In the Name of God

• Challenges in Diagnosis of Tuberculosis, for clinicians

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It is estimated that:

- **One third of the world’s population is infected with Mycobacterium tuberculosis**.

- **Each year, about 9 million people develop TB, of whom about 2 million die**.

- **Of the 9 million cases of TB worldwide that occur annually, about 1 million cases (11%) occur in children**.
Delays in TB Diagnosis

• Delay from onset of symptoms to start of treatment: median 68 days
• TB Deaths – delay from onset of symptoms to diagnosis 116 days
Recommended approach to diagnose TB

1- History of TB contact
2- Clinical signs and symptoms
3- Tuberculin skin testing (TST)
4- Bacteriological confirmation
5- Radiological confirmation
Clinical signs and symptoms

- The signs and symptoms can be non-specific.
- Many differential diagnoses.
A positive TST does not distinguish between TB infection and active disease.

A negative TST does not exclude TB disease.
X-rays often will show non-specific changes which are compatible with other illnesses such as pneumonia. Reading chest X-rays in children is a special skill.

- May be atypical in children
- May be atypical in immunosuppressed (including HIV)
- Cannot confirm diagnosis
- Cannot always distinguish between active and old disease
• Ziehl-Neelsen method:
• The smear is positive in only 50–80% of individuals with culture-confirmed pulmonary tuberculosis.
There must be 5,000 to 10,000 bacilli per milliliter of specimen to allow the detection of bacteria in stained smears.
Factors influencing the sensitivity of smears include staining technique, centrifugation speed, reader experience, and the prevalence of tuberculosis disease in the population being tested.
• Acid-fast bacteria seen on smear may represent either *M. tuberculosis* or non-tuberculous mycobacteria.
• Culture
• About 15–20% of adults with tuberculosis have negative sputum cultures.
• Among children, the proportion of culture-negative cases is much higher.
• False-positive cultures can also occur.
• In 2009, only 19% of all childhood TB cases were confirmed by culture – which clearly indicates that TB diagnosis in children remains a major challenge.
From 1985 to 1988 in the United States, 90% of tuberculosis cases in adults were bacteriologically confirmed, compared with 28% in children.
IGRAs
Evidence-based Tuberculosis Diagnosis
summaries of systematic reviews - #3

• The sensitivity and specificity of IGRAs for the diagnosis of pulmonary TB in adults in low and middle-income countries.

• pooled sensitivity estimates were : TSPOT 88%    QFT  84% .

• The specificity of both IGRAs was low : < 65% .

• There was no consistent evidence that either IGRA was more sensitive than the TST for the diagnosis of active TB.
Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review.

- Interferon-gamma assays that use Mycobacterium tuberculosis-specific region of difference 1 (RD1) may have advantages over the TST, in terms of higher specificity, better correlation with exposure to M tuberculosis, and less cross-reactivity due to BCG vaccination and non-tuberculous mycobacterial infection.

- However, THEY , may maximize specificity at the cost of sensitivity.
• Newest commercial IGRAs are superior, in comparison to the TST, for detecting confirmed active TB disease, especially when performed in developed countries.
Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement.

World Health Organization 2011

• Neither IGRAs nor the TST should be used for the diagnosis of active TB disease.
• IGRAs are more costly and technically complex to do than the TST.
• Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.
In specimens that are AFB smear positive, the sensitivity of the PCR is approximately 95%, with a specificity of 98%.

In specimens that are AFB smear negative, PCR is positive in 48–53% of the time, with a specificity remaining approximately 95%.
false-positive results.

Also, it can detect nucleic acids from dead as well as live M. tuberculosis and, therefore, can remain positive for long periods in patients who have completed tuberculosis therapy.
Evidence-based Tuberculosis Diagnosis
- systematic reviews - #4

Title: Commercial Nucleic-Acid Amplification Tests for the Diagnosis of Pulmonary Tuberculosis

- Sensitivity 85%
- Specificity 97%

conclusions: Commercial PCR tests alone cannot be recommended to replace conventional tests such as culture for diagnosing pulmonary TB.
- Adenosine deaminase (ADA) tests
- There is no evidence to support ADA tests for diagnosis of pulmonary TB.

- However, there is considerable evidence to support their use for diagnosis of pleural TB and to a slightly lesser extent for TB meningitis.
Anti-TB antibody test performance was universally poor, regardless of type of TB.
The TB test we need*

- Detection of active TB in adults regardless of HIV status
- Improved diagnostic in children
- Result that allow decision on treatment initiation
- Patient can receive result on the same day
- Point-of-care: easy to perform in peripheral health centres
- DST (preferable but not minimum requirement)
- Need to aim to a NON-sputum sample base test

*MSF led POC TB test consultation, 2009
So, despite many efforts, there is a long way to overcome the challenges of TB diagnosis.
Thank you for your attention.