We declare no competing interests.

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Authors' reply

We thank Nazir Ismail and colleagues for sharing unpublished findings from genomic data from the South Africa tuberculosis drug-resistance survey.[1] Unlike the objective of this survey, our goal was to specifically determine whether *rpoB* Ile491Phe-bearing *Mycobacterium tuberculosis* isolates obtained from patients with multidrug-resistant (MDR) tuberculosis were misclassified as isoniazid-monoresistant by standard diagnostic algorithms, in a centre receiving samples from four South African provinces.

Samples from all patients referred to the National Health Laboratory Service–Dr George Mukhari Tertiary Laboratory over the study period were cultured, irrespective of Xpert MTB/RIF results or treatment history. We screened isolates randomly selected from 1823 isoniazid-monoresistant strains among 37 644 *M tuberculosis*-positive cultures using four techniques to detect *rpoB* Ile491Phe.

Most of the Ile491Phe mutants were found to have unique individual (albeit closely related) single-nucleotide polymorphism (SNP) profiles by deep sequencing or whole-genome sequencing, excluding duplicates or laboratory contamination. Four isolates had indistinguishable genome sequences, commonly seen in transmission networks spanning several years.[2,3] These genomically identical isolates, like others separated only by a single SNP, were obtained within a 2-year period from different local clinics located within 20 km of one another. Such conjunction of spatiotemporal clustering and close genomic relatedness, with a rare compensatory mutation (*rpoC* Glu1033Ala) and other shared drug-resistance associated mutations, is strongly supportive of an outbreak.[2,3] Our results delineate the minimal outbreak extent, and we therefore suggested that further studies were warranted to assess the prevalence and spread of this mutation outside of the study population.

Although we agree with Ismail and colleagues, as well as Variava and Martinson,[4] that the association of the detected *Rv0678* mutations with bedaquiline resistance awaits formal demonstration, the observed independent emergences of different *Rv0678* mutations in groups of otherwise indistinguishable genomes are very unlikely to be due to simple genetic drift. Other *Rv0678* mutations are associated with resistance to bedaquiline or clofazimine.[5,6] Our temporal reconstruction suggests that such mutations arose around the year 2015, 2 years after the start of the bedaquiline clinical access programme, compatible with a link with bedaquiline use.

It is unfortunate that not all resistance mutations in *M tuberculosis* are picked up by rapid tests in use, and the *rpoB* Ile491Phe mutation is not the only resistance mutation missed. Moreover, such undetected mutants are not unique to South Africa.[7] Similarly to treatment regimens, diagnostic tests can drive amplification and spread of resistance. As concluded by Variava and Martinson,[4] better tests are needed to cope with the global problem of MDR tuberculosis.

PS is a consultant for Genoscreen. All other authors declare no competing interests.

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