Multidrug-resistant tuberculosis

The ideal number of drugs needed and treatment duration are crucial issues in the management of multidrug-resistant tuberculosis (MDR-TB). Thus, we read with interest the Article by the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017,[1] the results of which support our proposal,[2] from 2015, to classify anti-tuberculosis drugs on the basis of their toxicity, and sterilising or bactericidal activity.

The findings provide compelling evidence on the use of fluoroquinolones (levofloxacin or moxifloxacin), plus linezolid and bedaquiline as the base for the initial treatment of tuberculosis strains with rifampicin resistance or multidrug resistance.[1] However, we believe that had these drugs been used from the start, some of the findings of the meta-analysis,[1] namely the optimal number of drugs needed to treat the cases (five) and treatment duration (18–20 months), would need to be refined. Both results were obtained because most of the drugs included in the regimens that had been evaluated by the meta-analysis have no effect on treatment outcomes,[1] and many show poor or nil bactericidal and sterilising activity.[2–4] Two or three susceptible drugs, with good bactericidal and sterilising activity, is known to be enough to treat almost all cases of tuberculosis, even in individuals with MDR-TB.[5] Moreover, treatment duration could be reduced to 9–12 months if two or three sterilising drugs are included in the regimen.[2,3] Given that levofloxacin or moxifloxacin, linezolid, and bedaquiline have good bactericidal and sterilising profiles,[2,4] these three drugs, administered for 9–12 months, should theoretically be enough to cure rifampicin-resistant or MDR-TB.[6] In cases of fluoroquinolone resistance, fluoroquinolone could be replaced by clofazimine or delamanid, as both have good sterilising activity.[2,6]

We agree that clinical trials are needed to ascertain the optimal combination and treatment duration (because using only the required number of drugs would lower the toxicity and price of regimens) and to improve treatment adherence.

JAC was a member of the Green Light Committee of WHO from 2002 to 2013, coordinator of the MDR-TB Unit of the International Union against Tuberculosis and Lung Disease from 2006 to 2017, and a member of the writing committee of the WHO MDR-TB Guidelines of 2006, 2008, 2011, and 2016. We declare no competing interests.

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1 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment–2017. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392:** 821–34.
2 Caminero JA, Scardigli A. Classification of anti-TB drugs: a new potential proposal based on the most recent evidence. *Eur Respir J* 2015; **46:** 887–93.
3 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999; **3** (suppl 2)**:** S231–79.
4 Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. *Lancet Infect Dis* 2010; **10:** 621–29.
5 American Thoracic Society and Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am Rev Respir Dis* 1986; **134:** 355–63.
6 Caminero JA, Piubello A, Scardigli A, Migliori GB. Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases. *Eur Respir J* 2017; **50:** 1700648.

We commend the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017[1] on their important findings but have questions about the analyses. We understand that individuals not given the drug under study were matched multiple times by propensity scoring to individuals to whom the drug was given. Did the investigators control for this multiple matching in their analyses? Some clarity on how the random effects used (described as a random intercept and random slope for matched pairs for the logistic, mixed-effects model) relates to random effect for the included studies would also be helpful.

We suggest additions to the author-identified limitations of the meta-analysis. Although the analysis controlled for the number of drugs in a regimen, it is not clear whether it also controlled for the choice of drugs, or combination of drugs, used in the regimen. Both factors could be crucial when assessing the effectiveness of individual drugs. The investigators alluded to the role that companion drugs have in a regimen, where they can have the effect of making a drug look beneficial or not, but they are not explicit on how they took this fact into consideration in the analysis.

Since the exclusion of patients on shorter regimens was justified on the basis of another ongoing meta-analysis, would the authors explicitly limit the applicability of their findings to non-short regimens for treatment of multidrug-resistant tuberculosis?

The investigators conclude by saying that many of the drugs used at present are of uncertain benefit and so their use should be reassessed. We concur with that conclusion but are concerned that the results of their analysis are in danger of being over-interpreted.

