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Should treatment of low-level mono-resistant tuberculosis be different?

Dear Editor,

We thank Decroo and Van Deun for their interest in our article describing the treatment results of 59 patients with low-level rifampicin-resistant (RR) tuberculosis (TB) in Suriname. We appreciate their concerns regarding possible induction of multidrug-resistant (MDR) and extensively resistant (XDR)-TB, if rifampicin mono-resistant TB is not treated according to the recent WHO guidelines.

In our cohort all low-level rifampicin resistant *Mycobacterium tuberculosis* isolates (n = 32) examined showed the D435Y mutation, which is characterized by a substitution of the amino acid asparagine (Asp/D) by tyrosine (Tyr/Y) in *rpoB* codon 516. Patients were mostly treated with a standard first-line TB drug regimen, due to discrepant results between the genotypic and phenotypic drug-susceptibility testing (DST); these mutations were for a long time indicated as 'disputed', due to unknown level of resistance and clinical relevance.

The authors mentioned that our reference to Williamson et al. [1], who suggested to conduct a multi-centre retrospective study to correlate the different types of *rpoB* mutations with clinical outcome and our statement that our observational study is such a study that contains the largest set of patients infected by *M. tuberculosis* strains carrying the D435Y mutation, is "misleading". Clearly, it was not our intention to "claim" that our study was a multi-centre study and indeed our study did not include a variety of *rpo*B mutations. However, our study reported on the treatment results of a large data set of patients infected by a *M. tuberculosis* strain carrying the D435Y mutation. Subsequently, our suggestions for alternative treatment options only concern patients infected by this specific strain; our results are not generalizable to the treatment of patients with other disputed mutations. Nonetheless, our observation is valid for this frequently encountered type of cases and adds important information to the questions raised by Williamson *et al.*

We also share the concerns of Decroo and Van Deun regarding the possible higher relapse rates after treatment of RR-TB patients. In our study, we did show in univariate analysis that RR-TB patients had been significantly more often treated previously and had illicit drug use, than patients with drug-sensitive TB, but the correlation was (just) not significant in multivariate analysis (aOR 2.0; CI: 1.0–4.3). We provided additional details, such as DST and treatment result in the previous treatment episode (Table 4 in our article) for the 12 RR-TB patients who were previously treated. Decroo and Van Deun also assumed that all of these patients had RR-TB in the previous episode and stated that the treatment for RR-TB with D435Y mono-resistance was clearly inadequate. This is however unknown, because the DST results of the previous episode was only available in 5 patients (1 drug-susceptible and 4 rifampicin-resistant isolates) and unknown in 7 patients (6 diagnosed before 2012; the Xpert MTB/RIF testing was only introduced in Suriname in 2012). Two of the 4 (50%) RR-TB patients with a confirmed RR-TB relapse discontinued their treatment in the first episode, which most likely caused the recurrence of the disease.

We do agree with Decroo and Van Deun that our observational study shows how rifampicin resistance, if caused by disputed mutations, can be over- and under-estimated. The Xpert MTB/RIF in fact indicates rifampicin resistance in the classical sense, with no distinction between low and high level resistance. In phenotypic DST in the MGIT strains with such disputed mutations can score either rifampicin susceptible or resistant [2]. In reversed line blot assays such isolates will yield the disappearance of wildtype bands, while resistance bands will not show up. Only if the true nature of disputed mutations is revealed, like in whole genome sequencing, they are no longer 'disputed', but invariably associated with a certain (low) level of rifampicin resistance [2]. But also in extended MIC testing with multiple concentrations the low-level rifampicin resistance will be adequately visualized. These laboratory tests to reveal the exact nature of resistance mutations are generally not present in low and middle income settings. Within the Suriname-Netherlands collaboration all rifampicin-resistant *M. tuberculosis* isolates are heat-killed and sent to the Netherlands for WGS analysis, as soon as the culture becomes positive.

We fully agree with the authors that post-treatment monitoring is necessary to measure the efficacy of treatment adequately. Therefore, systematic follow-up of RR and multidrug-resistant (MDR)-TB at 3, 6 and 12 months post-treatment has now been incorporated in the programmatic management of all RR/MDR-TB patients in Suriname.

Isoniazid and rifampicin are the two most potent drugs in the treatment for TB. The WHO shorter (9–12 months) all-oral bedaquilin-containing regimen for the treatment of RR/MDR-TB includes high dose isoniazid, irrespective of isoniazid drug-susceptibility testing [3]. Molecular testing nowadays makes it increasingly possible to rapidly diagnose or exclude isoniazid resistance and differentiate between rifampicin mono-resistant and MDR-TB. This makes it possible to critically value the use of isoniazid in (RR-)TB treatment regimens. All tested RR-TB patients in our study, except one (in 2014), had rifampicin mono-resistant TB, and thus would benefit from isoniazid, even in standard dose. As argued in our paper, it may be worthwhile also to consider the use of triple-dose rifampicin in patients with borderline rifampicin mono-resistance. The currently used dose of rifampicin, 10 mg/kg, is in fact too low in the adequate treatment of TB. Higher doses of rifampicin up to 35 mg/kg are safe and well tolerated, and achieve much higher exposure in plasma [4].

Our observational study was never set up as a clinical trial and not powered to identify significant differences in the main outcomes, but should be considered as a 'study under operational conditions' closely monitoring effects and programmatic impact on RR-TB in Suriname. We like to affirm that the latest WHO treatment recommendations have been included in the TB treatment guidelines in Suriname. All RR-TB patients are discussed in a TB concilium, and if required treatment

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will be based on bedaquilin-containing WHO-recommended regimens.

Ethical statement

Ethical approval for this study was obtained from the Human Scientific Research Ethic Committee of the Ministry of Health of Suriname. The Dutch National TB Registration Committee approved the use of the data from the Netherlands for this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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