Novel Tools for the Detection of Active TB and Drug Resistance

TB Diagnostics Symposium
Ontario Agency for Health Protection and Promotion
Toronto, Ontario
October 8th, 2009

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PGY-5 Medical Microbiology
MSc Epidemiology
McGill University, Montreal, QC
Global TB Case Detection

- 2.6 million new smear + cases notified in 2007
- 64% of the estimated 4.1 million cases

- 5.3 million new cases overall notified in 2007
- 57% of the estimated 9.3 million cases

WHO Report 2009 – Global Tuberculosis Control
Conclusions:
- Highest rates ever recorded of MDR-TB
- Highest rates are in countries of the former Soviet Union and China
- Severely limited laboratory capacity has meant limited data availability in Africa
- Insufficient efforts in many areas of the world to treat and control MDR-TB
- Equipment to rapidly diagnose MDR-TB in 1 week instead of 3 months exists but most patients cannot access such services
- XDR-TB in 45 countries threatens to derail 10 years of progress in TB control and HIV management
- Extraordinary measures are needed in Eastern Europe: rapid detection, effective care, access to drugs
Microscopy 1882

Culture 1882

Chest X-ray 1896

Thanks to a resurgence of interest (along with massive funding)
... and advances in basic science

- Omics (genomics, proteomics, etc)
- Immunology
- Molecular Biology
- Biotechnology
- Nanotechnology
There is now a promising diagnostics pipeline

M. tuberculosis → Human host → Replication of M. tuberculosis → Immune response to M. tuberculosis

- Antigen detection tests (e.g., LAM, ELISA urinary antigen test, sputum antigen detection)
- Microscopic visualization of bacteria (e.g., LED microscopy, bleach microscopy)
- Culture-based growth detection tests (e.g., MODS, thin-layer agar, phage-based tests, colorimetric media)
- Nucleic acid amplification tests (e.g., LAMP, Xpert MTB, Transrenal DNA detection, Genotype MTBDRPlus)
- Volatile organic compounds (VOC) detection (e.g., E-Nose, biosensors)
- Cellular immune response: IFNγ assays (e.g., QuantiFERON-TB Gold, T-SPOT.TB), rd ESAT-6 skin test
- Humoral immune response: Antibody detection tests (e.g., serological tests)

Technology needs for Patient-Centered Care

Reference Lab
- Surveillance
- LJ - 40d
- Auto. LC 15d
- Manual 15d
- LPA 1d

Fraction of patients seen
- 5%
- 10%

Regional Lab

Peripheral Lab
- Smear - 60%
- LED +10%
- Manual NAAT +25%
- Auto NAAT +40%

Clinic / Health Post

Symptoms
- AG/AB
- Molecular
- VOC

Source: Foundation for Innovative New Diagnostics (FIND)
NEW TECHNOLOGIES
Smear Microscopy

- Simple, cheap
- High specificity
- Poor sensitivity
  - Especially with HIV coinfection
  - Especially with extrapulmonary TB
Optimizing Smear Microscopy

Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review

Karen R Steingart, Megan Henry, Vivienne Ng, Philip C Hopewell, Andrew Ramsay, Jane Cunningham, Richard Urbanczik, Mark Perkins, Mohamed Abdel Aziz, Madhukar Pait

Lancet Infect Dis 2006

Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review

Karen R Steingart, Vivienne Ng, Megan Henry, Philip C Hopewell, Andrew Ramsay, Jane Cunningham, Richard Urbanczik, Mark D Perkins, Mohamed Abdel Aziz, Madhukar Pait

Lancet Infect Dis 2006

Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review

S. R. Mase,*† A. Ramsay,* V. Ng,* M. Henry,*† P. C. Hopewell,*† J. Cunningham,*† R. Urbanczik,‡ M. D. Perkins,** M. A. Aziz,** M. Pai††

IJTLD 2007
New Policies on Smear Microscopy

Definition of a new sputum smear-positive TB case

The revised definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system.

Reduction of number of smears for the diagnosis of pulmonary TB

WHO recommends the number of specimens to be examined for screening of TB cases can be reduced from three to two, in places where a well-functioning external quality assurance (EQA) system exists, where the workload is very high and human resources are limited.

Front Loaded Specimen Collection?
Sputum Processing?
LED Fluorescent Microscopy?

