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Detection of Drug-Resistant Tuberculosis by Xpert MTB/RIF in Swaziland

TO THE EDITOR: Tuberculosis is a major global health problem that has worsened with the increasing emergence of *Mycobacterium tuberculosis* (MTB) complex strains that are resistant to rifampin (RIF) and isoniazid. As recommended by the World Health Organization (WHO), the timely detection of drug resistance with the use of rapid molecular diagnostic tests, such as the Xpert MTB/RIF assay (Cepheid), is essential for appropriate treatment of patients with tuberculosis and for limiting the further spread of multidrug-resistant disease.^{1,2}

We used 24-loci mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) analysis and spoligotyping to perform classic genotypic analysis of MTB complex strains from the most recent (2009) national survey of tuberculosis-drug resistance in Swaziland, a country with a high prevalence of tuberculosis (945 cases per 100,000 persons, or approximately 1%).³ We found that 38 of 125 multidrug-resistant strains (30%) that were isolated during the survey carried the *rpoB* I491F mutation, which confers resistance to rifampin (Table 1; and the Supplementary Appendix, available with the full text of this letter at NEJM.org). This mutation, which was previously reported with low frequency in clinical isolates from Hong Kong and Australia,⁴ is not detected by the Xpert MTB/RIF assay.

Xpert MTB/RIF, a cartridge-based point-of-care assay, is designed to identify rifampin resistance mutations in an 81-bp region of *rpoB* (codons 426 to 452). Its inability to detect the *rpoB* I491F outbreak strain raises new challenges, since Xpert MTB/RIF is used throughout most of Swaziland as the first-line diagnostic test for tuberculosis and for multidrug-resistant tuberculosis, as recommended by the WHO.⁵ Thus, the circulation of strains with the *rpoB* I491F

mutation substantially reduces the sensitivity of Xpert MTB/RIF-based diagnosis in Swaziland and presumably results in underdiagnosis and potentially inadequate treatment. This is problematic in a country where an estimated 26% of adults are infected with the human immunodeficiency virus (HIV) and 80% of patients with tuberculosis are coinfecting with HIV. In addition, coinfecting patients are more likely than

Table 1. Mutations in *rpoB* in 125 Multidrug-Resistant Strains from the 2009 Survey Regarding Tuberculosis-Drug Resistance in Swaziland.*

| Mutation | Strains with Mutation no. (%) | Mutation in <i>rpoB</i> Hot-Spot Region† |
|---------------|----------------------------------|--|
| D435F | 1 (0.8) | Yes |
| D435F, N437D | 3 (2.4) | D435F, yes; N437D, yes |
| D435V | 1 (0.8) | Yes |
| G442R,‡ I491F | 1 (0.8) | G442R, yes; I491F, no |
| H445D | 7 (5.6) | Yes |
| H445L | 6 (4.8) | Yes |
| H445Y | 6 (4.8) | Yes |
| I491F, R552C | 1 (0.8) | I491F, no; R552C, no |
| I491F | 38 (30.4) | No |
| QF432-433del | 1 (0.8) | Yes |
| S450L | 58 (46.4) | Yes |
| S450W | 1 (0.8) | Yes |
| Unmutated | 1 (0.8) | No |

* Mutations are listed according to numbering for the *Mycobacterium tuberculosis* H37Rv genome. Some strains carry two mutations.

† The hot-spot region of *rpoB* ranges from codon 426 to codon 452.

‡ This is a heterozygous single-nucleotide polymorphism.

HIV-negative patients to have multidrug-resistant infection.³ Further transmission of the *rpoB* I491F strain in this population is another likely consequence.

On the basis of these findings, Xpert MTB/RIF testing may be unreliable in Swaziland, since it can miss a substantial percentage of strains that may be resistant to rifampin. More studies are needed to assess the prevalence of similar mutations in neighboring countries.

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CORRECTIONS

Sensor Technology in Assessments of Clinical Skill (February 19, 2015;372:784-6). In the full author list published with the letter at NEJM.org, Dr. Pugh should have been listed as the final author, rather than as the third author. The letter is correct at NEJM.org.

Continuing Medical Education: D Is for Delay (December 4, 2014;371:2244). There was a mismatch between Question 1 of the CME examination and the published article. Question 1 has been replaced, and the examination is correct at NEJM.org.

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