

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.

TST

False-positive and False Negative tuberculin reactions.

- A positive TST does not distinguish between TB infection and active disease .
- A negative TST does not exclude TB disease.

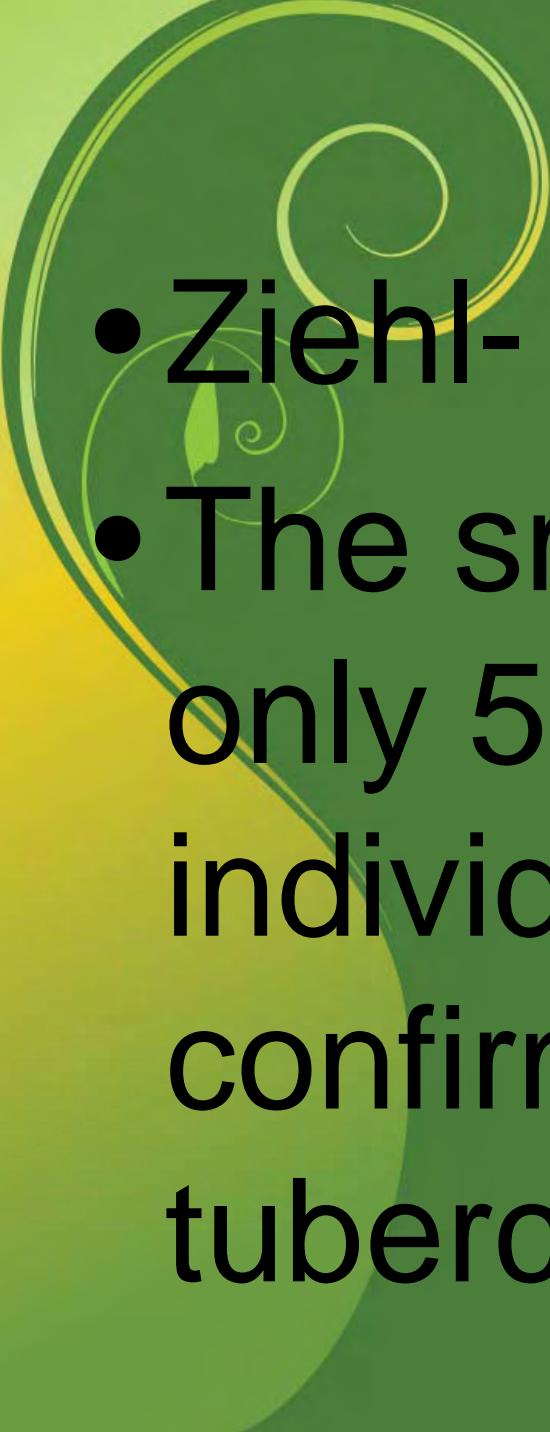
Chest X-ray


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**




- **MICROSCOPY**

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- Ziehl- Neelsen method :
 - The smear is positive in only 50–80% of individuals with culture-confirmed pulmonary tuberculosis.

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- There must be 5,000 to 10,000 bacilli per milliliter of specimen to allow the detection of bacteria in stained smears .


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- Factors influencing the sensitivity of smears include staining technique, centrifugation speed, reader experience, and the prevalence of tuberculosis disease in the population being tested.


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- 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.

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- 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 .

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- *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.**

Lancet Infect Dis. 2004 Pai M

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.

R Diel,
**interferon-gamma release assays for detecting TB
a meta-analysis**

- **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 .**



PCR

- ◎ 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 specimens. Specificity remains 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.**



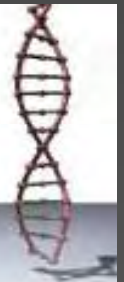
● Adenosine
deaminase
(ADA) tests

- 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

- 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.