Fluorescent LED Microscopy

- Higher Sensitivity than ZN (and possibly conventional FM)
- 46% time savings vs. ZN (equivalent to conventional FM)
- Advantages of FM but less expensive, requires less maintenance, no need for a dark room

Minion et al. unpublished
# Commercial LED Microscopes

## Table 1. Comparison of commercial light-emitting diode products currently available for TB diagnostics.

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Standalone microscope</th>
<th>Attachment</th>
<th>Light transmission</th>
<th>Battery powered</th>
<th>Weight (kg)</th>
<th>Cost (US $)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primo Star iLED</td>
<td>Carl Zeiss, Oberkochen, Germany</td>
<td>Yes</td>
<td>NA</td>
<td>Epifluorescent</td>
<td>Yes</td>
<td>9.5</td>
<td>4825</td>
<td>[101]</td>
</tr>
<tr>
<td>Lumin™</td>
<td>LW Scientific, Lawrenceville, GA, USA</td>
<td>No</td>
<td>Objective lens replacement (20, 40, 60 and 100× oil)</td>
<td>Epifluorescent</td>
<td>Yes</td>
<td>0.448</td>
<td>700–2000</td>
<td>[102]</td>
</tr>
<tr>
<td>ParaLens</td>
<td>QBC™ Diagnostics, Philadelphia, PA, USA</td>
<td>No</td>
<td>Objective lens replacement (40, 60 and 100× oil)</td>
<td>Epifluorescent</td>
<td>Yes</td>
<td>1.27</td>
<td>995</td>
<td>[103]</td>
</tr>
<tr>
<td>FlucoLED</td>
<td>Fraen Corporation Srl, Settimo, Milanese, Italy</td>
<td>No</td>
<td>Adaptor attached to base and filter installed on head of microscope</td>
<td>Transfluorescent</td>
<td>Yes</td>
<td>5</td>
<td>1977–3530*</td>
<td>[104]</td>
</tr>
<tr>
<td>CyScope®</td>
<td>Partec, Gorlitz, Germany</td>
<td>Yes</td>
<td>NA</td>
<td>Epifluorescent</td>
<td>Yes</td>
<td>2.7</td>
<td>2372–3699*</td>
<td>[105]</td>
</tr>
</tbody>
</table>

Challenges for current EQA program

Current External Lab QA program involves sending selected slides into SNRL for rechecking quarterly.

Auramine-stained slides will be faded and unreliable.

Minion, et al. unpublished
Other Potential Innovations

Mobile Phone Based Clinical Microscopy for Global Health Applications

David N. Breslauer¹,², Robi N. Maamari²,³, Neil A. Switz³, Wilbur A. Lam²,⁴, Daniel A. Fletcher¹,²,³

¹ UCSP/UC Berkeley Bioengineering Graduate Group, ² Department of Bioengineering, University of California Berkeley, Berkeley, California, United States of America, ³ Biophysics Graduate Group, University of California Berkeley, Berkeley California, United States of America, ⁴ Department of Pediatrics, University of California San Francisco, San Francisco, California, United States of America

Image processing techniques for identifying *Mycobacterium tuberculosis* in Ziehl-Neelsen stains

P. Sadaphal,⁎⁎ J. Rao,⁎ G. W. Comstock,⁎⁎ M. F. Beg⁎

⁎ Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, ‡ University Research Co., LLC, Bethesda, Maryland, USA; † School of Engineering Science, Simon Fraser University, Burnaby, British Columbia, Canada
Culture

- High Sensitivity
- Slow Turnaround Time, Expensive, Biosafety concerns
- Push towards liquid culture systems
  - Partly driven by HIV epidemic
  - Improves some problems while exacerbating others
New Policies on Culture-based Diagnostics

The use of liquid medium for culture and DST

WHO recommends, as a step-wise approach:

1. The use of liquid medium for culture and DST in middle-and low-income countries.
2. The rapid species identification to address the needs for culture and drug susceptibility testing (DST).

Taking into consideration that liquid systems will be implemented in a phased manner, integrated into a country specific comprehensive plan for laboratory capacity strengthening and addressing the following key issues:

1. Appropriate biosafety level;
2. detailed customer plan describing guarantees and commitments of the manufacturer;
3. appropriate training of staff;
4. maintenance of infrastructure and equipment in laboratories;
5. quick transportation of samples from the peripheral to the culture laboratory;
6. rapid communication of results.
FIND prices for BACTEC and MGIT and Country List

Enhancement of diagnostic capacity for TB and MDR-TB is urgently needed to scale-up access to care and treatment of MDR-TB. To help meet this challenge, FIND has collaborated in the development and evaluation of new TB diagnostic tools, including TB liquid culture and DST, rapid species identification, and line probe assay. WHO has officially endorsed the use of these technologies based on the thorough evaluation of the evidence of their effectiveness under actual program conditions. As part of its role in the development and evaluation process of these tools, FIND has successfully negotiated with three of the manufacturing partners to obtain significant price reductions in order to facilitate access to these diagnostic technologies. These discounts average 50% on diagnostic instruments, and 75% on reagents, and are available to high TB burden countries that wish to procure TB diagnostics for use in the public and non-profit health care sectors, and who procure these tools with funding from the government, UNITAID, or the Global Fund. Furthermore, the FIND-negotiated agreements contain provisions for further discounts as procurement volumes of reagents increase. As these become available FIND shall communicate the new prices to the TB community. In the case of the BBL MGIT Tubes List Nr. 245122 below, it is expected that price shall be reduced in the second quarter of 2009.

