References

1 Sotgiu G, Centis R, Dámbrosio L, *et al.* Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
2 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; 16: 447–454.
3 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. *Eur Respir J* 2013; 42: 288–290.
4 Lee M, Lee J, Carroll MW, *et al.* Linezolid for the treatment of chronic extensively drug-resistant tuberculosis. *N Eng J Med* 2012; 367: 1508–1518.
5 Koh WJ, Kwon OJ, Gwak H, *et al.* Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother* 2009; 64: 388–391.
6 Koh WJ, Kang YR, Jeon K, *et al.* Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; 67: 1503–1507.
7 Schönfeld N, Bergmann T, Vesenbeckh S, *et al.* Minimal inhibitory concentrations of first-line drugs of multidrug-resistant tuberculosis isolates. *Lung India* 2012; 29: 309–312.
8 Schön T, Juréen P, Chryssanthou E, *et al.* Wild-type distributions of seven oral second-line drugs against *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2011; 15: 502–509.
9 Honeybourne D, Tobin C, Jevons G, *et al.* Intrapulmonary penetration of linezolid. *J Antimicrob Chemother* 2003; 51: 1431–1434.
10 MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; 51 Suppl. 2:ii17–ii25.

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From the authors:

We thank T. Weiss and colleagues who wrote an interesting correspondence citing our research letter published in a previous issue of the *European Respiratory Journal* [1]. We compared the findings of an individual data meta-analytic observational cohort of extensively drug-resistant (XDR) tuberculosis (TB) patients [2] with those of the first experimental study on linezolid in XDR-TB subjects [3]. The results of both studies on the safety of this anti-TB drug underlined the advantage of prescribing a daily dosage of linezolid at a concentration ⩽600 mg, when compared with a dosage >600 mg, once daily, in terms of a reduced proportion of adverse events [2, 3]. Interestingly, the positive tolerability response with ⩽600 mg once daily of linezolid identified in both XDR-TB cohorts, had previously been confirmed in the larger, observational cohort of patients with a TB disease caused by *Mycobacterium tuberculosis* strains that were at least resistant to both isoniazid and rifampicin (multidrug-resistant (MDR) TB) [2].

T. Weiss and his colleagues discussed the importance of a low linezolid dosage (*i.e.* ⩽600 mg once daily) in patients with MDR-TB, providing the most significant *in vitro* evidence of the above mentioned clinical, observational and experimental, data; in particular, they described the minimal inhibitory concentrations (MICs) of linezolid in a collection of MDR (n=18) and non-MDR (n=130) *M. tuberculosis* strains, evaluated retrospectively in a German reference centre. The MIC for the MDR group ranged from 0.12 $\mu g \cdot mL^{-1}$ to 0.5 $\mu g \cdot mL^{-1}$, similarly to previous findings published by Schön *et al.* [4]. The MIC pattern was almost equal to that obtained in the non-MDR group. On this basis, the authors suggested a reduction of the current recommended linezolid dosage to 300 mg once daily, to decrease the probability of occurrence of linezolid-related adverse events, as well as their severity.

The current clinical trials should carefully keep into account the safety and tolerability profile of the new anti-TB drugs or of the new anti-TB regimens, not only for ethical issues ("*Primum non nocere*" or "first, do no harm", as stated by the French clinician Auguste Francois Chomel [5]), but also for the strict association between the occurrence of adverse events (particularly the severe ones), and the low adherence to anti-TB medications [6]. Patients can interrupt their prescribed treatment with relevant clinical and public-health consequences: clinical conditions can worsen and contagiousness can persist with potential transmission of *M. tuberculosis* strains (new infections) within the community. Additionally, the partial or permanent discontinuation of an antibiotic can favour the emergence of further resistances to other anti-tuberculosis drugs (*i.e.* reduction of the combined antibiotic pressure, which favours the emergence of resistant sub-populations). Those issues are amplified in individuals infected by *M. tuberculosis* strains with complex resistance patterns (*i.e.* resistance to first-, second-, and third-line drugs). When the therapeutic options are scant, such as when XDR-TB is diagnosed, it is crucial not to "lose" any single drug that can allow for the design of an efficacious anti-TB regimen.

We looked for the available evidence on the subject, carrying out a non-systematic PubMed-based review of the most important manuscripts published in the time period from 2007 to 2014. The keywords selected were linezolid and MDR-TB, and the recruited manuscripts included a significant proportion of

TABLE 1 Clinical studies assessing the efficacy/safety of a linezolid daily dosage of 300 mg in multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) patients

First author [ref.]	Patients n	Drug resistance	Study design	Main results
Koh [7]	24	MDR/XDR-TB	Retrospective	Sputum conversion in 92%
Alffenaar [8]	8	MDR/XDR-TB	Open-label, prospective, pharmacokinetic	Effective serum concentrations after 3 days of administration
Koh [9]	51	MDR/XDR-TB	Retrospective	Treatment success in 78%, neurotoxicity in 27%
Lee [3]	16	XDR-TB	Clinical trial	Adverse events in 69%

MDR-TB patients exposed to linezolid 300 mg once daily. The aim of the study did not represent a selection criterion.

Only a few manuscripts explored the efficacy and safety of a daily linezolid dosage of 300 mg (table 1) [3, 7–9]. The four studies demonstrated (with different epidemiological designs and end-points) a similar efficacy of linezolid at the daily dosage of 300 mg or 600 mg, and a better safety profile with the lower dose of the drug.

