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Three year evaluation of Xpert MTB/RIF in a low prevalence tuberculosis setting: A Scottish perspective

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Summary *Objectives:* Xpert MTB/RIF (Cepheid) is a rapid molecular assay shown to be sensitive and specific for pulmonary tuberculosis (TB) diagnosis in highly endemic countries. We evaluated its diagnostic performance in a low TB prevalence setting, examined rifampicin resistance detection and quantitative capabilities predicting graded auramine microscopy and time to positivity (TTP) of culture.
Methods: Xpert MTB/RIF was used to test respiratory samples over a 3 year period. Samples underwent graded auramine microscopy, solid/liquid culture, in-house IS*6110* real-time PCR, and GenoType MTBDRplus (HAIN Lifescience) to determine rifampicin and/or isoniazid resistance.
Results: A total of 2103 Xpert MTB/RIF tests were performed. Compared to culture sensitivity was 95.8%, specificity 99.5%, positive predictive value (PPV) 82.1%, and negative predictive value (NPV) 99.9%. A positive correlation was found between auramine microscopy grade and Xpert MTB/RIF assay load. We found a clear reduction in the median TTP as Xpert MTB/RIF assay load increased. Rifampicin resistance was detected.
Conclusions: Xpert MTB/RIF was rapid and accurate in diagnosing pulmonary TB in a low prevalence area. Rapid results will influence infection prevention and control and treatment

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measures. The excellent NPV obtained suggests further work should be carried out to assess its role in replacing microscopy.

Introduction

Diagnosing tuberculosis (TB) can be problematic as patients may present with a wide range of symptoms which may not be specific. In addition, the sensitivity of microscopy and smear positivity in respiratory TB ranges from 57 to 81%, potentially leading to misdiagnosis.[1] TB culture is the gold standard for diagnosing TB and allows drug susceptibilities to be tested. There have been developments in rapid automated mycobacterial liquid culture systems and time to detection of growth of mycobacterial species can be shortened significantly.[2] Even with these advances there could be delays in diagnosis, leading to later initiation of appropriate therapy and implementation of infection prevention and control measures.

Xpert MTB/RIF (Cepheid) is a rapid, direct molecular test for the diagnosis of pulmonary TB and detection of rifampicin (RIF) resistance, which is a marker of multidrug resistant TB (MDRTB).[3] It has been endorsed by the World Health Organisation (WHO) and extensive evaluation has found it to be sensitive and specific for pulmonary TB diagnosis and detection of RIF resistance in high endemic countries for suspected cases of MDRTB.[4] Xpert MTB/RIF has lower sensitivity in HIV-associated TB.[5] There is however, considerably less data on the use of Xpert MTB/RIF in low prevalence countries despite increased use.[6] Recently a study to examine the use of Xpert MTB/RIF versus AFB smear and culture to identify pulmonary TB found that the diagnostic performance of Xpert MTB/RIF in the United States was similar to higher TB prevalence sites in Brazil and South Africa.[7]

Scotland's TB incidence was 6.5 cases per 100,000 population in 2014 with low rates of MDR-TB (around 0.9%).[8] In that year, Scotland had an estimated rate of 1.51 diagnosed HIV-infected persons per 1000 population in adults aged 15—59 years (Glenn Codere, Health Protection Scotland, Personal Communication 14 December 2016). The UK National Institute for Health and Care Excellence (NICE) guidance recommends rapid diagnostic nucleic acid amplification tests for diagnosing pulmonary (including laryngeal) TB in adults if there is clinical suspicion of TB disease and the person has HIV or in circumstances in which rapid information about mycobacterial species would alter the persons care or in a situation where a large contact-tracing initiative is being explored.[9] Other guidance advises rapid detection of MDRTB is also recommended on the basis that filtering face piece (FFP3) masks respiratory protection should be used until MDRTB has been excluded.[10] The Public Health England (PHE) position statement published in July 2013 states that molecular testing of *Mycobacterium tuberculosis* complex (MTBC) on respiratory samples is superior to smear microscopy for the diagnosis of TB and should be accessible in all areas of Scotland, England and Wales with results available within 1—2 working days of the sample being taken.[11]

The objective of this study was to evaluate the performance of Xpert MTB/RIF for detection of pulmonary TB in patients from the Tayside region of Scotland which has a low TB and HIV prevalence. In addition we aimed to examine the quantitative capabilities of Xpert MTB/RIF in relation to predicting auramine stain grading, as well as looking at TTP of culture.

Materials and methods

Study design and clinical samples

This is a retrospective review and analysis of data collected for clinical purposes. Respiratory samples (sputum, bronchoalveolar lavage (BAL), induced sputum, and endotracheal aspirates (ETA)) were submitted over a 3 year period (February 2011 to March 2014) and tested by Xpert MTB/RIF at the Department of Medical Microbiology, Ninewells Hospital and Medical School, Dundee (NHD). Samples came from both hospital inpatient and community settings and were sent for graded auramine smear microscopy and culture using solid Löwenstein—Jensen (LJ) media (containing pyruvate as a growth supplement) and BACTEC MGIT 960 liquid media at the Scottish Mycobacteria Reference Laboratory (SMRL) at the Royal Infirmary of Edinburgh.

Xpert MTB/RIF

At NHD, a minimum of 1 ml raw sputum or BAL was collected from samples. Xpert TB/RIF was performed on a GeneXpert instrument with GX2.1 software (GX) according to the manufacturer's instructions. A 2 ml volume of sample reagent was added to each sample and shaken vigorously 10—20 times. This was incubated for 15 min at room temperature. At a point between 5 and 10 min of incubation the sample was shaken vigorously again 10—20 times. The liquefied sample was aspirated into a sterile transfer pipette until the meniscus was above the minimum mark then added to the Xpert MTB/RIF cartridge and then run on the machine according to the manufacturer's instructions. The GeneXpert DX System interpreted Xpert MTB/RIF results depending on the cycle threshold (Ct) value of MTB target present in the sample. When MTB was detected results were displayed as high (Ct $<$ 16), medium (Ct 16—22), low (Ct 22—28) or very low (Ct $>$ 28). These are known as the Xpert MTB/RIF assay load. Negative results were displayed as MTB not detected. Rifampicin resistance was reported as either detected, not detected or indeterminate.

Sample processing

Respiratory samples were sent to SMRL where they were liquefied and concentrated using Sputasol (1:1 v/v; Oxoid) and a loopful of sediment used to prepare a smear for auramine phenol microscopy using standard laboratory methods.[12] The number of AFB present was scored as: +