2. Chambaere K, Bilsen J, Cohen J, Onwuteaka-Philipsen BD, Mortier F, Deliens L. Trends in medical end-of-life decision making in Flanders, Belgium 1998-2001-2007. Med Decis Making 2011;31:500-10.
3. Belgian Official Collection of the Laws. The Belgian Act on Euthanasia of May 28th 2002. Ethical Perspect 2002;9:182-8.
4. Onwuteaka-Philipsen BD, Brinkman-Stoppelenburg A, Penning C, de Jong-Krul GJ, van Delden JJ, van der Heide A. Trends in end-of-life practices before and after the enactment of the euthanasia law in the Netherlands from 1990 to 2010: a repeated cross-sectional survey. Lancet 2012;380:908-15.

DOI: 10.1056/NEJMc1414527

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 coinfected with HIV. In addition, coinfected 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	Mutation in *rpoB* Hot-Spot Region†
	no. (%)	
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.

Elisabeth Sanchez-Padilla, M.D., M.P.H.

Epicentre
Paris, France

Matthias Merker, D.Sc., Sc.D.
Patrick Beckert, M.Sc.

Research Center Borstel
Borstel, Germany

Frauke Jochims, M.Sc.

Médecins sans Frontières
Geneva, Switzerland

Themba Dlamini, M.D.

National Tuberculosis Control Program
Mbabane, Swaziland

Patricia Kahn, Ph.D.

Médecins sans Frontières
New York, NY

Maryline Bonnet, M.D., Ph.D.

Epicentre
Paris, France

Stefan Niemann, D.Sc., Sc.D.

Research Center Borstel
Borstel, Germany
sniemann@fz-borstel.de

Drs. Sanchez-Padilla and Merker and Mr. Beckert contributed equally to this letter.

Supported in part by the European Union TB-PAN-NET (FP7-223681) project, the German Center for Infection Research, and Médecins sans Frontières–Switzerland.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010;363:1005-15.
2. Monitoring of Xpert MTB/RIF roll-out, Swaziland. Geneva: World Health Organization, 2013 (http://www.stoptb.org/wg/gli/assets/documents/map/2/Pdf_files/SWZ.pdf).
3. Sanchez-Padilla E, Dlamini T, Ascorra A, et al. High prevalence of multidrug-resistant tuberculosis, Swaziland, 2009-2010. Emerg Infect Dis 2012;18:29-37.
4. Siu GKH, Zhang Y, Lau TCK, et al. Mutations outside the rifampicin resistance-determining region associated with rifampicin resistance in Mycobacterium tuberculosis. J Antimicrob Chemother 2011;66:730-3.
5. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Geneva: World Health Organization, 2011.

DOI: 10.1056/NEJMc1413930

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
- Letters not related to a *Journal* article must not exceed 400 words.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of *Journal* articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.
- All letters must be submitted at authors.NEJM.org.

Letters that do not adhere to these instructions will not be considered. We will notify you when we have made a decision about possible publication. Letters regarding a recent *Journal* article may be shared with the authors of that article. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.

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.

THE *JOURNAL*'S WEB AND E-MAIL ADDRESSES

To submit a letter to the Editor: authors.NEJM.org

For information about the status of a submitted manuscript: authors.NEJM.org

To submit a meeting notice: meetingnotices@NEJM.org

The *Journal*'s web pages: NEJM.org