Diagnosis of Tuberculosis

Presenter: Dr. Juma Phoebe
MINI ROUND 25 MARCH 2015
outline

• Introduction
• Pathophysiology
• Challenges with TB diagnosis
• Diagnostic tests and their clinical utility
• conclusion
Questions....?

WHO recommends against which of the following tests for diagnosis of TB?

a. Fluorescence microscopy
b. urinary LAM
c. MODS
d. Serology
True or false

• Gene sequencing is the gold standard for TB diagnosis.
• In smear negative TB, sputum culture is of no added value.
• The bronchoalveolar lavage culture of a patient with pulmonary infiltrates is positive for mycobacteria. You suspect your patient has TB but you want to rule out non TB mycobacteria.

• Which test would you request for?
  1. PCR
  2. MTP64 antigen test
  3. check for cording
  4. Esat-6/CFP staining
  5. All the above
• Which of the following patients would be a candidate for Urinary LAM testing?
  – HIV -, spinal osteomyelitis, in Ethiopia
  – HIV+, CD4 10, fever, night sweats, normal CXR, in Uganda
  – HIV +, on HAART, pulmonary cavity in Canada
  – HIV -, renal transplant, sterile pyuria
Introduction

• A disease as old as mankind: scrofula, white plague, Potts disease
• Natural course: highly fatal
• 1882: Robert Koch isolated the causative agent
• Renee Laennec: invented the stethoscope
• 1993: WHO declared TB a global epidemic
• 2014: 9 million TB sufferers
Kenya

<table>
<thead>
<tr>
<th>High TB burden</th>
<th>High HIV burden</th>
</tr>
</thead>
</table>

Population 2013: 44 million

### Estimates of TB burden * 2013

<table>
<thead>
<tr>
<th></th>
<th>Number (thousands)</th>
<th>Rate (per 100 000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (excludes HIV+TB)</td>
<td>9.1 (5.5–12)</td>
<td>20 (12–27)</td>
</tr>
<tr>
<td>Mortality (HIV+TB only)</td>
<td>9.5 (7.5–12)</td>
<td>21 (17–27)</td>
</tr>
<tr>
<td>Prevalence (includes HIV+TB)</td>
<td>130 (60–200)</td>
<td>283 (156–447)</td>
</tr>
<tr>
<td>Incidence (includes HIV+TB)</td>
<td>120 (120–120)</td>
<td>288 (261–275)</td>
</tr>
<tr>
<td>Incidence (HIV+TB only)</td>
<td>48 (47–60)</td>
<td>109 (105–112)</td>
</tr>
<tr>
<td>Case detection, all forms (%)</td>
<td>75 (74–77)</td>
<td></td>
</tr>
</tbody>
</table>

### Estimates of MDR-TB burden * 2013

<table>
<thead>
<tr>
<th></th>
<th>New</th>
<th>Retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of TB cases with MDR-TB</td>
<td>2.6 (0.01–5.5)</td>
<td>13 (0.2–28)</td>
</tr>
<tr>
<td>MDR-TB cases among notified pulmonary TB cases</td>
<td>1 700 (7–3 700)</td>
<td>1 100 (17–2 300)</td>
</tr>
<tr>
<td>Country</td>
<td>Burden of TB incidence (no. of cases/100,000 individuals/yr)</td>
<td>Global rank (by estimated cases)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>333</td>
<td>21</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>246</td>
<td>5</td>
</tr>
<tr>
<td>Brazil</td>
<td>62</td>
<td>15</td>
</tr>
<tr>
<td>Cambodia</td>
<td>508</td>
<td>23</td>
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<tr>
<td>China</td>
<td>102</td>
<td>2</td>
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<tr>
<td>Democratic Republic of Congo</td>
<td>369</td>
<td>11</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>356</td>
<td>7</td>
</tr>
<tr>
<td>India</td>
<td>168</td>
<td>1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>285</td>
<td>3</td>
</tr>
<tr>
<td>Kenya</td>
<td>610</td>
<td>10</td>
</tr>
<tr>
<td>Mozambique</td>
<td>431</td>
<td>19</td>
</tr>
<tr>
<td>Myanmar</td>
<td>171</td>
<td>20</td>
</tr>
<tr>
<td>Nigeria</td>
<td>293</td>
<td>4</td>
</tr>
<tr>
<td>Pakistan</td>
<td>181</td>
<td>6</td>
</tr>
<tr>
<td>Philippines</td>
<td>296</td>
<td>9</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>110</td>
<td>11</td>
</tr>
<tr>
<td>South Africa</td>
<td>948</td>
<td>5</td>
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<tr>
<td>Thailand</td>
<td>142</td>
<td>17</td>
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<tr>
<td>Uganda</td>
<td>411</td>
<td>16</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>371</td>
<td>14</td>
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<tr>
<td>Vietnam</td>
<td>178</td>
<td>13</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>569</td>
<td>19</td>
</tr>
</tbody>
</table>

* See reference 211.
• Kenya is 15\textsuperscript{th} of the top 22 countries where 80\% of TB is found.
• 5\textsuperscript{th} in Africa
• Notified 103,159 TB cases in 2012
• 39\% also HIV positive
• Treatment success rates 87\% for new smear positive cases
• Detection rates at 65\% below the WHO standard 70\%
Mycobacterium tuberculosis
Pathophysiology of tuberculosis

Steps in the pathogenesis of tuberculosis:

1. Exposure to source
2. Aerosolization of droplet nuclei
3. Inhalation of bacteria
   - Bacteria reach lungs; enter macrophages (25-50%)
   - Bacteria multiply in macrophages
   - Granulomatous lesion begins to form (caseous necrosis)
     - Bacteria cease to grow; lesion calcifies (95%)
     - Lesion liquefies
     - Bacteria coughed up in sputum
     - Spread to blood, organs
     - Reactivation
     - Death
   - No infection (>50%)
4. Alveolar Macrophage

