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Reply to "Performance of the Xpert MTB/RIF Assay on Nonrespiratory Specimens and Accuracy of This Assay for Detection of Rifampin Resistance in a Low-Prevalence Setting"

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In our recently published paper "Integrating the Xpert MTB/RIF Assay into a Diagnostic Workflow for Rapid Detection of *Mycobacterium tuberculosis* in a Low-Prevalence Area" (1), we express our concerns on the accurate reporting of RIF results by the Xpert MTB/RIF assay and its limited use for nonrespiratory samples. With interest, we read the comments of Blaich and Frei (2) on our paper, in which they report on (i) the accurate Xpert assay RIF results for 65 clinical specimens that became MTB culture positive and 29 MTB cultures and (ii) the detection of MTB in 17 out of 18 MTB culture-positive nonrespiratory clinical specimens which were submitted to their laboratory.

In future, we will continue to be cautious about reporting Xpert RIF results for the following reasons: (i) we have repeatedly (also more recently) detected false-negative and false-positive Xpert RIF results, which were confirmed by DNA sequencing of the *rpoB* gene directly from the clinical samples and their corresponding cultures (3, 4), and (ii) the reporting of RIF results by the Xpert system relies solely on the decreased occurrence (or absence) of wild-type probe hybridization. It is important to note that our recommendation to confirm Xpert RIF resistance results by DNA sequencing before reporting is also supported by a clear statement in the October 2013 CDC weekly newsletter on Xpert RIF results, which is as follows: "Because the prevalence of RMP resistance is low in the United States (about 1.8% of TB cases), a positive result indicating a mutation in the *rpoB* gene of MTBC should be confirmed by rapid DNA sequencing for prompt reassessment of the treatment regimen and followed by growth-based drug susceptibility testing (DST)" (5).

While the Xpert MTB/RIF system is established for respiratory samples, standard specimen preparation protocols for its use on nonrespiratory specimens are not available. Furthermore, nonrespiratory samples are characterized in groups because of their large diversity; they include urine, biopsy specimens, cerebrospinal fluid (CSF), etc. (6). In general, the sensitivity of detection of MTB in nonrespiratory samples by molecular methods is lower than with respiratory samples, mainly because assays and extraction methods are designed primarily for analysis of respiratory samples. The diversity of the nonrespiratory-specimen groups is an important reason for observing different sensitivities in comparative studies, and users should be aware of the limitations of analysis of nonrespiratory samples. Therefore, guidelines for the processing of nonrespiratory samples are needed. Unfortunately, the method of preparation of their nonrespiratory specimens is not described in the letter of Blaich and Frei.

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