Reviewer’s report

Title: Spot sputum samples are at least as good as early morning samples for identifying Mycobacterium tuberculosis

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Reviewer: J. Lucian Davis

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Summary

Murphy et al present the findings of a secondary analysis of the ReMoxTB trial designed to answer the question, "Are early morning sputum samples superior to spot samples for TB diagnosis and monitoring for adverse outcomes of treatment?" (ReMoxTB was a large, multi-country study which evaluated the efficacy of moxifloxacin-based regimens for shortening of treatment duration for active tuberculosis). Comparing the results of smear microscopy, solid culture, and liquid culture for 1115 paired baseline and 2995 paired follow-up sputa from 1931 patients, the authors show that either timing of sputum collection - spot or early morning - identifies similar proportions of TB patients. For some key outcomes, such as time-to-positivity in solid culture as well as in liquid culture, spot specimens are superior for TB diagnosis. For treatment monitoring and prediction of adverse treatment outcomes, the two specimen types performed similarly.

These findings provide important information for global TB control policy because a large amount evidence shows that requiring an additional clinic visit for submission of an early morning sputum specimen is associated with high rates of loss to follow-up from the diagnostic process, especially in routine clinical settings. For patients who do return to clinic to provide early morning sputum, the extra visits are associated with substantial financial harm for poor patients, who make up the majority of those undergoing TB evaluation in high-burden countries. These findings challenge nearly 60 years of dogma that early morning specimens are superior to spot specimens. As the authors note, these data also provide support for a widely overlooked 2011 WHO policy recommending that same-day collection of sputum specimens be allowed as an alternative to two-day sputum collection strategies. Because WHO's 2015 End TB Strategy calls for patient-centered strategies for control and elimination of TB as one of its three main pillars - as well as an end to catastrophic costs of TB evaluation and treatment - this manuscript provides important information to advance that goal.

Main criticisms and concerns

Methods

Reporting should follow the STARD guidelines and checklist (Ann Intern Med. 2003;138:40-44.)
Please provide a definition for MGIT false positive results. Is this when MGIT machines report liquid cultures positive, but the speciation algorithm excludes Mtb?

Please state the definition of unfavourable TB treatment outcomes.

Results

Please present information in the text or a flow diagram to show how patients / samples were selected / excluded for the sub-study.

Are you able to present characteristics of sputum, e.g. distribution of sputum quality and volume? Did these characteristics differ between spot and early morning specimens?

For follow-up specimens, was there any difference between spot and early morning specimens in the proportion successfully collected?

While I understand that all patients received instruction on how to produce a good quality sputum, I would suppose that collection of most if not all spot specimens is supervised, while most if not all collection of early morning specimens is unsupervised. Do these results suggest to you a possible beneficial effect of supervision on the quality of sputum collection (for baseline and/or follow-up specimens). Could this explain some of the difference between your findings and those of previous studies, which I believe came primarily from operational settings, where supervision of specimens is less common?

Please report the number of patients in this sample with an adverse outcome.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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None

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