Current FIND-negotiated prices, along with the list of countries eligible for the discounts, as negotiated by FIND with BD are listed below:

<table>
<thead>
<tr>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD BACTEC™ MGIT™ 960 System</td>
<td>USD 38,950.00</td>
</tr>
<tr>
<td>BBL MGIT Tubes List Nr. 245122 Reagents</td>
<td>USD 205.00/100</td>
</tr>
</tbody>
</table>
New Policies on Culture-based Diagnostics

- MODS?
- TLA? 2009
- NRA?
- CRI?
- Phage?
Microscopically Observed Drug Susceptibility (MODS)

- Direct inoculation of patient specimens – detection & DST
- Liquid culture – more sensitive than LJ
- Microcolony detection – faster turnaround time
- Biosafety?
- Specificity of ID?
Thin Layer Agar (TLA)

- Direct inoculation of patient specimens – detection & DST
- Solid media – easier to manipulate
- Microcolony detection – faster turnaround time
- Biosafety?
- Specificity of ID?
Nitrate Reductase Assay (NRA)

- Based on MTB’s ability to reduce nitrate to nitrite
- Simple
- Sensitive detection of small amount of metabolic biproduct improves turnaround time
- Prevalence of nitrate reductase negative strains of MTB?

KNO$_3$ - containing media

Add reagent to drug-free slant day 7 (repeat day 10, 14)

Color development = growth
Colorimetric Redox Indicators (CRI)

- Based on reduction of indicator by growing MTB
- MIC determination using microdilution
- Detection of active metabolism improves turnaround time
- Biosafety concerns?
- Suitable for reference labs?

Incubate microdilution plate 7 days

Add indicator to all wells, incubate overnight

Color change = growth
Mycobacteriophage Assays (FASTPlaque™)

- Based on amplification of phage viruses in live MTB
- 2 day turnaround for detection & DST
- Minimal biosafety concerns
- BUT ...
- High rates of contaminated or uninterpretable tests
- High rate of false positives
### GRADE Summary Table – Novel Culture Methods

<table>
<thead>
<tr>
<th>Diagnostic (Reference)</th>
<th># Studies (# Participants)</th>
<th>Pooled Accuracy Estimates from Meta-Analyses</th>
<th>Sens</th>
<th>Spec</th>
<th>Turnaround Time</th>
<th>Contamination Rates</th>
<th>Quality of Evidence</th>
<th>Costs</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODS (1)</td>
<td>9 studies (1474 participants)</td>
<td>0.980 0.994</td>
<td>11.6 days</td>
<td>6.3%</td>
<td>Moderate</td>
<td>Equipment: ++ Consumables: ++</td>
<td>Training: extensive Infrastructure: ++/+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLA (1)</td>
<td>3 studies (439 participants)</td>
<td>1.00 1.00</td>
<td>11.1 days</td>
<td>11.8%</td>
<td>Low</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: extensive Infrastructure: ++/+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phage – FASTPlaque (2)</td>
<td>12 studies (2945 participants)</td>
<td>0.950 0.953</td>
<td>1 – 2 days</td>
<td>20.4%</td>
<td>Very Low</td>
<td>Equipment: ++ Consumables: +++</td>
<td>Training: moderate Infrastructure: ++/+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRI (3)</td>
<td>31 studies (2498 participants)</td>
<td>0.980 0.990</td>
<td>7 – 14 days</td>
<td>5%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: extensive Infrastructure: +++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRA (4)</td>
<td>19 studies (2304 participants)</td>
<td>0.970 1.00</td>
<td>9 days</td>
<td>4.8%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: moderate Infrastructure: ++/+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WHO-endorsed rapid test for DST (for comparison)**

| LPA (5)                | 12 studies (4937 participants) | 0.981 0.987 | 1 – 2 days | Moderate | Equipment: +++ Consumables: +++ | Training: moderate Infrastructure: ++/+++ |

Minion et al. unpublished
MDR-XDRTB Color Test for Regional Laboratories*

1. **Liquefaction & decontamination in transport medium at room temperature**

2. **Direct application of 2 drops to selective thin layer agar for incubation in room air for MDRTB testing & XDRTB screening**

3. **Color growth detection & microscopy confirmation of morphology**

![Image of Petri dishes with different color patterns]

Biosafety similar to sputum microscopy because sputum is smeared directly onto the plate which is then permanently double-sealed until autoclaving.