Immune suppression:

- Reactivation
Pathophysiology continued
Challenges in Tuberculosis Diagnosis

• Novel diagnostic methods
  – How to apply
  – Who to test
  – Which specimens
• Heavy reliance on clinical diagnosis
  – Complacency on the part of clinicians
• Passive case finding
• Low detection rates: only 65% are diagnosed
• Long time to get results using gold standard tests
• Economic:
  • Lack of reference labs to culture TB
  • Access to diagnostic centre challenges
Overview of diagnosis

• Clinical diagnosis:
  – exposure history, screen for symptoms, chest radiograph

• Lab diagnosis:
  – Latent TB: tests which detect the immune response
    • TST
    • IGRA
  – Active TB: detect the bacteria
    • Smear
    • Culture: solid media and liquid media
    • Nucleic acids: gene sequencing, gene xpert, line probe assays,
    • Antigen testing
    • Drug sensitivity testing
    • Serology for TB
Clinical diagnosis

• Symptoms and chest x-rays
• Symptoms:
  – cough and fever- any duration
  – Night sweats 3wks
• Sensitivity is 93%
• Specificity is 36%
• NPV is 97% safely initiate latent TB treatment
• CXR and Symptoms are screening tools
Symptoms and CXR

• **Validity of clinical symptoms and chest radiography in predicting pulmonary TB at the KNH, Nairobi, Kenya.**
  
  Dr. Odhiambo Francesca Akoth 2008
  population 271pts, cough >2wks
  Compared CXR findings with gold standard: TB culture
  46% culture +ve, 55% HIV
  CXR has a positive predictive value of 70 to 74%
  Didn’t validate CXR as diagnostic tool

• **A systematic review of sensitivity and specificity of symptom and CXR screening for active TB in HIV negative persons and unknown HIV status.**
  
  – WHO. Int. report march 2013
  
  Analysis of databases; EMBASE, MEDLINE, LILIACS, 21 publications
  CXR sensitivity 90% any abnormality, specificity: 56% low
  Prolonged cough sensitivity of 34%, specificity of 94%
Cost-effectiveness of CXR for TB diagnosis, a cost-effectiveness analysis, Nairobi, Kenya.

- Enrolled 1389 persons. Rhodes Clinic
- Performance of CXR was compared against the gold standard
- Sensitivity vs. specificity: 80 vs. 67%
- More cost effective to do sputum's then CXR only in sputum smear negative

Kenya TB Guidelines

- “All patients with chest xray features suggestive of TB should have sputum specimens submitted for microbiological examination. It is a major omission to diagnose TB on the basis of a Chest xray.”
Laboratory Diagnosis

- Latent TB Vs. Active TB
- Latent TB: (Detect an immune response to TB)
  - TST- tuberculin skin test
  - IGRAs- Interferon gamma release assays
- Active tuberculosis: (Detect the tubercle bacillus)
  - Diagnosis:
    - Smear microscopy
    - Liquid growth media
    - Solid growth media
    - Molecular probes
    - Gene sequencing
  - Drug susceptibility testing:
    - MGit, DST
    - Agar proportion
- Novel methods for resource limited settings:
  - Molecular:
    - Xpert MTB/ RIF (Gene Xpert)
    - Line probe assays (Hain Assay, INNO-LIPA Rif. TB)
- Phenotypic: (MODS)
Principle of Immunodiagnosis

Presentation of mycobacterial antigens

Antigen-presenting cell → Memory T cell

Skin test

In vitro blood test

IFN-γ, TNFα, IL8, etc.

Results expressed as IFN-γ (pg/mL) or IU/mL

Results expressed as number of IFN-γ secreting T cells (spot-forming cells)

Tuberculin Skin Test

Whole blood diluted or undiluted/peripheral blood mononuclear cells

Nocardia farcinica antigens (e.g., BCG, ESAT-6, CFP10, MPT64)

Incubation (over 3-4 hours or 5-6 days)

Sensitized T cells release IFN-γ

IFN-γ production measured using ELISA (e.g., QuantiFERON-TB) or ELISPOT (e.g., T SPOT-TB)

TNFα, IL8, etc.
Tuberculin Skin Test

• Well validated, 100 yrs.
• Tests for prior sensitization to mycobacterial antigens
• PPD derivative, 170 proteins, not specific
• Limited value for diagnosis: high prevalence areas/BCG vaccination
• Useful for diagnosis in low prevalence areas
• Measures mediated immunity response after 48-72hrs
• Mediated by IFN gamma., TNF alpha and TNF beta
• BCG vaccination almost invariably results in a tuberculin conversion.
  – Reactions >10mm develop within 8-12wks after vaccination
  – Rapid waning of the tuberculin reaction occurs in those vaccinated as neonates

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**Tuberculin Skin Test (PPD)**

<table>
<thead>
<tr>
<th>&gt; 5 mm induration</th>
<th>&gt; 10 mm induration</th>
<th>&gt; 15 mm induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV (poor CMI)</td>
<td>High prevalence ↓ reactivity (steroids, malnutrition)</td>
<td>All others (low probability)</td>
</tr>
<tr>
<td>High suspicion (close contact, fibrotic CXR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(c) 2004, Susan Hadley, M.D.
IGRAs

- Whole blood assays
  - Detect the effector T cell response to stimulation by TB antigens
  - Response: IFN gamma release
  - Ag: ESAT 6, CFP 10, TB7.7
  - Test +ve in M tuberculosis, africanum, bovis, kansasii, marinum and szulgai

- IGRAS are in vitro tests of Cell mediated immunity

<table>
<thead>
<tr>
<th></th>
<th>Quantiferon</th>
<th>Quantiferon Gold in tube</th>
<th>TSPOT</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>78%</td>
<td>70%</td>
<td>90%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Pai M et al, Ann Int Med 2008; 149: 177
IGRA USE