Well-designed, prospective, studies are needed to assess the pharmacokinetic/pharmacodynamic profile of linezolid and its *ex/in vivo* efficacy at the proposed new dosage (300 mg once daily).

A more extensive understanding of linezolid pharmacokinetic parameters, accompanied by quality *in vitro* data, will shed further light on the best strategies to reduce drug exposure to sensitive target anatomical sites (*e.g.* bone marrow and peripheral nerves) in order to maintain efficacy and lower adverse events.

A recently introduced technology, known as therapeutic drug monitoring (TDM) can guide the clinician to tailor the dosage in individuals with a fast linezolid metabolism or in any clinical conditions where the daily 300 mg dosage is not sufficient. The future clinical frontier will rely on by-passing standard dosages and favouring a more individualised, metabolism-focused treatment approach [10, 11].

It is straightforward that the classical clinical trials are necessary to assess the general efficacy, safety, and tolerability of a new drug; however, to maximise the risk/benefit ratio, *i.e.* safety/efficacy, it is key to provide experimental data assessing the individual variability.

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Low linezolid dosage ⩽600 mg a day for MDR-TB patients can reduce the occurrence of linezolid-related adverse events http://ow.ly/AtTVm

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References

1 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. *Eur Respir J* 2013; 42: 288–290.
2 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
3 Lee M, Lee J, Carroll MW, *et al.* Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367: 1508–1518.
4 Schön T, Juréen P, Chryssanthou E, *et al.* Wild-type distributions of seven oral second-line drugs against *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2011; 15: 502–509.
5 Hooker W. *Physician and Patient*. New York, Baker and Scribner, 1847. p. 219.
6 Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis* 2010; 14: 382–390.
7 Koh WJ, Kwon OJ, Gwak H, *et al.* Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother* 2009; 64: 388–391.

8 Alffenaar JW, van Altena R, Harmelink IM, *et al.* Comparison of the pharmacokinetics of two dosage regimens of linezolid in multidrug-resistant and extensively drug-resistant tuberculosis patients. *Clin Pharmacokinet* 2010; 49: 559–565.
9 Koh WJ, Kang YR, Jeon K, *et al.* Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; 67: 1503–1507.
10 Srivastava S, Peloquin CA, Sotgiu G, *et al.* Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment? *Eur Respir J* 2013; 42: 1449–1453.
11 Bolhuis MS, van Altena R, van Soolingen D, *et al.* Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients. *Eur Respir J* 2013; 42: 1614–1621.

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Key role of tuberculosis services funding mechanisms in tuberculosis control and elimination

To the Editor:

We read with interest the systematic review by Tanimura *et al.* [1], looking at the existing studies focusing on costs and income loss incurred by tuberculosis (TB) patients and their families in low- or middle-income countries, and the related editorial [2]. The TB-related "catastrophic expenditures" are one of the main reasons that prevent patients completing their treatment, thus making TB control challenging. Based on the new post-2015 strategy of the World Health Organization (WHO), the authors strongly advocate for universal health coverage and social protection.

TB-related direct and indirect costs and cost-effectiveness of TB interventions are crucial, and the *European Respiratory Journal* has published several important contributions including the cost of an individual treatment (which is enormous in case of extensively drug-resistance (XDR)-TB) [3] and the corresponding costs projected for the whole of Europe [4]. Furthermore, the important study by Floyd *et al.* [5] demonstrated the cost-effectiveness of managing multidrug-resistant (MDR)-TB cases in Eastern Europe.

The WHO Regional Office for Europe developed a 5 year plan (2011–2016) to prevent and combat MDR-/XDR-TB in the WHO European region with a conservative estimated budget of US$5.2 billion. The costing scenario was based on the average cost of 3 months inpatient care for MDR-TB patients. Under this scenario, 38% of the budget would be for inpatient care. If the average length of hospital stay is 8 months as it is in many countries in the region (a figure driven by admission habits in Eastern Europe, as the duration of hospital stay in Western Europe is generally much lower), the percentage for inpatient care would be above 70% of the overall budget. Analysis of various costing scenarios showed that, with variations in inpatient care, the budget for implementation of the plan could range from US$3.7 billion to US$9.8 billion [6]. Implementation of the plan leads to average direct savings of US$7 billion.

Last but not least, a recent report on the XDR-TB outbreak in Milan [7], although not formally evaluated with economic analysis, underlined the large number of activities (which represent large costs) necessary for managing micro-epidemics in low TB incidence countries and the importance of preventing TB as far as possible.

The concepts of TB elimination (*i.e.* <1 case per million population) and the role of TB prevention are clearly embedded in the new WHO post-2015 Global Strategy [8–10]. If TB elimination is to be reached, we believe that other economic topics need to be discussed in detail. Among them, incorrectly conceptualised mechanisms of TB service funding might render the adoption of new cost-saving strategies impossible.

In a recent study [11], the authors presented the case of Armenia as an example of what happens in all countries belonging to the former Soviet Union. In these settings (relevant TB incidence and very high MDR-TB prevalence [5]), the organisation of TB services is based on a vertical and specialised system with extensive hospitalisation, which is expensive and, in absence of adequate infection control practices, favours nosocomial MDR-TB transmission. The expenditures of TB services, for example staff salaries, inpatient and ambulatory care costs, are covered by the government.