AJN is Co-Chief Investigator of the STREAM trial. B-TN, CB, and KF are Chief Investigator, Medical Monitor, and Senior Statistician respectively, of the TB-PRACTECAL trial.

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1 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392:** 821–34.

Management of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis has never been easy, mirrored by the low proportion of successfully treated patients with MRD-TB of just 55% globally. In 2018, WHO released a Rapid Communication[1] recommending the use of levofloxacin (or moxifloxacin), bedaquiline, linezolid, clofazimine and cycloserine (or terizidone) in longer MDR-TB regimens, largely on the basis of findings of the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017.[2]

Several issues, summarised in the appendix, might arise from the manner in which the meta-analysis[2] was done. The analysis focused on the efficacy of individual drugs, neglecting effectiveness of the regimen in its own right. The proportion of patients included in the individual patient data meta-analysis that showed treatment success was 61%. Thus, combining powerful toxic drugs might not ensure a high proportion of treatment success if a substantial number of patients is lost to follow-up. The use of bedaquiline in South Africa is associated with a reduction in all-cause mortality.[3] However, in patients with MDR-TB treated with bedaquiline, the interim proportion of treatment success, after at least 18 months of treatment, was only 49%.[3]

The rapid communication emphasised the need to exclude drug resistance before starting patients on treatment. Unfortunately, drug susceptibility testing of the prioritised drugs might not be available in resource-limited settings. As the combined use of fluoroquinolone and bedaquiline in patients with undetected fluoroquinolone resistance can increase the risk of acquiring resistance to bedaquiline, guidance on the use of bedaquiline in patients without drug susceptibility testing for fluoroquinolones is required.

Bedaquiline is needed for the treatment of patients with fluoroquinolone-resistant MDR-TB and of patients who cannot tolerate a fluoroquinolone. For MDR-TB without fluoroquinolone and second-line injectable drug resistance, shorter regimens for MDR-TB achieve a high proportion of treatment success[4] without including bedaquiline. Thus, bedaquiline is preserved as a salvage regimen.

The efficacy of a longer regimen, consisting of bedaquiline, fluoroquinolone, linezolid, clofazimine, and cycloserine can be high but its effectiveness remains unknown and the potential toxicity (especially QT prolongation and bone marrow suppression) cannot be neglected. If the proportion of patients with MDR-TB with treatment success in this novel approach remains considerably low, indiscriminate use of bedaquiline can potentially turn out to be disastrous. It might be wiser to encourage countries with a high burden of MDR-TB to scale up shorter regimens.

We declare no competing interests.

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1 WHO. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Geneva: World Health Organisation, 2018.

2 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392:** 821–34.

3 Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018; **6:** 699–706.

4 Aung KJM, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014; **18:** 1180–87.

5 Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9153 patients. *PLoS Med* 2012; **9:** e1001300.

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Authors' reply

We thank José A Caminero and colleagues for their Correspondence. We agree that our findings[1] leave uncertainty about optimal duration and number of drugs needed to treat patients with multidrug-resistant tuberculosis (MDR-TB). In our study,[1] the optimal number of effective drugs (based on the maximal odds of success with lowest odds of mortality) was five in the initial phase and four in the continuation phase and the total optimal duration of treatment was 19–22 months. However, this analysis included all patients treated, many of whom did not receive the three drugs found most effective in our analyses: later-generation fluoroquinolones, linezolid, and bedaquiline, which are considered core drugs in the new recommendations by WHO.[2] It is certainly plausible that if these three core drugs are used, fewer additional drugs would need to be used and for a shorter period of time to achieve such excellent treatment outcomes.[3]

We agree the strongest evidence to support recommendations for optimal treatment of MDR-TB will come from randomised trials. However, such trials involve large numbers of patients, who must be followed up for many years, rendering them slow and expensive. In addition, the individual

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See **Online** for appendix