- IGRAs miss 10-30% of active TB cases therefore not used as a rule out TB test
- IGRA sensitivity drops with advancing immunosuppression:
  - Less affected than the TST
  - TSPOT less affected than the Quantiferon
  - Indeterminate results
  - Poor concordance between TST, TSPOT and Quantiferon
- IGRA levels can’t be used to monitor treatment: inconclusive results
IGRAs in High Burden Countries

Pooled sensitivity:

Overall
77%

High burden countries
69%

Low burden countries
83%

Dheda K et al, Current Opinion in Pulmonary Medicine 2009, 15:188
IGRAs

• WHO policy statement 2011

“insufficient data and low quality evidence to support the use of IGRAs in low and middle income countries.”
# Guidelines for IGRA/TST use

## Contact Investigation in Adults - Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Guideline or position statement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST alone</td>
<td>WHO, Brazil, ECDC (high-incidence countries)</td>
</tr>
<tr>
<td>TST followed by IGRA, if TST positive (either IGRA only in BCG vaccinated persons or independent of BCG vaccine)</td>
<td>Canada (low-risk contacts), Germany, Italy, Switzerland, Spain, Saudi Arabia, Netherlands, Norway, Bulgaria, Portugal, Ireland, ECDC (low-incidence countries), and for UK and South Korea only in adults &lt;35 of age</td>
</tr>
<tr>
<td>Both TST and IGRA</td>
<td>Canada (high-risk contacts), Czech Republic, Croatia, Austria, Australia (IGRA may be considered in addition)</td>
</tr>
<tr>
<td>Either TST or IGRA</td>
<td>USA, Denmark, Finland (IGRA preferred if BCG vaccinated in all three countries), South Korea (only in adults &lt;35 of age), Austria</td>
</tr>
<tr>
<td>IGRA alone</td>
<td>Slovakia, Japan, France</td>
</tr>
</tbody>
</table>
Who should be screened for LTB?

- High risk of reactivation:
  - HIV
  - CKD
  - Renal transplant patients
  - Diabetics
  - Anti TNF alpha

- Health care workers?:
  - A high prevalence of LTB among 5th year students 30%
Sputum smear

- Simple, cheap
- Confirms diagnosis in high prevalence areas
- Identifies the greatest transmitters
- Identifies those most likely to die
- Low sensitivity low specificity
- Can't distinguish species
- Can't tell Drug susceptibility
- Can't distinguish dead or live organisms
- Low sensitivity 50-60%
- KNH study: sens/sp 71/90%
Improving accuracy of a sputum smear

• Take at least 2 sputa, 3rd increases sensitivity only 2-5%

• Specimen concentration and decontamination- sensitivity increased 15-20%

• Fluorescence microscopy
  – Auramine stain: mycobacteria fluoresce
  – Increases sensitivity 10%
  – Shortens time to diagnosis
  – Ideal for high volumes
  – Expensive
  – Light emitting diode technology
TB CULTURE

- Necessary because of the low sensitivity of direct smear microscopy
- Culture can detect only 10-100 per ml
- Can detect PTB in 80% of cases
- Better suited to some specimens (BM, blood, aspirates)
- Its cost effective to add culture to sputum smear
- Conventional media: solid media LJ and Middle brook
- Liquid media: contain an indicator for bacterial growth
- Solid media culture is the GOLD STANDARD for TB diagnosis
TB culture

- Solid media
- LJ and middlebrook
- Colonies are buff coloured
- Contain inhibitors to prevent growth of contaminants
- 4-6 wks to get a visible growth
Tb culture

• Liquid culture media
  – Earlier results
  – Detect CO2 production, or O2 consumption
  – E.g. BACTEC, MGIT
  – 1-3wks to get a report
  – Time to Result depends on inoculum size
  – Expensive, technologically demanding
Performance of TB culture in EPTB

• Variable but mostly poor
• Pleural TB: 24-58-%
• TB meningitis: 52-87%
• Abdominal TB: 7-87%
• Lymph node TB: 62% FNA, 71% biopsies
TB: Drug Sensitivity Testing

“Phenotypic Testing”
- Conventional:
  - Method of proportion
- Liquid Culture:
  - growth or absence of it in liquid media
- MODS:
  - microscopic observation of growth/cording in presence of drugs
- Phage based assay

“Genotypic Testing”
- Molecular methods:
  - Line probe assay: INH/Rifampin
  - Cepheid XPERT TB: Rifampin
  - Sequencing

Longer Time
Limited Drugs tested
TB Culture

- **Microscopic Observation Drug susceptibility**
  - Done in multi-well culture plates
  - Results visible in days 10 days
  - Drug susceptibility and diagnosis are done simultaneously
  - Sensitivity 98%
  - Specificity 99% RIF
  - Specificity 91% INH

- MTB can be distinguished from other mycobacteria on the basis of its cording
Diagnosis of MDR-TB: MODS

Peruvian study of 3,760 samples:

- Sensitivity of detection: 97.8% for MODS, 89% for Bactec, 84% for L-J media
- Time to diagnosis: 7 days for MODS, 22 days for Bactec, 68 days for L-J
- Concordance of drug-susceptibility testing between MODS and gold standard:
  - INH: 97%
  - RIF: 100%
  - MDR-TB: 99%

Diagnosis of MDR-TB: MODS

- MODS to rule out active TB prior to initiating isoniazid preventive therapy (IPT) in patients beginning ART
  - Peruvian study of 471 HIV+ IPT candidates:
    - 27 positive by MODS, 22 positive by LJ, 7 smear+ 
    - 96% MODS positive after 2 weeks
    - MDR detected by MODS simultaneously in 2 pts
    - MODS more accurate than clinical algorithms involving symptoms, CXR findings, etc.