*Carlton Evans, Welcome Trust, Peru*
NAAT

- High specificity and PPV

- Sensitivity is lower and highly variable
  - Especially in extrapulmonary
  - Especially in smear negative – reduced utility in HIV+

- Expensive – limited applicability in developing countries
Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis

Madhukar Pai, Laura L Flores, Nitika Pai, Alan Hubbard, Lee W Riley, and John M Colford Jr

Nucleic acid amplification tests for the diagnosis of tuberculous lymphadenitis: a systematic review

P. Daley, S. Thomas, M. Pai
* Christian Medical College, Vellore, India; † McGill University, Montreal, Quebec, Canada

Commercial Nucleic-Acid Amplification Tests for Diagnosis of Pulmonary Tuberculosis in Respiratory Specimens: Meta-Analysis and Meta-Regression

Daphne L. Ling, Laura L. Flores, Lee W. Riley, Madhukar Pai
1 Division of Epidemiology, School of Public Health, University of California, Berkeley, Califomia, United States of America, 2 Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, San Francisco, California, United States of America, 3 Division of Infectious Diseases, School of Public Health, University of California, Berkeley, Califomia, United States of America, 4 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
2009 Updated CDC Guidelines

Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

Updated Recommendation

NAA testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities. The following testing and interpretation algorithm is proposed.
Line Probe Assays

- Detection of MTB & RIF-resistance ($rpoB$)
- Requires extraction, amplification
- Colorimetric development using immobilized probes
- Expensive
- Feasible in peripheral settings?

Inno-LiPA Rif.TB assay
Innogenetics, Belgium

GenoType MTBDRplus assay
Hain Lifescience GmbH, Germany
New Policy on Line Probe Assays

WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis

D.I. Ling*, A.A. Zwerling* and M. Pai*

Rapid diagnosis of drug-resistant TB using line probe assays: from evidence to policy

Daphne I Ling, Alice A Zwerling and Madhukar Pai*
Expanding and accelerating access to diagnostics for patients at risk of MDR-TB

Description of the project

A. Project title: Expanding and accelerating access to diagnostics for patients at risk of multi-drug resistant tuberculosis (MDR-TB)
B. Timeframe: Project duration: 2009-2011, starting on the date of the final signature of the Memorandum of Agreement.
C. Amount committed by UNITAID: US$ 26 129 897
D. Lead partner: Global Laboratory Initiative (GLI), Stop TB Department, World Health Organization
E. Other partner(s): Global Drug Facility (GDF), Stop TB Partnership, World Health Organization
   - Foundation for Innovative New Diagnostics (FIND)
Loop Mediated Isothermal Amplification (LAMP)

- Simplified NAAT, does not require a thermocycler, detection by fluorescence
- Rapid (1 hour)  
  High throughput
- Sensitivity 97%, Specificity 99%  
  (culture reference)
- Feasible in high burden settings?

Eiken Chemical Co., Tokyo, Japan
GeneXpert® MTB/RIF Test

Workflow
• sputum
• simple 1-step external sample prep. procedure
• time-to-result < 2 h
• throughput: ≥ 16 tests / day / module
• no need for biosafety cabinet
• integrated controls
• true random access

Performance
• specific for MTB
• sensitivity better than smear, similar to culture
• detection of rif-resistance via rpoB gene

Product and System Design
• test cartridges for GeneXpert System
• several GeneXpert modules can be combined in 1 workstation
• swap replacement of detection unit
• ~1 day technician training for non-mycobacteriologists
Serology

- Attractive ... especially if point of care (POC) option
- >80 antigenic targets evaluated and several commercial assays developed
- All existing serologic tests have failed to demonstrate adequate accuracy
  - Although still marketed and sold by many companies and used in developing countries!

