following items: regimens used for FLD and SLD and the procedure of drug registration, number of expected FLD-treated patients and MDR-/XDR-TB patients in 2010, inventory levels of all FLD and SLD including estimated days of stock-outs for 2010, country policy on drug buffer stocks, sources of finance for FLD and SLD, procurement procedures, and capacity and procedures for enforcing optimal

TABLE 1 First- and second-line drugs available to treat susceptible and multidrug-resistant tuberculosis in five European Union Countries

Drug	Countries where utilised n/5 total	Countries where not registered	Availability		
			Rarely	Generally	Always
First-line oral agents					
Isoniazid	5	A			A–E
Rifampicin	5	A			A–E
Ethambutol	5	A			A–E
Pyrazinamide	5	A			A–E
Injectables					
Streptomycin	5			E	A–D
Amikacin	5			B, E	A, C, D
Kanamycin	3	A		E	A–C
Capreomycin	5	A		B, E	A, C, D
Fluoroquinolones					
Ciprofloxacin#	4				B–E
Ofloxacin#	5				A–E
Levofloxacin	2	B		E	C, D
Moxifloxacin	5			A, E	B, C, D
Gatifloxacin	1	B			C
Oral bacteriostatic					
Etionamide	3	E	C	B	D
Protionamide	4	A	C		A, B, E
Para-aminosalicylic acid	5	A	C	B, E	A, D
Cycloserine	5	A	C	E	A, B, D
Terizidone	2	E	C	B	
Thiacetazone	1	B, E	C		
Rifabutin	4		E		B, C, D
Amoxicillin/Clavulanic acid	4	B	E	A	C, D
Clarithromycin	5			A	B–E
Clofazimine	3	E	C		B, D
Linezolid	4			A	B, C, D
Inmipenem/Cilastatin	1	B			C

A: former Soviet Union, intermediate tuberculosis (TB) incidence, high multidrug-resistant (MDR)-TB prevalence; B: northern Europe, low TB incidence, low MDR-TB prevalence; C: southern Europe, low TB incidence, low MDR-TB prevalence; D: southern Europe, intermediate TB incidence, low MDR-TB prevalence; E: central Europe, intermediate TB incidence, low MDR-TB prevalence. #: not recommended if later-generation fluoroquinolones are available [10].

drug use (*e.g.* guidelines). The responses were supplemented by interviews with knowledgeable individuals in selected countries (*e.g* the National TB Programme manager).

The qualitative and quantitative findings for the five reference centres (representing the overall estimated needs for the country) are described in table 1.

Single national treatment guidelines jointly addressing both drug-susceptible and drug-resistant TB were not available in any of the five countries. Four countries had guidelines for the management of drug-susceptible TB, three specifically for MDR-TB treatment and one for XDR-TB treatment. Out of four countries that monitored adherence to the existing guidelines in the public sector, two reported complete and two incomplete adherence with international guidelines (for instance, in some retreatment cases, streptomycin was stopped and replaced by ciprofloxacin). No information was available on adherence in the private sector.

The majority of drugs were available in all five countries. Surprisingly, however, numerous oral bacteriostatic drugs (including etionamide/protionamide, para-aminosalicylic acid, cycloserine, rifabutin and clofazimine) were ''rarely'' available in two countries and several drugs (including FLD) were not registered in four countries. In one country, the FLDs as well as most SLDs were not registered at all, but their use was allowed through a ''one-time annual import license'', with the requirement that the drugs were licensed in the EU, USA or Canada. Some SLD recommended by the WHO to manage MDR/XDR-TB cases (kanamycin, capreomycin, some fluoroquinolones, etionamide and cycloserine) were not registered in two of the countries [11].

The funding scheme to procure FLD and SLD was heterogeneous in the surveyed countries. One country, under the GF, reported a centralised funding scheme. The other four countries reported varied systems with central or regional government funding, or the health insurance systems covering the costs. Costs were still perceived as a barrier for the treatment of MDR/XDR-TB for linezolid- and moxifloxacin-containing regimens in two countries.

Stock-outs of drugs were reported to occur, including FLDs such as pyrazinamide in one country and all SLD in another. The causes for the inconsistent supply were recorded as a lack of drug registration and drug availability, withdrawal from the market by companies in a free economy setting and the absence of funding for purchase.