Reddy Clin Infect Dis 2010
Rapid susceptibility Testing

• FASTPlaque-Assay
  – Based on mycobacterial phage
  – Quickly detects bacteria and RIF resistance directly from sputum
  – Variable specificity

• NRA- Nitrate Reductase Assays
  – Add KNO3 to the agar
  – Viable bacteria reduce nitrate to nitrite
  – Greiss reagent colour change
<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear microscopy</td>
<td>10%–65% [3*, 4*, 66, 67]</td>
<td>89%–99%</td>
</tr>
<tr>
<td>Conventional (light) microscopy</td>
<td>45%–73% [29, 30, 68]</td>
<td>98%–100%</td>
</tr>
<tr>
<td>Fluorescence microscopy/LED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid culture</td>
<td>Usually reference</td>
<td>Usually reference</td>
</tr>
<tr>
<td>Thin layer Agar</td>
<td>74%–97% [69, 70]</td>
<td>Not reported</td>
</tr>
<tr>
<td>Automated liquid culture</td>
<td>Equivalent or superior to solid culture [71]</td>
<td>100%</td>
</tr>
<tr>
<td>MODS</td>
<td>71%–98% [37]</td>
<td>93%–100%</td>
</tr>
<tr>
<td>Nitrate reductase assay for DST</td>
<td>97% [38] (RIF) 96% (INH)</td>
<td>100% 99%</td>
</tr>
<tr>
<td>Mycobacterio-phage assay for DST</td>
<td>96–99%[39] (RIF)</td>
<td>95%–98%</td>
</tr>
</tbody>
</table>
# Molecular Basis for MTB Drug Resistance

## Table. Gene loci involved in conferring drug-resistance in *Mycobacterium tuberculosis*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Product</th>
<th>Reported frequency in resistant strains (^a) (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>rpoB</td>
<td>B-subunit of RNA polymerase</td>
<td>&gt;95</td>
<td>45-48,68-71</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>katG</td>
<td>Catalase-peroxidase</td>
<td>60-70</td>
<td>39-48</td>
</tr>
<tr>
<td></td>
<td>oxyR-ahpC</td>
<td>Alky hydro-reductase</td>
<td>~20</td>
<td>36</td>
</tr>
<tr>
<td>INH-Ethionamide</td>
<td>inhA</td>
<td>Enoyl-ACP reductase</td>
<td>&lt;10</td>
<td>46-48</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>rpsL</td>
<td>Ribosomal protein S12</td>
<td>60</td>
<td>46-48</td>
</tr>
<tr>
<td></td>
<td>rrs</td>
<td>16s rRNA</td>
<td>&lt;10</td>
<td>113-117</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>gyrA</td>
<td>DNA gyrase</td>
<td>&gt;90</td>
<td>107</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>pncA</td>
<td>Amidase</td>
<td>70-100</td>
<td>92-94</td>
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<tr>
<td>Ethambutol</td>
<td>embCAB</td>
<td>EmbCAB</td>
<td>69</td>
<td>88</td>
</tr>
</tbody>
</table>

\(^a\)Mutation frequencies are as determined by sequencing and polymerase chain reaction-single strand conformational polymorphism (PCR-SSCP) analysis.

Rattan A, Emergin Infectious Diseases, 1998
<table>
<thead>
<tr>
<th>Assay</th>
<th>Manufacturer</th>
<th>Method</th>
<th>Material</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PLR</th>
<th>NLR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplified MTD</td>
<td>Gen-Probe Inc., San Diego, CA, USA</td>
<td>Transcription-mediated amplification</td>
<td>DNA from decontaminated sputum</td>
<td>86.0 (74.2 to 93.7)</td>
<td>99.3 (96.3 to 100.0)</td>
<td>57.6</td>
<td>0.1</td>
<td>[11,16]</td>
</tr>
<tr>
<td>COBAS® TaqMan® MTB Test</td>
<td>Roche Molecular Diagnostics, Pleasanton, CA, USA</td>
<td>RT-PCR</td>
<td>DNA from decontaminated sputum</td>
<td>91.5 (86.9 to 96.1)</td>
<td>98.7 (98.0 to 99.4)</td>
<td>-</td>
<td>-</td>
<td>[17,18]</td>
</tr>
<tr>
<td>M. tuberculosis PCR</td>
<td>Qiagen, Hilden, Germany</td>
<td>RT-PCR</td>
<td>DNA from decontaminated sputum</td>
<td>97.8 (93.6 to 95.5)</td>
<td>85.1 (75.8 to 91.8)</td>
<td>6.54</td>
<td>0.03</td>
<td>[19]</td>
</tr>
<tr>
<td>artus® M. tuberculosis PCR</td>
<td>Qiagen, Hilden, Germany</td>
<td>RT-PCR</td>
<td>Untreated sputum</td>
<td>88.2 (81.4 to 92.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[20]</td>
</tr>
<tr>
<td>Loopamp® Tuberculosis Complex Detection Reagent Kit</td>
<td>Eiken Chemical, Tokyo, Japan</td>
<td>LAMP</td>
<td>Untreated sputum</td>
<td>88.2 (81.4 to 92.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[20]</td>
</tr>
<tr>
<td>Amplicor MTB</td>
<td>Roche Molecular Diagnostics, Pleasanton, CA, USA</td>
<td>PCR amplification of 16S RNA</td>
<td>DNA from decontaminated sputum</td>
<td>-</td>
<td>26.04 (17.04 to 39.80)</td>
<td>0.15</td>
<td>0.11 to 0.22</td>
<td>[11]</td>
</tr>
<tr>
<td>Cobas Amplicor</td>
<td>Roche Molecular Diagnostics, Pleasanton, CA, USA</td>
<td>PCR amplification of 16S RNA</td>
<td>DNA from decontaminated sputum</td>
<td>-</td>
<td>58.59 (37.77 to 90.86)</td>
<td>0.17</td>
<td>0.13 to 0.22</td>
<td>[11]</td>
</tr>
<tr>
<td>LCx</td>
<td>Abbott Laboratories, USA, Abbott Park, IL, USA</td>
<td>Ligase chain reaction</td>
<td>DNA from decontaminated sputum</td>
<td>88.9 (82.5 to 96.3)</td>
<td>96.8 (95.1 to 98.5)</td>
<td>26.91</td>
<td>0.16</td>
<td>[11,21]</td>
</tr>
<tr>
<td>BD Probe Tec Direct</td>
<td>Becton Dickinson, Sparks, MD, USA</td>
<td>Strand Displacement amplification</td>
<td>DNA from decontaminated sputum</td>
<td>77.5 (72.0 to 83.0)</td>
<td>98.0 (97.1 to 98.9)</td>
<td>20.11</td>
<td>0.06</td>
<td>[11,22]</td>
</tr>
<tr>
<td>Xpert® MTB/RIF</td>
<td>Cepheid Inc., Sunnyvale, CA, USA</td>
<td>RT-PCR</td>
<td>Smear-positive sputum</td>
<td>98.0 (98.0 to 99.0)</td>
<td>99.0 (99.0 to 99.0)</td>
<td>0.04</td>
<td>0.10</td>
<td>[13,14,23-28]</td>
</tr>
<tr>
<td>Xpert® MTB/RIF</td>
<td>Cepheid Inc., Sunnyvale, CA, USA</td>
<td>RT-PCR</td>
<td>Smear-negative sputum</td>
<td>75.0 (72.0 to 78.0)</td>
<td>99.0 (99.0 to 99.0)</td>
<td>0.04</td>
<td>0.10</td>
<td>[13,14,23-28]</td>
</tr>
</tbody>
</table>

