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Title An assessment of Nucleic Acid Amplification Testing for Active Mycobacterial Infection

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Aim

To conduct a systematic review on nucleic acid amplification testing (NAAT) for the diagnosis of (1) *Mycobacterium tuberculosis* (MTB) infections in persons with clinical signs and symptoms of tuberculosis (TB), or (2) non-tuberculous mycobacteria (NTM) infections in patients suspected of having an NTM infection.

Conclusions and results

NAAT for the diagnosis of MTB infections

NAAT would be a useful addition to acid fast bacilli (AFB) microscopy and culture in the diagnosis of both pulmonary and extrapulmonary TB. Patients with a positive AFB test result or a positive NAAT are most likely to have culture-positive TB, and it becomes almost certain if both tests are positive. No useful information can be obtained directly from a negative AFB result and a negative NAAT result should be interpreted with reference to the AFB result—a negative NAAT result in a patient who was AFB-positive almost completely eliminates the likelihood of being MTB culture-positive (patients most likely have an NTM infection). Conversely, a negative NAAT result in a patient who was AFB-negative does not eliminate the possibility of having culture-positive disease.

Comparison of AFB, NAAT, and AFB plus NAAT using culture as the reference standard showed that AFB plus NAAT has the highest false-positive rate, at 12%, with NAAT alone at 6% and AFB alone at 2%. A false-positive result means that a patient will receive treatment for a short time (until clinical unresponsiveness is noted or culture results are available) for a disease they do not have. However, as culture is an imperfect reference standard, a large proportion of these false-positive patients may actually have clinical disease. AFB microscopy alone has the highest false-negative rate, at 38%, with NAAT alone and AFB plus NAAT being much lower at 11% and 6%, respectively. The consequences of a false-negative result are much more severe, as the patient may remain untreated for a longer time period and could potentially spread the disease to more individuals in the community.

The use of NAAT enables quicker diagnosis and treatment of patients with TB, especially in those who are NAAT-positive and AFB-negative. It also reduces the duration of unnecessary and/or over-treatment for TB, especially in those patients who are NAAT-negative and AFB-positive.

The accuracy of NAAT compared with culture-based drug sensitivity testing indicates that NAAT can accurately identify patients with rifampicin-resistant MTB. Thus, NAAT could be used to inform the best type of antibacterial treatment of TB patients. This would help avoid side effects such as hepatitis from inappropriate use of rifampicin, and earlier appropriate treatment for rifampicin resistance would also reduce the risk of developing MDR-TB.

NAAT for the diagnosis of NTM

Culture is an imperfect reference standard, and meta-analyses of studies investigating the diagnostic accuracy of NAAT, AFB microscopy and culture using a clinical reference standard suggested that most patients who were NAAT-positive and culture-negative may have had clinical disease. Overall, NAAT appears to be able to identify a larger proportion of patients with an NTM infection than either AFB microscopy or culture. However, these results should be viewed with caution due to the small number of studies included and the wide 95%CIs for many of the analyses.

Cost-effectiveness of NAAT

The cost-effectiveness of NAAT is affected by the extent of use of clinical judgement in initial treatment decisions. In the extreme scenario, in which clinical judgment is not exerted (i.e. treatment initiation decisions are based on the results of testing), NAAT is most cost-effective due to improved sensitivity in conjunction with AFB, thereby reducing the number of patients who would have been untreated on the basis of AFB results alone. However, in the scenarios in which clinical judgement perfectly identifies TB or in which clinical judgment is used as the basis to treat all patients, the benefits of NAAT are restricted to identifying rifampicin resistance, and so are accrued in a very small proportion of the population tested (2% of 22% = 0.44%).

Methods

A systematic review was performed on the safety, effectiveness, cost-comparison of NAAT. Medline, Embase, The Cochrane Library, and several other biomedical databases, HTA and other internet sites were searched (1990- June 2014). The reference lists of included studies and relevant reviews were pearled. Studies were included in the review using pre-determined PICO selection criteria and reasons for exclusion were documented. Study quality was appraised, data extracted in a standardised manner, and findings synthesised narratively, or with meta-analyses where possible.

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