In all five countries, new cases were treated following WHO-recommended Category I regimens; in one country the intermittent regimen was used during the continuation phase of treatment [11]. In four countries, TB drugs were available based on medical prescription only, among which two countries specified having restricted drug-availability and prescription limited to TB hospitals only. One country specified that there is general agreement that rifampicin is used only for TB (with the exception of meningitis prophylaxis).

Four countries replied that their national guidelines for community acquired pneumonia recommend the use of fluoroquinolones, although two specified that they should be second-line treatment only.

One of the golden principles of anti-TB therapy is that DST-tailored regimens should not be interrupted (unless major adverse events occur), as inadequate regimens and/or treatment durations are key causes for drug-resistance development. As most EU countries do not meet the GF eligibility criteria for funding, a significant reduction of resources available for TB control is affecting SLD procurement in a number of countries. Complete and appropriate patient treatment is thus also jeopardised.

Registration of an anti-TB drug in one EU country should be recognised (at least temporarily) in all other parts of the EU. Quality-assured FLD and SLD should be easily accessible and follow clear procurement systems, regardless of the levels of MDR-/XDR-TB in that country. Emergency and non-emergency mechanisms should also be identified to allow exchange of drugs between countries in the unfortunate event of a drug stock-out or before expiring, respectively. Companies producing anti-TB drugs should notify their intention to withdraw a drug from the market to national health authorities in advance, to allow alternative solutions to be identified at an early stage (as for instance, financial incentives to prevent the interruption of production that frequently occurs due to commercially driven reasons).

National governments need to ensure adequate funding for procuring anti-TB drugs. A key step to securing optimal drug availability and use in the EU is to ensure that all countries adopt clear, regularly updated, evidence-based national treatment guidelines for both susceptible and drug-resistant TB. Furthermore, European Standards for TB prevention and control need to be implemented as part of a comprehensive international consultation process [9, 10].

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Continuous positive airway pressure delivered by oronasal mask may not be effective for obstructive sleep apnoea

To the Editors:

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for patients with moderate to severe obstructive sleep apnoea (OSA). The treatment of OSA with CPAP was first conceptualised using a nasal-only interface because the pressure delivered through the nose would be transmitted to the back of the upper airway and would push the palate anteriorly [1]. Since the first description, the CPAP industry has developed a large number of different interfaces in order to improve patient comfort and adherence to treatment. Patients with OSA frequently present nasal obstruction and oronasal interfaces may be used to deliver CPAP. Nasal and oronasal masks are often used interchangeably and the choice of CPAP delivery interface for OSA therapy remains largely based on clinical experience. However, patients with OSA on oronasal mask are less adherent to CPAP for reasons that are not completely understood [2]. One recent randomised trial [3] and a preliminary report [4] suggest that the effectiveness of CPAP for treating OSA is variable when delivered by an oronasal interface. We describe a well-documented patient in whom CPAP was not effective when an oronasal mask was used due to the posterior displacement of the tongue.

A 69-yr-old Japanese–Brazilian, body mass index 26.1 $kg \cdot m^{-2}$, presented to the outpatient sleep clinic complaining of typical symptoms suggestive of OSA, including loud snoring, witnessed apnoeas and excessive daytime sleepiness. The patient had a positive medical history of systemic hypertension and diabetes mellitus. A standard overnight polysomnography (Alice 5; Philips Respironics, Murrysville, PA, USA) confirmed severe OSA, with apnoea-hypopnoea index (AHI) 76 events per h and lowest oxygen saturation 58%. An in-laboratory manual CPAP titration study was performed with an oronasal mask because of reported oral breathing during sleep. CPAP was gradually increased up to 16 cmH_2O with no clear elimination of OSA at any single CPAP. The overall AHI during the CPAP titration with oronasal mask was 32 events per h and the lowest oxygen saturation was 78%. The patient was then scheduled for a new CPAP titration study that was initiated with a nasal mask, with elimination of OSA at CPAP of 7 cmH_2O. The mask was changed to an oronasal mask during the second half of the study. In contrast to the first half and similar to the first titration study, OSA was not abolished and obstructive hypopnoeas persisted despite a progressive raise of CPAP up to 16 cmH_2O (fig. 1). We therefore hypothesised that CPAP delivered by an oronasal interface was not effective due to posterior displacement of the tongue caused by oral pressure. The patient was submitted to a sleep endoscopy study in the early morning using an intravenous infusion of midazolam that was slowly titrated until initiation of sleep, as previous described [5]. The endoscope was inserted through a latex-sealed hole in the mask to directly visualise the upper airway. The oropharyngeal region was