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Letter

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Response to: Comments on the sensitivity and specificity of a new molecular test for *Mycobacterium tuberculosis* and resistence to Rifampin

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Linked Article

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Dear Editor,

We appreciate the interest of Dr. Hatemi in the performance of Xpert MTB/RIF (Xpert) to detect pulmonary TB as published in the NEJM.[1,2] Their question related to differentiation between MTB and non-tuberculous mycobacteria (NTM) is clearly important and was addressed in a separate publication by Helb et al.[3] In that study, Xpert remained negative when challenged with 20 NTM strains at concentrations of 106 cfu/ml. Moreover, mixing NTMs at 105 cfu/ml with 200 cfu of MTB did not interfere with the detection of either *M. tuberculosis* or rifampin resistance.[4] Conversely, NTM growth may frequently confound culture. In our report, 3/23 patients excluded for NTM-positive cultures were Xpert-positive. Two were confirmed to have mixed NTM+MTB cultures. The single patient who was culture-positive for NTM only was Xpert positive in all 3 sputum samples, and PCR curves showed typical wild-type configuration. This patient likely had TB, with cultures overgrown by a fast-growing NTM. Xpert may thus be helpful in diagnosing TB despite NTM colonization that would have otherwise confounded culture. The high specificity reported also by other groups[5,6] is not surprising: Xpert targets a TB-specific sequence, and analytic studies have not shown cross-reactivity against 89 other pathogens or respiratory commensals.[7] Though hemi-nested, the Xpert reaction is carried out in a closed cartridge, and there have thus far been no reports of amplicon contamination.

We concur that Xpert may detect culture-negative patients treated for pulmonary TB on clinical grounds. As reported, of 105 patients with culture-negative samples who were treated for tuberculosis on the basis of clinical symptoms in this study, 29.3% had positive results on the MTB/RIF test. However, we did not assess the treatment outcomes for these patients and a different study design will be required to quantify Xpert accuracy in these patients. In general, clinical management is a poor benchmark against which to determine diagnostic accuracy. Fever in the tropics, for example, is frequently managed as malaria even when no parisitologic or molecular evidence of malaria can be found.

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Xpert sensitivity in our study was compared to a rigorous reference standard composed of 3 smear microscopy examinations (1 direct, 2 on resuspended pellets), 2 liquid and 2 solid cultures. The sensitivity of a single, direct Xpert in this study was equivalent to a single solid culture. Even in research settings, the average sensitivity of sputum microscopy for culture-positive pulmonary TB is under 60% in immunocompetent populations,[8-15] and substantially lower among people infected with HIV.[10,16-19]

The sensitivity analysis is also problematic. Patients who were smear and culture negative, but were treated for tuberculosis because of clinical and radiological findings were called the "clinical tuberculosis" group by the authors. However these patients were excluded from the tuberculosis group when sensitivity was calculated. Especially those patients who are clinically diagnosed with tuberculosis and respond well to anti-tuberculosis treatment, but are smear and culture-negative, are an important group to study the performance of the proposed test. A diagnostic test would prove to be valuable if it was shown that it diagnoses such cases better than the routine methods. Otherwise acid smear microscopy is cheaper and widely available, and the percentage of tuberculosis patients that are smear-negative and MTB/RIF-positive, even after performing the latter three times, is not impressively high (20.7%).

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