resistance and thereby the spread of MDR-TB. In addition, TDM may help to reduce the time to sputum conversion as it optimises drug exposure, thereby preventing transmission to others. For these reasons, TDM will probably be cost effective.

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Wider use of TDM in complex TB cases could improve therapeutic management and prevent emergence of drug resistance http://ow.ly/CQx9j

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From the authors:

We read with interest the correspondence from A. Daskapan and colleagues commenting on our article [1] describing a complex tuberculosis (TB) outbreak in Milan, Italy, caused by extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* [2, 3].

In Rome, Italy, in July 2014, the European Respiratory Society (ERS) and the World Health Organization (WHO) developed the Global Framework for TB Elimination in countries with low TB incidence, which focused on the concept of TB elimination (defined as less than one TB case per million population) [4–7]. A recent ERS/WHO survey [7] demonstrated that several areas relevant for TB elimination are not fully

covered in Europe, so any intervention shedding light on best practices contributing to improved clinical management will help us go further in the direction of TB elimination.

The contribution by A. Daskapan and colleagues is very interesting for at least two reasons. First, it shows the way towards improved management of HIV-positive individuals affected by TB. The use of therapeutic drug monitoring (TDM) was crucial, as it demonstrated the patient's low absorption of rifampicin (the pivotal drug in the first-line anti-TB regimens used) when administered orally. Intravenous use of the same drug allowed it to reach acceptable blood concentrations and to achieve a successful treatment outcome. Reduced absorption of rifampicin is a rare but known phenomenon, and it can be easily detected (and corrected) with modern techniques, as described by A. Daskapan and colleagues.

In our patient, we checked immediately for HIV status but the result was negative. Moreover, we had an early detection of rifampicin resistance by Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and for this reason rifampicin was not included in the initial regimen. Our treatment decisions were based on the availability of results from a complete drug susceptibility test (DST). Unfortunately, even in presence of drug-related adverse events, we did not have the possibility of performing TDM in this patient's management, and dosages for drugs off-label for the patient's paediatric age were decided on the basis of the available literature or in an empirical way. However, especially considering the well-known differences in pharmacokinetics of anti-TB drugs between children and adults [8], we agree that TDM, if available, appears to be a useful tool for management of children with complicated TB.

1	Mexico City, Mexico
2, 3	Boston and Atlanta, USA
4	Santiago, Chile
5	Guadeloupe, France
6	Buenos Aires, Argentina
7	Porto, Portugal
8	London, UK
9	Barcelona, Spain
10	Le Hamma, Algeria
11	Cotonou, Benin (candidate SRL)
12	Antwerp, Belgium
13	Stockholm, Sweden
14	Riga, Latvia
15	Copenhagen, Denmark
16, 17	Borstel and Gauting, Germany
18	Prague, Czech Republic
19	Zagreb, Croatia
20, 21	Milan and Rome, Italy
22	Cairo, Egypt
23	Kampala, Uganda
24	Johannesburg, South Africa (candidate SRL)
25	Karachi, Pakistan
26	New Delhi, India (National Cente of Excellence)
27	Chennai, India
28	Seoul, Republic of Korea
29	Tokyo, Japan
30	Hong Kong, China (SAR)
31	Bangkok, Thailand
32, 33	Brisbane and Adelaide, Australia

FIGURE 1 World Health Organization tuberculosis supranational reference laboratory (SRL) network.

TB elimination can be reached by improving clinical [1] as well as public health management [9] of the existing TB cases. TDM is a technique that allows easy checking of first- and second-line drug blood concentrations, at the same time ensuring they are above the minimal inhibitory concentration but not so high as to boost adverse events that might cause the loss of the drug. It is obvious that in difficult-to-treat XDR-TB cases or other complex cases [2, 3] the loss of one or two drugs due to adverse events can determine the patients' deaths, as the minimum number of necessary active drugs can no longer be reached.

The second important contribution of the correspondence by A. Daskapan and colleagues is that it opens the way towards a public health approach to the availability of TDM services. To demonstrate its feasibility, we have summarised in figure 1 the distribution of DST supranational reference laboratories belonging to the WHO network. The aim of these laboratories is to support national reference laboratories in performing quality DST for first- and second-line drugs in all TB cases, as recommended by the new global WHO post-2015 strategy [4]. This implies the capacity to send *M. tuberculosis* strains (or clinical samples) at regular intervals from national reference laboratories to the supranational reference laboratory. Although a few decades ago this process was considered difficult to achieve, it works well nowadays, allowing the WHO and partners to provide technical assistance to countries and to collect quality prevalence data on drug resistance that informs the annual WHO global report.

