Diagnostic test of rifampicin resistance in mycobacterium tuberculosis: a meta-analysis

Ma B, Qi GQ, Li HM, Zhu BD, Yang KH

CRD summary
This review concluded that the MB/BacT and BACTEC MGIT 960 liquid media-based tests were highly sensitive and specific for the rapid detection of rifampicin-resistant tuberculosis. The authors recommended that these tests should replace the BACTEC 460 test. These conclusions appear too strong for the limited data available and should be viewed with caution.

Authors' objectives
To assess the diagnostic accuracy of radioactivity-free cultivation and detection technologies for rapid detection of rifampicin resistant Mycobacterium tuberculosis (tuberculosis).

Searching
PubMed, EMBASE, BIOSIS Previews and Web of Science were searched from 1990 to 2010 and the Chinese Biomedical Literature Database was searched from 1978 to 2010. Search terms were reported and included methodological terms for test accuracy studies. Google Scholar was searched, experts were contacted, and bibliographies of retrieved articles were screened to identify additional studies.

Study selection
Studies that assessed the diagnostic accuracy of specified liquid media-based test kits for the detection of rifampicin-resistant tuberculosis were eligible for inclusion. Liquid media-based test kits had to be BACTEC MGIT 960, BACTEC 9000MB, MB/BacT, Manual MGIT, Difco ESP, or MB-Redox. Included studies were required to use an appropriate reference standard (such proportion method, radiometric BACTEC 460 method, or conventional susceptibility test) to confirm diagnosis and to report sufficient data to construct a 2x2 contingency table.

Most of the included studies were conducted in Europe; the rest were conducted in China. Most studies reported using the BACTEC 460 System as the reference standard; one study used Lowenstein-Jenson. Included studies assessed the MB/BacT, BACTEC MGIT 960 and Manual MGIT. No further details were provided.

Two reviewers independently assessed the titles and abstracts for potential relevance. Any disagreements were resolved by discussion. The authors did not specify how full papers were screened for inclusion.

Assessment of study quality
Two reviewers independently assessed the methodological quality of included studies using the 14-item QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool.

Data extraction
Two reviewers independently extracted the numbers of true positive, false negative, false positive and true negative results for each test and study. Estimates of sensitivity and specificity were calculated. Discrepancies were resolved by discussion.

Methods of synthesis
Pooled estimates of sensitivity and specificity, and positive and negative likelihood ratios, with 95% confidence intervals (CIs), were calculated for each test, using a random-effects model. A summary receiver operating characteristic (SROC) curve was constructed for the BACTEC MGIT 960 test, using the Moses-Littenberg model. The area under the curve (AUC) and Q* index were calculated.

Results of the review
Six studies (584 patients, range 36 to 156) were included in the review. The results of methodological quality assessment were not reported, although the authors noted that none of the included studies reported blinding of the
investigators.

No studies on the BACTEC 9000MB system or the Difco ESP tests met the inclusion criteria.

**MB/BacT test** (two studies, 202 patients): For the detection of rifampicin-resistant tuberculosis, the pooled estimate of sensitivity was 100% (95% CI 81 to 100) and the pooled estimate of specificity was 99% (95% CI 97 to 100). The pooled positive likelihood ratio was 65.12 (95% CI 16.42 to 258.19) and the pooled negative likelihood ratio was 0.06 (95% CI 0.01 to 0.4).

**BACTEC MGIT 960 test** (five studies, 464 patients): The pooled estimate of sensitivity was 100% (95% CI 96 to 100) and the pooled estimate of specificity was 96% (95% CI 93 to 98). The pooled positive likelihood ratio was 29.84 (95% CI 5.24 to 169.87) and the pooled negative likelihood ratio was 0.03 (95% CI 0.01 to 0.11). The summary receiver operating characteristic curve gave an area under the curve of 0.9943 and a Q* of 0.9704.

**Manual MGIT test** (one study, 36 patients): The reported sensitivity was 100% (95% CI 84 to 100) and the specificity was 96% (95% CI 87.3 to 98). The positive likelihood ratio was 51.55 (95% CI 3.30 to 805.55) and the negative likelihood ratio was 0.05 (95% CI 0.00 to 0.70).

**Authors’ conclusions**
Both the MB/BacT and BACTEC MGIT 960 tests had high sensitivity and specificity for the detection of rifampicin-resistant tuberculosis.

**CRD commentary**
The review addressed a clearly stated objective and defined appropriate inclusion criteria. A number of sources were searched for relevant studies, but the use of search terms for test accuracy studies (which have been shown to reduce search sensitivity) may have resulted in some studies being missed. Measures were taken throughout the review process to minimise error and/or bias, although it was unclear whether these measures were applied throughout the study selection process (the process of screening full papers for inclusion was not described).

The methodological quality of included studies was assessed, but results were not reported and insufficient study details were reported, so it was not possible to assess the reliability of individual study results. The generation of pooled estimates (sensitivity, specificity, etc) using a random-effects model was of questionable value given the considerable heterogeneity present in some data sets. The use of bivariate or hierarchical summary receiver operating characteristic models have been generally recommended over the Moses and Littenberg model and may have been more appropriate in this case. The inclusion in the same summary receiver operating characteristic analysis of studies using two different reference standards was of questionable validity; the only study which did not use the BACTEC 460 test appeared to be an outlier.

The authors’ conclusions appear too strong for the limited data available and should be viewed with caution.

**Implications of the review for practice and research**
**Practice**: The authors recommended that the BACTEC 460 system should be replaced by MB/BacT or BACTEC MGIT 960 as the final diagnostic test for rifampicin-resistant tuberculosis.

**Research**: The authors stated that more studies are needed on the diagnostic accuracy of other radioactivity-free cultivation and detection technologies to determine their sensitivity and specificity for rifampicin-resistant tuberculosis.

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