*Sales of many of these commercial assays have now been discontinued.

NAAT, Nucleic acid amplification techniques; NLR, Negative likelihood ratio; PLR, Positive likelihood ratio.
Molecular diagnosis of TB

• Highly sensitive and specific

• Nucleic acid amplification tests:
  – Direct:
    • high sensitivity and specificity (95-95%)
    • Detect 1-10 organisms per ml
    • FDA approved for use on sputum but can be used on other samples
    • CSF sensitivity 59% and specificity 98%
    • E-MTD and AMPLICOR
  – Automated:
    • Gene Xpert
Gene xpert

- Revolution in TB diagnosis
- Results for resistance testing and diagnosis in 2hrs
- Since 2010 has been endorsed by WHO for the diagnosis of suspected MDRTB in HIV pts with TB
- 95% of mutations for rifampicin are in region of rpoB gene
- Mono-resistance to rifampicin is rare.
- Most RIF resistant strains are also INH resistance

- Sensitivity 73-84%
- Specificity 98%
## Xpert MTB/RIF- Pulmonary TB

<table>
<thead>
<tr>
<th>Country</th>
<th>Clinical population</th>
<th>Patient selection</th>
<th>Sensitivity of smear microscopy, % (95% CI)</th>
<th>Sensitivity of single Xpert MTB/RIF assay test, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of outpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehme et al, 2011</td>
<td>South Africa, Uganda, India, Peru, Azerbaijan, Philippines</td>
<td>Outpatients (HIV+ and HIV-) with cough ≥ 2 weeks</td>
<td>HIV+ : 44.6% (37.7–51.6); HIV- : 68.6% (63.5–73.3); p &lt; 0.001</td>
<td>HIV+ : 82.4% (76.7–86.9); HIV- : 90.7% (87.2–93.4); p &lt; 0.08</td>
</tr>
<tr>
<td>Theron et al, 2011</td>
<td>South Africa</td>
<td>Outpatients (HIV+ and HIV-)</td>
<td>HIV+ : 50.0% (36.1–63.9); p = 0.01</td>
<td>HIV+ : 69.6% (55.2–80.1); HIV- : 82.0% (73.4–89.6); p = 0.09</td>
</tr>
<tr>
<td>Scott et al, 2011</td>
<td>South Africa</td>
<td>Outpatients (mostly HIV+) with suspected TB with cough for ≥ 2 weeks</td>
<td>HIV+ : 54% (38–69)</td>
<td>HIV+ : 84% (69–93)</td>
</tr>
<tr>
<td>Lawn et al, 2011</td>
<td>South Africa</td>
<td>Outpatients (HIV+) enrolling in an antiretroviral treatment clinic</td>
<td>HIV+ : 22.2% (13.3–33.6)</td>
<td>HIV+ : 58.3% (46.1–69.8)</td>
</tr>
<tr>
<td><strong>Studies of hospital inpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Grady et al, 2012</td>
<td>Zambia</td>
<td>Hospital medical inpatient admissions (HIV+ and HIV-)</td>
<td>All who could produce sputum samples</td>
<td>HIV+ : 52.8% (45.1–60.4); HIV- : 68.6% (33.0–64.4); p = 0.71</td>
</tr>
<tr>
<td>Balcels et al, 2012</td>
<td>Chile</td>
<td>Hospital medical inpatients (HIV+)</td>
<td>Admission with suspected TB and symptoms &gt; 10 days</td>
<td>HIV+ : 66.7% (39.1–86.2)</td>
</tr>
<tr>
<td>Carrquiñy et al, 2012</td>
<td>Peru</td>
<td>Hospital medical inpatients (HIV+)</td>
<td>Admission with suspected TB and cough &gt; 10 days plus abnormal chest radiograph plus additional symptoms</td>
<td>HIV+ : 68.9% (54.3–80.6)</td>
</tr>
</tbody>
</table>

TB = tuberculosis. MTB = Mycobacterium tuberculosis. RIF = rifampicin.

