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Cost-Effectiveness of Different Strategies for Amplified *Mycobacterium tuberculosis* Direct Testing for Cases of Pulmonary Tuberculosis[▽]

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We conducted a decision analysis to assess and compare four algorithms for amplified *Mycobacterium tuberculosis* direct (MTD) testing of respiratory specimens in terms of cost-effectiveness. The most cost-effective strategy was one in which smear-positive specimens but not smear-negative specimens were diluted prior to MTD testing.

The amplified *Mycobacterium tuberculosis* direct (MTD) test (Gen-Probe Inc., San Diego, CA) can be a useful tool for diagnosis of pulmonary tuberculosis (PTB) (2, 6, 7, 9). However, its sensitivity can be impaired by amplification-inhibitory substances present either in specimens or in specimen decontamination reagents (1, 3, 5, 11, 13). Specimen dilution can reduce the impact of amplification inhibition on MTD sensitivity (8, 11, 12), but to our knowledge there is no published information about the cost-effectiveness (CE) of specimen dilution strategies.

To improve sensitivity and maintain the short turnaround time and clinical utility of the MTD assay, in April 2004, the TB laboratory of the Maryland Department of Health and Mental Hygiene (DHMH) initiated a strategy in which two MTD tests were performed simultaneously for each respiratory specimen: one test used an undiluted aliquot of the processed specimen (conventional method), and the other test used a 1:10 dilution of the processed specimen (dilution method). The diluted specimen was prepared by adding 450 μl of sterile distilled water to 50 μl of the processed specimen (12). We recently performed a retrospective review of MTD data from the Maryland DHMH Laboratory (7, 8). A total of 491 respiratory specimens from 491 individuals were tested using both the conventional and dilution methods, and mycobacterial culture results were used as the gold standard for PTB diagnosis. For smear-positive specimens, the dilution strategy improved MTD sensitivity from 83.2% (conventional method) to 99.1% (dilution method). However, dilution had no impact on MTD sensitivity for smear-negative specimens (8). We reasoned that the simultaneous performance of tests using the conventional and dilution methods may not be the most cost-effective strategy. The objective of the current study was to compare different specimen dilution algorithms for MTD testing in terms of CE during the evaluation of PTB suspects.

A decision tree model of different algorithms for MTD testing was developed. Four possible MTD testing strategies were constructed. (i) For the "CDC strategy," the conventional method was performed regardless of specimen smear result, and smear-positive/MTD test-negative specimens were retested using an internal amplification positive control to assess for the presence of inhibitors (3). (ii) For the "simultaneous testing strategy," both conventional and dilution methods were performed simultaneously for each specimen. (iii) For the "smear-positive dilution strategy," the dilution method was used for smear-positive specimens, and the conventional method was used for smear-negative specimens. (iv) For the "sequential dilution strategy," the conventional method was first performed on all specimens, and specimens yielding negative or equivocal MTD results were subsequently retested using the dilution method.

CE was measured in terms of cost per correct PTB diagnosis, using as the gold standard the final culture result (*M. tuberculosis* complex versus not of the *M. tuberculosis* complex) and the laboratory perspective. For each branch of the analysis tree, probability variables were obtained from our previous study (8). For equivocal MTD results, the probability of correct diagnosis was considered as zero. The total cost associated with MTD testing, including the performance of controls, was estimated for the study period at our laboratory. MTD detection reagents were sold in kits of 50 tests at a cost of $1,020/kit, and a median of 32.5 tests per week were used. The cost of general laboratory supplies used for MTD testing (e.g., gloves, pipette tips, and tubes, etc.) was estimated at $19.53/week. MTD testing required an average technician time of 12 h/week with a wage of $22.82/h. The cost per respiratory specimen tested was obtained by dividing the total cost by the number of MTD tests during the study period. Therefore, the cost per MTD test performed was $47.37. Sensitivity analysis was

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performed to identify the thresholds at which changes in input parameters affected the ranking of the MTD testing strategies assessed in the base case analysis. Decision tree construction and CE and sensitivity analyses were performed using TreeAge Pro Healthcare module 2007 (TreeAge Software Inc., Williamstown, MA).

During the 2-year study period, the total costs and the final probabilities of correct diagnosis by the MTD test were $27,759 and 0.91 for the CDC strategy, $46,518 and 0.96 for the simultaneous testing strategy, $23,259 and 0.94 for the smear-positive dilution strategy, and $41,070 and 0.96 for the sequential dilution strategy. In the base case, the CE analysis demonstrated expected costs per PTB suspect with a correct diagnosis as follows: $68.29 for the CDC strategy, $102.69 for the simultaneous testing strategy, $53.40 for the smear-positive dilution strategy, and $90.96 for the sequential dilution strategy.

Since the two lowest-cost strategies (the CDC strategy and the smear-positive dilution strategy) differed in the approach to MTD testing of smear-positive specimens, we performed a sensitivity analysis for the following parameters: proportion of tested specimens that were smear positive, proportion of smear-positive specimens that were culture positive for *M. tuberculosis*, and MTD sensitivities of conventional and dilution methods for smear-positive specimens. The smear-positive dilution strategy remained more cost-effective than the CDC strategy when the proportion of smear-positive specimens decreased to values as low as 0.10 ($55.94 versus $68.17, respectively), and when TB prevalence among smear-positive specimens decreased to values as low as 0.10 ($53.36 versus $64.09, respectively). Below a dilution MTD sensitivity threshold of 0.63 and above a conventional MTD sensitivity threshold of 0.96, the CDC strategy became more cost-effective than the smear-positive dilution strategy, although the difference in CE between the strategies was minimal (for example, $62.92 versus $65.46, respectively, when the conventional MTD sensitivity was 1.00 and the dilution MTD sensitivity was 0.60). However, the latter would be an unusual scenario, since to our knowledge studies comparing conventional and dilution MTD testing methods have shown an increased sensitivity for the dilution method among smear-positive respiratory specimens (8, 10, 12).

Using a single respiratory specimen, the smear-positive dilution strategy correctly diagnosed 99.1% (115/116) of smear-positive PTB patients, while the CDC strategy correctly diagnosed only 83.6% (97/116). Therefore, 18 smear-positive PTB patients correctly diagnosed by the smear-positive dilution strategy would need an additional specimen collected and tested when using the CDC strategy, since initial MTD testing was nondiagnostic for these patients by the CDC strategy.

Our study has important limitations. First, it was retrospective and based on test performance and costs from our laboratory. Since test performance could differ in other settings, we used sensitivity analysis to explore the impact of changes in input parameters on CE. Second, our observed conventional MTD sensitivity was slightly lower than that described in some other studies, and this could have contributed to an underestimation of the CE of the CDC strategy. However, to adjudicate discordant results between MTD testing and mycobacterial culture, several studies showing very high conventional MTD sensitivity used discrepant analysis (1, 4, 5, 13), a process which could have lead to an overestimation of MTD performance. We did not use discrepant analysis in our study. Finally, we did not estimate costs associated with delayed or missed TB diagnosis.

We conclude that, in our laboratory, an MTD testing strategy that incorporates the dilution of smear-positive but not smear-negative respiratory specimens is more cost-effective than the described alternative strategies. Our results may help guide the development of optimal MTD testing algorithms.

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