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Missed opportunities for detecting MDR-TB in South-Africa. Increasing epidemiological importance of a rifampicin resistance mutation undetected by commercial molecular assays

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Background: Rapid molecular assays to detect rifampicin resistance in *Mycobacterium tuberculosis* (MTB) have revolutionized the detection of resistance to this most important drug. However, up to one third of the multi-drug resistant tuberculosis (MDR-TB) cases in Swaziland harbor the Ile491Phe *rpoB* mutation (previously reported as Ile572Phe), which is unrecognized by the commercial molecular assays designed to detect *rpoB* mutations located within the 81 bp so-called rifampicin resistance determining region (RRDR). Furthermore, the resistance associated with this specific mutation has been reported as difficult to identify by phenotypic drug susceptibility tests, in particular when using the phenotypic BACTEC MGIT 960 test (Beckton Dickinson). These tests are widely used in South-Africa, where the Xpert MTB/RIF assay (Cepheid) has recently been introduced as first-line test replacing smear microscopy. Studies performed prior to the introduction of the Xpert MTB/RIF did not reveal an epidemiological importance in regard to the Ile491Phe *rpoB* mutation in South-Africa. Our aim was to evaluate if the wide-spread utilization of commercial molecular assays that miss the Ile491Phe *rpoB* mutants played a role in the selection of such mutants.

Material/methods: We selected 277 positive cultures from the Dr George Mukhari tertiary laboratory, Gauteng province in South-Africa. All these MTB strains had been reported as INH mono-resistant strains according to both the Hain MTBDR*plus* test (Hain Life science) and the BACTEC MGIT 960 phenotypic assay. We performed a MAS-PCR developed at Université catholique de Louvain that specifically targets the Ile491Phe *rpoB* mutation. All resistant and undetermined PCR results were confirmed by *rpoB* Sanger sequencing.

Results: Out of the 259 strains for which a PCR result was available (93.5% of total), 200 (77,2%) presented a wild-type result. Resistance was reported for 40 strains (15,4%) among which 35/38 (92,1%) were confirmed by Sanger. In total, 37/259 (14.3%) INH mono-resistant strains were re-classified as MDR-TB due to the presence of the Ile491Phe *rpoB* mutation.

Conclusions: We showed that a significant proportion MDR-TB cases in the Gauteng province of South-Africa are not detected by current diagnostic strategies, which rely mainly on commercial molecular assays that do not detect the Ile491Phe *rpoB* mutation. This mutation is associated with poor rifampicin based treatment outcome at similar frequency as the common *rpoB* mutations. This high frequency of the Ile491Phe mutation highlights the limits of current commercial solutions, and stresses the importance for other South-African provinces and countries to monitor the presence and the evolution of this mutation and adjust their diagnostic algorithms as needed. The frequency of this mutation among MDR-TB cases may be even higher, as it is probable that a proportion of strains harbouring the *rpoB* Ile491Phe mutation were detected as resistant by the phenotypic BACTEC MGIT 960 test, and therefore not included in this study.