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From the authors:

We read with interest the comments by M.S. Bolhuis and co-workers on our article discussing the role of linezolid in treating multidrug-resistant (MDR) tuberculosis (TB) failures in India [1]. First, we would like to underline that our study was carried out in field conditions in a country with a high burden of MDR-TB cases and limited resources. We thank M.S. Bolhuis and co-workers for the opportunity to discuss the different perspectives of the Indian setting and those of a high-level tertiary hospital in a high-income country (India has one of the best existing TB control programmes).

M.S. Bolhuis and co-workers correctly conclude that only a randomised trial comparing linezolid *versus* a placebo, in addition to an adequate background regimen using drug susceptibility testing (DST) and therapeutic drug monitoring (TDM), would provide comprehensive results on efficacy and safety of linezolid. However, we have three main comments.

First of all, although the best way to provide high-quality data on the possible efficacy of a drug (or a combination of drugs) in TB treatment is to perform a randomised clinical trial (RCT), this is particularly complicated to organise in the treatment of patients affected by MDR-TB, and is even more complicated if they have previously been exposed to second-line anti-TB drugs (SLDs).

In fact, to date, no RCT has been developed showing the possible efficacy of any of the drugs presently used in the treatment of the MDR-TB patients [2], including fluoroquinolones and injectable antimycobacterial agents (which are presently recommended by the World Health Organization) [3].

Among the key difficulties to mention are the ethical issues related to randomisation of MDR-TB patients receiving SLDs when only a few drugs are still effective (*e.g.* in extensively drug-resistant TB cases and those failures who had been previously exposed to several cycles of treatment with different drugs) and the difficulty in attributing a specific outcome to a specific drug composing the prescribed cocktail merit a special discussion [2, 3].

Secondly, DST for linezolid has not been standardised and is difficult to perform both in low- and high-income countries, so that its clinical reliability is still largely unknown. There is still much debate over whether *in vitro* results can be extrapolated to a clinical response [4].

Thirdly, although important, performing linezolid TDM systematically in all patients receiving the drug is unrealistic in India,

although it is recommendable in high-level reference centres located in high-income countries [5].

Based on the comments above, we reinforce the reason why we used the word “could”: “Linezolid could have played a key role” [1]. We cannot be totally sure that we are correct in attributing the encouraging outcome of our patients to linezolid only.

Although we agree on the importance of implementing directly observed therapy, this was not unfortunately possible for all cases treated in our setting. An argument indirectly demonstrating that the patients belonging to our cohort received the drugs is that treatment outcomes were satisfactory. This is why we still believe that the low proportion of adverse events is not a consequence of poor compliance.

We have a last comment on price and quality of drugs. It is well known that the price of drugs is largely influenced by the market location and by many other factors, so that a lower cost in India is not necessarily associated with lower quality. Indian manufacturers producing the drug we used in our study are subject to quality controls according to the national legislation in force, including the approval of the Drug Controller General of India before marketing. Also, as discussed above, the positive outcome achieved indirectly demonstrates the drug was active.

In conclusion, although our study [1] is affected by several limitations, it represents a useful contribution to support those clinicians who are dealing with difficult-to-treat MDR-TB patients daily, those desperately needing linezolid as a third or fourth active drug, and those designing an effective regimen. We agree that more evidence on linezolid efficacy, safety and tolerability is necessary: any well-designed study shedding light on the topic will be most welcome.

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Recommendations for epidemiological studies on COPD

To the Editors:

The authors of the European Respiratory Society Task Force report on recommendations for epidemiological studies on chronic obstructive pulmonary disease (COPD) are to be commended for a thorough review leading to firm and well-founded recommendations [1]. This is an important step towards harmonising the definition of COPD and better understanding the true burden of COPD around the world. However, we would like to raise two points.

In their report (p. 1263), the authors state: “A recent report from an 11-yr follow-up study of 4,965 subjects aged ≥ 65 yrs at baseline, showed that subjects with an FEV₁/FVC ratio <0.7 but above the 5th percentile still had an increased risk of death and COPD-related hospitalisation compared with asymptomatic subjects with normal lung function” [1] (citing previous results [2]). The citation and interpretation of the findings are incorrect. First of all, MANNINO *et al.* [3] misrepresented their own findings by stating that the risk of death in that group was increased; the adjusted odds ratio (95% CI 0.96–1.3) was not significantly different from that in healthy controls [4, 5]. Secondly, the authors conceded that the “measure of COPD-related hospitalisations was too inclusive”, which likely further overestimated the odds ratio [6].

The Task Force recommends that “spirometric values should be post-bronchodilatory whenever possible” [1]. We are not aware of any other field in medicine where a diagnosis of disease is rejected because a therapeutic drug moves a finding from the abnormal to the normal range. Moreover, the normal range is invariably derived from healthy individuals who were not administered that medicine. It is well known that in healthy subjects with no risk of COPD, bronchomotor tone is relieved by short-acting bronchodilators, so that forced expiratory volume in 1 s (FEV₁) and FEV₁/forced vital capacity (FVC) may increase by up to 9%, but there are also decreases in the ratio in many individuals [7]. The recommendation to measure post-bronchodilator spirometry therefore requires the use of post-bronchodilator reference values. As bronchodilators simply move the 5th percentile for FEV₁, FVC and FEV₁/FVC upwards, at any age, the percentage of subjects below that percentile compared with pre-bronchodilator values is very similar in subjects at risk or without risk of COPD [7]. It seems, therefore, that administering bronchodilator drugs to healthy subjects for deriving post-bronchodilator reference values is an exercise in futility. There are also ethical issues, side-effects and contra-indications that

need to be taken into account before giving healthy people a bronchodilator. The emphasis on post-bronchodilator spirometry will lead doctors to gradually adopt it routinely and disregard baseline values, putting elderly subjects particularly at risk [8, 9]. It will increase the cost of lung function testing and lead to very costly new studies to establish post-bronchodilator predicted values, which will take many years to complete. Yet, we already know which subjects are at risk of early death and morbidity: those in whom pre-bronchodilator FEV₁/FVC is below the 5th percentile [10]. We therefore posit that the routine measurement of post-bronchodilator values should be discouraged.

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