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

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Dear editor, Gopie and colleagues speculate that triple-dose rifampicin in the World Health Organization (WHO) 6-month Category 1 regimen (Cat1) will cure rifampicin-resistant TB (RR-TB) in Suriname [1]. All RR-TB isolates tested belonged to a single clone with the “disputed” 435Tyr low-level *rpoB* mutation, susceptible to isoniazid and other drugs. Regardless of baseline rifampicin susceptibility 78% of all patients registered were treated successfully and about 1% experienced treatment failure after standard first-line (normal-dose) treatment, with in some patients little effective modifications. Although passive relapse follow-up was recognized as the main study limitation, the possible extent of its impact was overlooked.

Among 59 Surinam NTP RR-TB registrations, 20% (12/59, with 9/12 relapses) were retreatments, significantly higher than 8% (46/564, $P < 0.01$) among those with rifampicin-susceptible TB. The effectiveness of first-line treatment for RR-TB with 435Tyr mono-resistance was thus clearly inadequate. Without post-treatment monitoring, the reportedly high success rate is not a reliable measure of relapse-free cure. Indeed, repeated relapse after standard first-line treatment is typical for “disputed” low-level RR-TB [2]. RR-TB transmission uninterrupted by first-line treatment is also suggested by the Surinam RR-TB prevalence, highest of the WHO Americas region. Despite correct 435Tyr resistance diagnosis by Xpert MTB/RIF since its roll-out in 2012, the proportion with RR rose further to 12% in 2018 [1].

In our opinion, this report is an example of the under-estimated threat posed by a good number of *rpoB* mutations with disputed significance for relevant rifampicin resistance. They are often missed in phenotypic, growth-based DST (pDST). Partial inhibition by the drug on top of (strongly) reduced fitness does retard growth in presence of rifampicin to such an extent that resistance has no chance to be identified, particularly with rapid automated methods such as MGIT [3]. Also genotypic methods can miss resistance, particularly in case of heteroresistance, when both mutant and wildtype DNA are present. Due to the presence of wildtype DNA Xpert probes do not drop out but are delayed [4], whereby the resistance cut-off will rarely be reached. In our collection, heteroresistance is found more frequent for these disputed *rpoB* mutations. Disputed mutations also pose a problem for line probe assay (LPA) interpretation. On LPA all disputed show an absent or weak

wildtype band, even harder to detect with heteroresistance.

RR-TB repeatedly misdiagnosed and/or undertreated with (mainly) first-line drugs results in repeated recurrences and periods of transmission, which explains their epidemiological importance. We have reported a large series of outcomes with unmodified rifampicin-throughout WHO regimens, with about 75% failure or relapse, very similar to rates for non-disputed mutations [2]. During repeated rifampicin-based treatment resistance will at some point amplify, while compensatory mutations may restore fitness. A first Surinam strain already showed a low-level *inhA* isoniazid resistance mutation, undetectable by LPA. Outbreaks with disputed 430Pro, 445Asn, 452Pro and 491Phe have been reported. First Tugela Ferry, with 100% mortality the birth of the term “XDR”, caused by a 435Tyr MDR besides a 452Pro MDR [5]. The transmission chain showed that the 452Pro strain first attained high-level RR by acquiring a very rare 435Gly mutation, before amplifying to XDR. In Eswatini a 491Phe MDR strain, always missed by MGIT and undetectable by Xpert or LPA, became the driver of the RR-TB endemic after acquiring a compensatory *rpoC* mutation, and its clones with rv0678 bedaquiline resistance mutations are now appearing [6].

The authors claim that second-line TB treatment is not justified for isoniazid-susceptible 435Tyr-TB, based on their “largest” set of outcomes for such patients. This statement is misleading, because it concerns only one strain, atypically rifampicin mono-resistant, as shown by their own collection in the Netherlands [1], and our own. Though more than welcome, the results of their planned trial on the efficacy of triple-dose rifampicin first-line treatment may not be valid for the large majority of 435Tyr-TB. Besides, considering the 4–13 RR-TB cases detected annually in Surinam, it is questionable whether the study will be sufficiently powered to identify a difference for the main outcomes of interest: bacteriological failure, relapse and acquired resistance with additional mutations conferring resistance to rifampicin or other main drugs.

The authors encourage treatment tailored to the mutation identified and co-resistance rather than standard second-line treatment for all RR-TB. They also point out the benefit of maintaining isoniazid in the treatment regimen for the treatment of their strains, but this is a feature of for instance the shorter RR-TB regimen as well [7]. Tailored treatment

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may very well be beneficial to individual patients in some settings. However, when the necessary expertise and resources for testing are not available or accessible to the large majority of RR-TB patients, trying to make it work forcedly through referrals for state-of-the-art testing is bound to fail. Even with a standardised approach, implementation challenges are so common that a good regimen for RR-TB has to be sturdy, not only just enough. While in the original TB chemotherapy trials the effectiveness of the isoniazid/rifampicin/pyrazinamide combination could not be improved by adding ethambutol or streptomycin [8], for mass programmatic treatment one companion drug was always added to the intensive phase, together with directly supervised intake meant to protect the core drug. The first African country documented to reach 5% RR prevalence among new patients was Ivory Coast, that went for isoniazid/rifampicin/pyrazinamide without companion nor supervised intake [9].

The newly published WHO report on isoniazid and rifampicin resistance recommends standard second-line treatment for all RR-TB, irrespective of the mutation, besides halving the rifampicin critical concentration for MGIT and agar proportion, the least sensitive pDST methods [10]. The term “disputed” was abandoned.

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.

References

- [1] Gopie FA, Commiesie E, Baldi S, Kamst M, Kaur D, de Lange WCM, et al. Should treatment of low-level rifampicin mono-resistant tuberculosis be different? *J Clin Tuberculosis and Other Mycobacterial Diseases*. 2021;100222.
- [2] Van Deun A, Aung KJM, Bola V, Lebeke R, Hossain MA, Bram de Rijk W, et al. Rifampin drug resistance tests for tuberculosis: challenging the gold standard. *J Clin Microbiol*. 2013;51:2633–40.

- [3] Rigouts L, Gumusboga M, Bram de Rijk W, Nduwamahoro E, Uwizeye C, de Jong B, et al. Rifampin resistance missed in automated liquid culture systems for *Mycobacterium tuberculosis* isolates with specific *rpoB* mutations. *J Clin Microbiol*. 2013; 51:2641–5.
- [4] Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *J Clin Microbiol*. 2010;48: 2495–501.
- [5] Ioerger TR, Koo S, No EG, Chen X, Larsen MH, Jacobs Jr WR, et al. Genome analysis of multi- and extensively-drug-resistant tuberculosis from KwaZulu-Natal. *South Africa. PLoS One*. 2009;4:e7778.
- [6] Makhado NA, Matabane E, Faccin M, Pinçon C, Jouet A, Boutachkourt F, et al. Outbreak of multidrug-resistant tuberculosis in South Africa undetected by WHO-endorsed commercial tests: an observational study. *Lancet Infect Dis*. 2018;18: 1350–9.
- [7] World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. 2016 update. World Health Organization Document. 2016;WHO/HTM/TB/2016.04:1-59.
- [8] 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.
- [9] Dosso M, Bonard D, Msellati P, Bamba A, Coulibaly D, Vincent V, et al. Primary resistance to antituberculosis drugs: a national survey conducted in Côte d’Ivoire in 1995–1996. *Int J Tuberc Lung Dis*. 1999;3:805–9.
- [10] World Health Organization. Technical Report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine). 2020.

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