A similar exercise can also be considered for TDM, taking into account that "dry drops" are easier and cheaper to send than infectious materials (TB strains), so that ordinary mail can be used at really low cost. From this perspective, relatively few laboratories, strategically located in the different continents, might perform TDM at least for the most difficult cases (*e.g.* patients with lack of clinical/microbiological response at 2 months, those presenting (or potentially presenting) adverse events to the treatment, multidrug-resistant and XDR-TB cases and/or HIV-positive individuals).

The high cost of TDM represents a significant financial burden, discouraging a public health approach towards its use (*e.g.* the total cost for testing four drugs at 2 and 6 h after observed oral doses is US$560 (C.A. Peloquin, Infectious Disease Pharmacokinetics Laboratory, University of Florida, Gainesville, FL, USA; personal communication), and this does not include the cost of collecting, processing and shipping the samples). However, the savings in the amount of drugs prescribed and in the costs related to the reduction of adverse events will be able to pay for its cost.

Considering the role that TDM can have in reducing drug dosage (and the important monetary savings that can achieved with linezolid today, or bedaquiline and delamanid in the future), we support the idea of developing further evidence not only on the clinical use of TDM but also on the possible development of a well-organised public health vision, allowing more and more patients to benefit from this test.

@ERSpublications
Evaluation of TDM in assessing appropriateness of drug dosage in complex TB cases
http://ow.ly/CUEyW

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CPAP holiday: are we there yet?

To the Editor:

We appreciated the article by Rossi *et al.* [1] entitled "Is continuous positive airway pressure necessarily an everyday therapy in patients with obstructive sleep apnoea?", as well as the corresponding editorial [2], recently published in the *European Respiratory Journal*. Indeed, there are limited data on the evolution of obstructive sleep apnoea (OSA) during continuous positive airway pressure (CPAP) therapy and whether this treatment is required on a daily basis.

Although as Rossi *et al.* [1] freely admitted, their study was not without flaws, we feel that some issues should be further addressed and discussed. The use of pulse oximetry to diagnose sleep apnoea is not recommended [3], as it may underestimate the degree of the disease, which was exactly what was being studied in this case. In addition, it is possible that the increase in the Epworth Sleepiness Scale score observed in group 2 patients independently of OSA recurrence might be explained by respiratory events and sleep arousals not diagnosed by that examination. Thus, this stands as an important limitation.

As from the 125 patients enrolled in the study, only nine (7%) patients did not have OSA recurrence after 2 weeks (in 89 patients, it recurred within 4 days and those patients were not further evaluated), we think that the overall conclusions are excessively optimistic. Additionally, we would like to inquire whether the patients who stopped CPAP treatment and did not have a return of OSA even after 2 weeks (n=9) had a greater reduction in weight since the beginning of treatment than other patients. No reference to this possible variation is made in the article and we feel this is highly relevant. Concerning the CPAP treatment, we wonder if the pressure used in those patients was significantly lower than in those in whom OSA returned.

As there are no clear recommendations in clinical practice regarding for how long CPAP should be suspended before evaluating OSA persistence in order to stop the therapy, as for example, after a significant loss of weight, we feel that this study could be of guidance. It allows us to admit that it could be prudent only to perform the sleep evaluation 2 weeks after withdrawing CPAP, as 55% of patients that did not have OSA recurrence after 4 days had more than 10 events per hour at the 2-week evaluation, and this should be highlighted.

The hypothesis of the study was based on reports of various changes in the upper airway (inflammation, oedema, trauma to tissues, *etc.*) in patients with OSA, and the assumption that CPAP reduced the palatal "clatter and bang" of untreated OSA [2]. Although the physiological processes behind it are perceptible, there is no evidence this it actually occurred in those cases; for the time being, it is only speculation.

The authors suggested that a more flexible approach to CPAP use might improve overall compliance. This is a very delicate and important point. Recent studies have showed very good adherence and compliance to CPAP treatment [4–6], while others have reported that those who have good compliance in the initial days are more likely to have long-term adherence [4, 7].

Few head-to-head trials have been performed evaluating differences in adherence to daily drugs and intermittent dosing schedules, as most comparative trials of intermittent and daily agents focused on efficacy rather than adherence [8]. Adherence seemed better with intermittently dosed agents than daily dosed agents under the same conditions [8, 9]. Nevertheless, it is widely recognised that data for oral drug