Table 3: Studies assessing the diagnostic accuracy of the Xpert MTB/RIF assay compared with culture in patients with HIV investigated for pulmonary tuberculosis.
### Gene xpert on other specimens

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Comparison (No. of studies, No. of samples)</th>
<th>Median (%) pooled sensitivity (pooled 95% CrI)</th>
<th>Median (%) pooled specificity (pooled 95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node tissue and aspirate</td>
<td>Xpert MTB/RIF compared against culture (14 studies, 849 samples)</td>
<td>84.9 (72–92)</td>
<td>92.5 (80–97)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)</td>
<td>83.7 (74–90)</td>
<td>99.2 (88–100)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Xpert MTB/RIF compared against culture (16 studies, 709 samples)</td>
<td>79.5 (62–90)</td>
<td>98.6 (96–100)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)</td>
<td>55.5 (51–81)</td>
<td>98.8 (95–100)</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>Xpert MTB/RIF compared against culture (17 studies, 1385 samples)</td>
<td>43.7 (25–65)</td>
<td>98.1 (95–99)</td>
</tr>
<tr>
<td></td>
<td>Xpert MTB/RIF compared against a composite reference standard (7 studies, 698 samples)</td>
<td>17 (8–34)</td>
<td>99.9 (94–100)</td>
</tr>
<tr>
<td>Gastric lavage and aspirate</td>
<td>Xpert MTB/RIF compared against culture (12 studies, 1258 samples)</td>
<td>83.8 (66–93)</td>
<td>98.1 (92–100)</td>
</tr>
<tr>
<td>Other tissue samples</td>
<td>Xpert MTB/RIF compared against culture (12 studies, 699 samples)</td>
<td>81.2 (68–90)</td>
<td>98.1 (87–100)</td>
</tr>
</tbody>
</table>

Crl, credible interval; the CrI is the Bayesian equivalent of the confidence interval.
Gene Xpert

• Should be initial test in suspected MDRTB or HIV associated TB
• Can be used as an initial diagnostic test to diagnose TB
• Can be used as a follow on test for smear negative specimens in suspected TB
• Should be used in preference to conventional microscopy and culture as the initial test for CSF specimens in TB meningitis suspects
• Can be used on non respiratory specimens e.g lymph nodes, gastric aspirates.

WHO policy recommendations. 2013
THE GENEXPERT ALGORITHM

Gene Xpert

TB, Rif resistance
- Enroll on MDR regimen and ART if HIV +
  - DST FL, SL
  - If any resistance for injectable and/or FQ use XDR regimen
  - For PDR and mono-resistant TB, treat as per guidelines

TB, no R resistance
- Treat cat I, II (Offer HIV testing) Do DST for other FL drugs
  - If resistant refer to clinical team for treatment using the National

No TB detected
- X-ray, broad spectrum antibiotics, clinical condition
  - If no resistance continue Rx
  - SS follow up month 2/3 and 5
    - SS+ve
      - Culture & DST
    - SS-ve

Other diagnosis
- Culture and DST

Indications for GeneXpert

MDR TB Surveillance:
- All retreatment cases: a) Failures b) Relapses c) Return after default
- DR TB contacts
- Smear positive refugees
- Health Care workers with TB

TB Diagnosis:
- HIV positive Smear negative
- Diagnosis of TB in children
- TB screening for the symptomatic patients for and on IPT

Success
Other Molecular tests

• **Line probe assays**
  – Employ PCR/ hybridisation
  – Detect the most common mutations that confer drug resistance
  – Speciation
  – Results available after 5hrs
    • E.g. immunolipa: used on solid media culture, detects RIF resistance
  – Genotype MTBDRplus: used on solid or liquid media cultures. RIF/INH resistance
    • MDRTBsl: picks ethambutol, fluoroquinolones, aminoglycosides
  – Detect single nucleotide polymorphisms
Figure 13: Schematic representation of the three LPA procedures. The first procedure is DNA extraction, followed by amplification of genes with biotinylated primers. Then, the amplified DNA is hybridized to probes and the bands visually detected by means of a colour-forming enzymatic reaction involving streptavidin adhering to biotinylated primers.
## Table 2 Commercially available LPAs for TB detection in clinical specimens

<table>
<thead>
<tr>
<th>Assay</th>
<th>Manufacturer</th>
<th>Method</th>
<th>Material</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INNO-LiPA</td>
<td>InnoGenetics, Gent, Belgium</td>
<td>PCR amplification/hybridization</td>
<td>DNA from decontaminated smear-positive sputum</td>
<td>93.0 (92.0 to 94.0)</td>
<td>83.0 (81.0 to 85.0)</td>
</tr>
<tr>
<td>Rif.TB</td>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INNO-LiPA</td>
<td>InnoGenetics, Gent, Belgium</td>
<td>PCR amplification/hybridization</td>
<td>DNA from decontaminated smear-negative sputum</td>
<td>65.0 (58.0 to 71.0)</td>
<td>96.0 (94.0 to 97.0)</td>
</tr>
<tr>
<td>Rif.TB</td>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hain GT</td>
<td>Hain Lifescience GbmH, Nehren, Germany</td>
<td>PCR amplification/hybridization</td>
<td>DNA from decontaminated sputum</td>
<td>92.0 (90.0 to 94.0)</td>
<td>-</td>
</tr>
<tr>
<td>MTBDRplus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; LPA, line-probe assay.
Conjugate Control
Amplification Control
*M. tuberculosis* complex

*gyrA* Locus Control
*gyrA* wild type probe 1
*gyrA* wild type probe 2
*gyrA* wild type probe 3
*gyrA* mutation probe 1
*gyrA* mutation probe 2
*gyrA* mutation probe 3A
*gyrA* mutation probe 3B
*gyrA* mutation probe 3C
*gyrA* mutation probe 3D

