The above mentioned limitations do not allow us to reach a definitive conclusion on the role of TDM of linezolid in patients with drug-resistant tuberculosis. The need to reduce the doses of linezolid to be administered long term in patients with tuberculosis to limit the development of drug-related adverse events, and the risk that subtherapeutic exposure (as in the case of concomitant rifampicin administration) may limit the efficacy of linezolid-based antituberculous treatment, call for feasible tools to monitor the adequacy of drug exposure in clinical practice. We believe that, presently, TDM still represents the best available option to address these issues.

@ERSpublications
A study of linezolid TDM in tuberculosis is at odds with studies in Gram-positive bacterial infections http://ow.ly/WXKQY

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From the authors:

We read with great interest the comments from D. Cattaneo and co-workers on our article describing a retrospective study in multidrug-resistant tuberculosis (MDR-TB) patients receiving linezolid tailored to the individual patient using therapeutic drug monitoring as part of their regular treatment [1]. Cattaneo and co-workers correctly summarise that one of our findings was that we did not observe any significant differences between exposure to linezolid and adverse events. Indeed, this observation may be surprising with a toxic drug like linezolid, but it is not a reason to rule out therapeutic drug monitoring as a tool for optimising the treatment regimens of TB patients. The explanation for this lies in the design of our study, the characteristics of the patient population, and the specific dosing regimen used for MDR-TB patients.

First, we would like to reiterate that we performed our study in a retrospective cohort of MDR-TB patients. We included 58 patients that received linezolid and that had therapeutic drug monitoring data available, but included no controls. Patients received individualised treatment regimens, based on drug susceptibility data. Therapeutic drug monitoring was performed and linezolid dosages were subsequently

reduced while maintaining sufficient exposure, representing the standard of care at our TB centres [2]. Consequently, one must be cautious about extrapolating the findings to clinical practice or other therapeutic settings without confirmation in a prospective study.

Second, Cattaneo and co-workers state that one of the limitations of our study is that factors that are known to interfere with linezolid, *e.g.* exposure, age, body weight, renal function and/or co-medication, were not included in the statistical analysis. We agree that, possibly, factors not captured in our analysis might influence linezolid exposure. Indeed, we did not report age since the cohort in our research letter was relatively young, with a median (interquartile range) age of 30 (25.2–37.3) years. TB commonly affects young adults [3]. In our study, age was not correlated to increased linezolid exposure. Co-medication may be important, as drug–drug interactions may influence the exposure of linezolid [4]. Although the mechanism is not fully elucidated, linezolid may be a P-glycoprotein substrate [5]. We did include the use of P-glycoprotein modulators as a parameter in our analysis. An alternative hypothesis is that linezolid is, in part, metabolised by cytochrome P450 (CYP)3A4 [6]. Unfortunately, we did not collect data on concomitant CYP3A4 usage. However, it should be noted that rifampicin is not co-administered with linezolid in MDR-TB patients.

Finally, we agree with Cattaneo and co-workers that the two therapeutic settings are different and would like to highlight one important difference: the dosage of linezolid that was used. In contrast with the registered dose of linezolid, *i.e.* 600 mg twice daily for up to 28 days for Gram-positive infections, when administered for MDR-TB patients receive linezolid at much lower doses, *e.g.* 300 mg once or twice daily, for a longer period of time (*e.g.* up to 18–24 months), and these doses are reduced based on therapeutic drug monitoring. Correspondingly, the trough concentrations that were found in our study were relatively low. Patients had a mean±SD minimum serum concentration of 3.1±2.2 $mg{\cdot}L^{-1}$, well below the threshold of 7–8 $mg{\cdot}L^{-1}$ that Cattaneo *et al.* [7] and others established as a predictor for thrombocytopenia. In a meta-analysis of MDR-TB patients receiving linezolid, only 11.8% had thrombocytopenia [8]. This is in contrast with ∼50% of the cohort studied by Pea *et al.* [9], in which patients with a broad range of indications were included and linezolid was administered at a median dose of 15 $mg{\cdot}kg^{-1}$ per day, *i.e.* ∼1200 mg per day, for a median of 63 days.

In conclusion, despite the fact that our retrospective study [1] suffers from limitations, one of the strengths of our study is that it demonstrates the clinical complexity of MDR-TB patient management and the great efforts that are made to reduce toxicity and enhance tolerability of complex multidrug regimens. The way forward would be to design larger, international, multicentre, pharmacokinetic prospective studies to determine the role of therapeutic drug monitoring of linezolid in MDR-TB patients. We strongly agree with the conclusion of Cattaneo and co-workers that there is still room for therapeutic drug monitoring of linezolid in patients with MDR-TB.

@ERSpublications
A retrospective study demonstrates the clinical complexity of MDR-TB patient management: TDM of linezolid is useful http://ow.ly/Xm2EA

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Inclusion of children with airway disease for the development of spirometry reference data

To the Editor:

When establishing normative data for the development of spirometric reference equations, generally measurements have to fulfil internationally accepted criteria [1, 2] and should be derived from data taken from healthy subjects. In their recent publication Lum *et al.* [3] discussed how "healthy" children should be when selecting reference samples for spirometry. They investigated this in the context of a study designed to explore ethnic differences in the lung function of school children aged 5–11 years from London. They recommended including children with current respiratory tract infection, a history of prior asthma or minor pre-existing risk factors, such as prematurity and low birth weight in normative analysis.

In contrast, we have come to a different conclusion, and we advocate that recommendations for patient samples should be less inclusive in the development of reference data. Our group analysed data from our LUNOKID study (LUng function NOrmal values for KIDs in Germany), where we measured lung function (N=5104; aged 4–18 years) between 2007 and 2009 in three German communities under field conditions [2, 4, 5]. Spirometric reference values were developed with the same regression model used by the Global Lung Initiative (GLI) [6]. For the reference data set, the following subgroups (not overlapping) were excluded. 1) Subjects with asthma diagnosis ever (n=417); a) with no current asthma medication (n=195) and b) with current asthma medication (n=222). 2) Upper respiratory tract infection (RTI) on the day of the investigation (n=734) (without asthma). 3) lower RTI within 6 weeks prior to testing (n=180) (without asthma and without upper RTI). 4) Children who have ever been diagnosed with wheezy bronchitis ("obstructive", "asthmatic" or "spastic bronchitis") (n=629) (without asthma and either an upper or lower RTI).

From the total group, 3205 children fulfilled American Thoracic Society (ATS)/European Respiratory Society (ERS) quality criteria. Compared to healthy children, the proportion of visually acceptable manoeuvres was lower in children with upper RTIs on the day of investigation (72% and 62%, respectively; $p<0.01$), whereas it was higher in asthmatics (80%; $p<0.01$). No further statistically significant differences related to the fulfilment of quality criteria were observed.

Using all acceptable tests, mean z-scores were then calculated for the subgroups (table 1). As suggested by Hall *et al.* [7] and Thompson *et al.* [8] a difference in z-score of 0.5 was considered relevant. The mean LUNOKID based z-scores for the healthy reference children are zero by definition [4]. Children with a history of physician diagnosed asthma had relevantly lower mean z-scores for forced expiratory volume in 1 s (FEV_1)/forced volume capacity (FVC) irrespective of current treatment (−0.52 and −0.66). Furthermore, the standard deviation for this group was higher than the expectation (=1), and it was higher than in the other groups. No relevant mean differences were found for the other subgroups or for the total study population when all subgroups were included. These findings are in accordance with the observations