In endemic countries, it is fair to say that every family doctor has treated at least one patient with tuberculosis (TB). TB is a leading cause in morbidity and mortality worldwide, affecting over 10.4 million people with 1.8 million deaths worldwide in 2015. Over 95% of TB deaths occur in low- and middle-income countries (1).

The heart of the problem is diagnosis. Early identification of TB is paramount to reduce spread of the disease and limit its burden. An estimated 49 million lives were saved through TB diagnosis and treatment between 2000 and 2015 (1).

But where do we stand in this matter? This chapter aims to describe the current diagnostic tools available, briefly explore new technologies and to present an observation on the value of clinical diagnosis.

**What are the Diagnostic Methods Available for Pulmonary TB?**

**Acid fast bacilli (AFB) smear**

This is probably the most well known method for TB diagnosis. Ziehl-Nielsen staining of respiratory samples (sputum or bronchoalveolar lavage) with subsequent optic microscopic examination to find bacilli is the mainstay of quick diagnosis in most healthcare settings (2).

Its advantages are low cost, relatively simple technology and fast delivery of results (only takes a couple of hours). Its problems, however, have been consistently scrutinised in the recent years. Its sensitivity varies between 45-80%, being lower in AIDS and immunosuppression (3). This translates to a high amount of false negatives and dangerously reassuring results. This test also intensely depends on examiner expertise and experienced technicians are not always available.

**Mycobacterial culture**

Culture of respiratory samples in specific mycobacterial culture media is considered the gold standard for the diagnosis of pulmonary TB (2). This test might detect a number of TB patients undiagnosed with AFB smears.

However, there are even more limitations. First, culturing pathogenic bacteria poses biological hazard and therefore, compliance to a series of technical requirements and safety measures is necessary. Microbiology laboratories that process TB-related materials often employ high-technology with very specifically designed facilities. This
may not be available in most parts of the world. Furthermore, cultures take weeks even when the most recent methodologies are used (2).

In solid media, time to positivity is around 3-4 weeks, whereas in liquid media with automation (more expensive and less available) it is around 1-3 weeks. After this, identification is also necessary, which could take some more time (days to a couple of weeks). This delay is a major concern, as the disease might be progressing (more severe disease and sequelae) and spreading to others while test results are still unavailable.

What are the New and Promising Diagnostic Methods?

All the aforementioned limitations (especially low sensitivity and time) underscore the need of new tests and research has been increasingly published on this topic. Two of these tests are further discussed below.

**Quick TB PCR - GeneXpert MTB/RIF**

The Xpert MTB/RIF assay is an automated nucleic acid amplification test that can simultaneously identify *M. tuberculosis* and rifampicin resistance. The results are generally available within 2 hours. The assay is designed to identify *M. tuberculosis* specifically (other acid-fast bacilli will yield negative results) and rifampicin-resistance mutations rpoB gene (useful for determining the initial treatment regimen) (4).

This test has improved sensitivity over smear microscopy and very high specificity (5,6). The Xpert MTB/RIF assay has received endorsement by the World Health Organization and is simple to perform with minimal training, not prone to cross-contamination, and requires minimal biosafety facilities.

**Point-of-care urinary Lipoarabinomannan (LAM)**

This is a promising marker for tuberculosis in the immunosuppressed host, especially in low-income countries. LAM is one of three major groups of interrelated lipopolysaccharides within the mycobacterial cell wall. The mechanism whereby LAM enters the urine is still unclear. It can be detected with ELISA, but also with point-of-care immunochromatography, like a pregnancy urinary test (7).

This essay is fast, requires minimal training and no specific laboratory facilities. It has been studied in many countries with promising results and the added benefit of having increased sensitivity the more immunosuppressed the patient is. For many places of the world, such a test might be an option to consider. The test still requires validation for different populations. Accordingly, research in the primary care setting is called for.

If There are No Specific TB Tests Available: How Good is Clinical Diagnosis?

In 1998, a Pakistani group presented their work on the WONCA Europe Congress in Dublin (8). They described 200 patients which were treated for TB without specific testing. Patients received "empiric" therapy based on epidemiological and clinical data with the only tests available being a chest x-ray and a blood picture. Their results are very interesting.

Of the 200 treated patients, all improved completely, by clinical and imaging parameters. This underscores that in the absence of all the diagnostic methods an experienced family doctor might still make the right diagnosis and benefit patients where the treatment is available.

Take Home Messages

- TB is a leading cause of morbidity and mortality throughout the world
- Prompt and reliable diagnosis is paramount
- Diagnostic tests
  - *the old*
**AFB smear**: available and fast, but low sensitivity (specially in the immunocompromised) and requires expertise

**Culture**: gold standard but time consuming and requires advanced facilities

- **Diagnostic tests**
  - **the new**
    - **Quick TB PCR - XpertMTB/RIF**: fast, highly specific, better sensitivity than AFB, endorsed by the WHO, detects rifampicin resistance, requires only minimal facilities
    - **Urinary LAM**: fast, point-of-care, excels in the immunosuppressed, no need for specific facilities, but still requires further study

- Where no specific tests are available, clinical diagnosis by primary care physicians is key for treatment initiation and might still provide excellent results

**Original Abstract**

http://www.woncaeurope.org/content/abstract-no-1223-workshop-rapid-and-early-diagnosis-tuberculosis-developing-world

**References**