*rrs* Locus Control
*rrs* wild type probe 1
*rrs* wild type probe 2
*rrs* wild type probe 3
*rrs* wild type probe 3
*rrs* mutation probe 1
*rrs* mutation probe 2

*embB* Locus Control
*embB* wild type probe 1
*embB* wild type probe 1A
*embB* wild type probe 1B
*embB* mutation probe 1A
*embB* mutation probe 1B

Colored marker

Resistance

FLQ + AG/CP + EMB
FLQ + EMB
FLQ + EMB
WHO analysis on line probe assays

- Pooled sensitivity >95% and specificity approaching 100%
- Sensitivity for detection of INH resistance: 90%
- Specificity for INH resistance 99%
- Sensitivity for RIF resistance 99%
- Specificity for RIF resistance: 97%
Urinary LAM

- Constituents of mycobacterial cell wall
- Constitutes 15% of wt of the bacterium
- Urine: easy to collect, children
- Non invasive test
- High negative predictive value to rule out TB in patients with advanced AIDS.
Urine LAM

- Massive diagnostic yield of HIV associated TB using rapid urine assays in South Africa
  - Observational study
  - Looking for improved methods of diagnosing TB in hospitalised patients
  - At autopsy many HIV patients had disseminated TB- missed diagnosis
  - HIV patients included in the study- 427pts
  - Sputum, blood and urine taken
  - 139 had TB
  - Urine xpert picked 59%, urine LAM 38.1%, sputum xpert 26.6%, aputum microscopy 19.4%
  - Rapid tests picked 69.1 % of cases and 85.1% in CD4<100
• Diagnostic accuracy of urinary LAM in HIV infected patients.
  – Nakanyingi et al.
  – Setting: Uganda, RSA
  – HIV+ with signs of TB
  – 1013 participants
  – Sensitivity: 53.7% CD4< 100 sensitivity 67.9%
  – Specificity 97.6%
  – Conclusion: urine LAM detected >50% of TB cases in CD4 <100
  – Sensitivity higher at lower CD4.
Sensitivity (%) of TB Diagnostic Methods in HIV-TB co-infected patients

- Alere Determine TB LAM Ag
- Sputum smear microscopy
- Xpert MTB/RIF

<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>Alere Determine TB LAM Ag</th>
<th>Sputum smear microscopy</th>
<th>Xpert MTB/RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 200</td>
<td>4.0%</td>
<td>24.0%</td>
<td>44.0%</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>24.0%</td>
<td>39.0%</td>
<td>45.7%</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>30.5%</td>
<td>30.5%</td>
<td>34.8%</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>71.7%</td>
<td>71.7%</td>
<td>51.7%</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>75.9%</td>
<td>75.9%</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

Sensitivity (%) of TB Diagnostic Methods in HIV-TB co-infected patients.
SEROLOGICAL TESTS for TB

• WHO policy statement:
• Strongly recommends against the use of serological tests.
• Mostly used in India and other countries where weak regulatory authorities
• For @ case of correctly diagnosed TB there are 6 false positives
• Cost per test is 30 dollars
• WHO metanalysis
• Reviewed 67 studies
• 32 from low and middle income countries
• Sensitivity: 1-60%
• Specificity: 53 – 99%
• Low sensitivity: missed diagnosis
• Low specificity: false positives
<table>
<thead>
<tr>
<th>Company</th>
<th>Kit</th>
<th>Assay technique</th>
<th>Sensitivity &amp; Specificity from package insert</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anda Biologica, Strasbourg, France</td>
<td>anda-TB ELISA</td>
<td>ELISA</td>
<td>not listed, refers to publications</td>
<td><a href="http://www.andabiologica.com">http://www.andabiologica.com</a></td>
</tr>
<tr>
<td>Omega Diagnostics, Alva, Scotland</td>
<td>Pathozyme TB Complex Plus</td>
<td>ELISA</td>
<td>37 &amp; 100%</td>
<td><a href="http://www.omegadiagnostics.com">http://www.omegadiagnostics.com</a></td>
</tr>
<tr>
<td>Tulip Group, Goa</td>
<td>Qualisa TB</td>
<td>ELISA</td>
<td>100 &amp; 99%</td>
<td><a href="http://www.tulipgroup.com">http://www.tulipgroup.com</a></td>
</tr>
<tr>
<td>Tulip Group, Goa</td>
<td>Serocheck-MTB</td>
<td>Rapid</td>
<td>100 &amp; 99%</td>
<td><a href="http://www.tulipgroup.com">http://www.tulipgroup.com</a></td>
</tr>
<tr>
<td>Span Diagnostics, Surat</td>
<td>TB Spot Ver 2.0</td>
<td>Rapid</td>
<td>80 &amp; 99%</td>
<td><a href="http://www.span.co.in">http://www.span.co.in</a></td>
</tr>
<tr>
<td>Span Diagnostics, Surat</td>
<td>Mycowell</td>
<td>ELISA</td>
<td>94 &amp; 97%</td>
<td><a href="http://www.span.co.in">http://www.span.co.in</a></td>
</tr>
<tr>
<td>J Mitra, New Delhi</td>
<td>TB IgG, IgM, IgA ELISA</td>
<td>ELISA</td>
<td>80 &amp; 97%</td>
<td><a href="http://www.jmitra.co.in">http://www.jmitra.co.in</a></td>
</tr>
<tr>
<td>Bisen Biotech, Gwalior</td>
<td>TB SCREEN TEST</td>
<td>Rapid</td>
<td>94 &amp; 98%</td>
<td><a href="http://www.bisenbiotechindia.com">http://www.bisenbiotechindia.com</a></td>
</tr>
<tr>
<td>Lab Care Diagnostics Pvt Ltd, Sarigam</td>
<td>Accucare Rapid TB Test</td>
<td>Rapid</td>
<td>&gt;80% sensitivity and specificity</td>
<td><a href="http://www.labcarediagnostics.com/RapidTest_sub.html">http://www.labcarediagnostics.com/RapidTest_sub.html</a></td>
</tr>
<tr>
<td>Tashima Inc, Bangalore</td>
<td>TB IgG/IgM 3 Line Rapid Test</td>
<td>Rapid</td>
<td>93 &amp; 100%</td>
<td><a href="http://www.tashima.net">http://www.tashima.net</a></td>
</tr>
</tbody>
</table>

Source: Ref. 13
<table>
<thead>
<tr>
<th>Form of tuberculosis</th>
<th>Type of test (Number of studies, datasets, or tests evaluated)</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Commercial (7)*</td>
<td>DOR = 6.35 (95% CI 0.59, 67.98) with associated sensitivity of 34%</td>
<td>Dinnes et al\textsuperscript{15}</td>
</tr>
<tr>
<td></td>
<td>In-house (1)*</td>
<td>DOR = 1.77 (95% CI 0.44, 7.10) with associated sensitivity of 25%</td>
<td></td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>Commercial (4)</td>
<td>DOR = 9.30 (95% CI 2.27, 38.18) with associated sensitivity of 43%; DOR = 11.60 (95% CI 0.00, 201,005.99) with associated sensitivity of 73%</td>
<td>Dinnes et al\textsuperscript{15}</td>
</tr>
<tr>
<td></td>
<td>In-house (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Commercial (68)</td>
<td>Sensitivity (10 to 90%) and specificity (47 to 100%) were inconsistent</td>
<td>Steingart et al\textsuperscript{16}</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>Commercial (21)</td>
<td>Sensitivity (0 to 100%) and specificity (59 to 100%) were inconsistent</td>
<td>Steingart et al\textsuperscript{17}</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Rapid commercial tests (19 tests)</td>
<td>Sensitivity (1 to 60%) and specificity (53 to 99%) were inconsistent; test performance was diminished in HIV-infected individuals</td>
<td>WHO/TDR (Report)\textsuperscript{19}</td>
</tr>
<tr>
<td></td>
<td>In-house (254)</td>
<td>Candidate antigens for an antibody detection-based test in HIV-infected and non-infected persons were identified: recombinant malate synthase [Rv1837c; pooled sensitivity 73% (95% CI 58, 85)] and Tbf6 plus DPEP multiple antigen [pooled sensitivity 75% (95% CI 50, 91)]; protein antigens achieved high specificities; multiple antigens provided higher sensitivities than single antigens</td>
<td>Steingart et al\textsuperscript{18}</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Commercial (67)</td>
<td>Sensitivity (0 to 100%) and specificity (31 to 100%) were inconsistent</td>
<td>Steingart et al\textsuperscript{20}</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>Commercial (25)</td>
<td>Sensitivity (0 to 100%) and specificity (59 to 100%) were inconsistent</td>
<td>Steingart et al\textsuperscript{20}</td>
</tr>
</tbody>
</table>

*Includes studies meeting at least two design-related criteria. WHO/TDR, WHO Special Programme for Research and Training in Tropical Diseases; DOR, Diagnostic odds ratio.
Other molecular tests

• Assays for antigens:
  – Ag 85: a structural component of TB, ELISA using anti AG 85 antibodies done on liquid culture for earlier diagnosis
  – MPT64: a structural protein

• Gene sequencing:
  – Direct detection of DNA in samples such as sputums
  – Rapid test, can distinguish species

• PCR for TB:
  – Can be done on histology specimens preserved with formalin
  – 100% sensitive and 93% specific
Adjuncts

- Pleural fluid: adenosine deaminase, interferon gamma and lysozyme
  - Ada is the most useful
  - Sensitivity and specificity depend on levels
  - False negatives: lung cancer, empyema, parapneumonic effusion

- Tubulostearic Acid:
  - A structural component of mycobacteria
  - Rapid sensitive and specific test for TB
  - Used on sputum, bronchial aspirates and CSF
  - Can be used for retrospective diagnosis of TB meningitis in patients already on Rx. Remains positive upto 8mths
# Performance Summary Molecular Tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleic acid amplification tests</td>
<td>93% [42] (AMTD/Amplicor)</td>
<td>84%</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>73%–90% [44] (smear – specimens)</td>
<td>98%</td>
</tr>
<tr>
<td>Line-probe assay for DST</td>
<td>99% [72] (RIF) 99% (INH)</td>
<td>99% 100%</td>
</tr>
<tr>
<td>LAMP</td>
<td>49%–98% [45]</td>
<td>99%</td>
</tr>
<tr>
<td>Serology</td>
<td>10%–90% [73]</td>
<td>47%–100%</td>
</tr>
<tr>
<td>Urine Ag (LAM)</td>
<td>0%–85% [47–49]</td>
<td>94%–100%</td>
</tr>
</tbody>
</table>
conclusion

• Chest x-rays and clinical symptoms are screening tests for active TB shouldn’t be used for diagnosis
• Sputum smear has low sensitivity and specificity, culture is the GOLD standard
• Actively screen at risk patients for Latent TB.
• Early case finding as opposed to passive case finding to reduce burden of TB.
• Kenyatta Diagnostic tests available:
  – Fluorescent microscopy
  – Culture: LJ and BACTEC
  – Line probe assays
  – Gene xpert
  – ALL FREE
• Thank you!
Acknowledgements

• Dr. A. Sheikh
• Members of the Department
• My colleagues
• “If the importance of a disease for mankind is measured from the number of fatalities which are due to it, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. Statistics have shown that 1 in 7 of all humans die of TB.”

— Robert Koch