A systematic review of commercial serological antibody detection tests for the diagnosis of extrapulmonary tuberculosis
Karen R Steingart, Megan Henry, Suman Laal, Philip C Hopewell, Andrew Ramsay, Dick Menzies, Jane Cunningham, Karin Weldingh, Madhukar Pai
Thorax 2007

Commercial Serological Antibody Detection Tests for the Diagnosis of Pulmonary Tuberculosis: A Systematic Review
Karen R. Steingart, Megan Henry, Suman Laal, Philip C. Hopewell, Andrew Ramsay, Dick Menzies, Jane Cunningham, Karin Weldingh, Madhukar Pai
PLoS Medicine 2007

Performance of Purified Antigens for Serodiagnosis of Pulmonary Tuberculosis: a Meta-Analysis
Clin Vaccine Immunol 2009
WHO/TDR evaluation of 19 commercial serologic tests for TB: poor accuracy

Figure 4. ROC curve of commercial rapid tests for the diagnosis of pulmonary tuberculosis (all patients, n=355)

Antigen Detection

- **Urinary Lipoarabinomannan (LAM)**
  - ELISA-based test
  - Clearview™ TB (Inverness, UK)
  - Optimal specimen, rapid turnaround (2.5 hrs)
  - Potential for POC “dipstick”

- Initially evaluations were promising
  - Boehme et al. 2005: 80% sensitivity; 99% specificity

- **BUT ...**

- Subsequent studies have failed to demonstrate similar performance

- Indicated for HIV+?
- Improved sensitivity with low CD4?
Disappointing LAM performance

Minion et al. Unpublished
Challenges for diagnostic research – Avoiding Optimism Bias

- Inappropriate study designs
- Inappropriate study populations
- Transferability and Reliability
- Selective reporting of results
- Unjustified positive conclusions
- Publication Bias
- Rapid licencing, commercialization and marketing of tests before adequate evaluation
If exposure and disease are not associated

False positive study

Hot topic Bias Publication Bias

100 studies will be designed

If $\alpha = 0.05$

5 studies show false positive results

Positive results bias

5 studies will be published

Likely to be meta-analyzed

THE FALSE POSITIVE RESEARCH CYCLE

(Choi, 1998)

Courtesy: Bernard Choi, PHAC
Challenges for diagnostic research – Ensuring Quality

- Bias due to inappropriate reference standards
- Spectrum bias
- Verification bias
  - Partial verification
  - Differential verification
- Review bias (lack of blinding)
- Incorporation bias
Towards Complete and Accurate Reporting of Studies of Diagnostic Accuracy: The STARD Initiative

Patrick M. Bossuyt,1* Johannes B. Reitsma,1 David E. Bruns,2,3 Constantine A. Gatsonis,4 Paul P. Glasziou,5 Les M. Irwig,6 Jeroen G. Lijmer,1 David Moher,7 Drummond Rennie,8,9 and Henrica C.W. de Vet,10 for the STARD Group

APPENDIX 1 | STANDARDS FOR REPORTING OF DIAGNOSTIC ACCURACY (STARD) CHECKLIST

Section and topic

<table>
<thead>
<tr>
<th>Item #</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
</tr>
<tr>
<td>2.</td>
<td>Were selection criteria clearly described?</td>
</tr>
<tr>
<td>3.</td>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>4.</td>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests (disease progression bias)</td>
</tr>
<tr>
<td>5.</td>
<td>Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnostic accuracy? (partial verification bias)</td>
</tr>
<tr>
<td>6.</td>
<td>Did patients receive the same reference standard regardless of the index test result? (differential verification bias)</td>
</tr>
<tr>
<td>7.</td>
<td>Was the reference standard independent of the index test? (i.e. the index test did not form part of the reference standard)? (incorporation bias)</td>
</tr>
<tr>
<td>8.</td>
<td>Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
</tr>
<tr>
<td>9.</td>
<td>Were the index test results interpreted without knowledge of the results of the reference standard? (test review bias)</td>
</tr>
<tr>
<td>10.</td>
<td>Were the reference standard results interpreted without knowledge of the results of the index test? (diagnostic review bias)</td>
</tr>
<tr>
<td>11.</td>
<td>Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (clinical review bias)</td>
</tr>
<tr>
<td>12.</td>
<td>Were uninterpretable/intermediate test results reported?</td>
</tr>
<tr>
<td>13.</td>
<td>Were withdrawals from the study explained?</td>
</tr>
</tbody>
</table>
Challenges for diagnostic research – Moving Beyond Accuracy

- “accuracy is a surrogate for patient-important outcomes”
- Results in low quality evidence for policy recommendations
Blueprint for new diagnostics development

- Demonstration of test accuracy will not be enough

Stop TB Partnership’s New Diagnostic Working Group 2009
Stop TB Research Movement
Landscape of TB Diagnostic Research: PRELIMINARY RESULTS

Majority of TB diagnostic studies are focused on accuracy

Abstracts included in the preliminary results
3922

Abstracts available
3230 (82%)

Original Study
3129 (97%)

Abstracts excluded: No abstract available
692 (18%)

Abstracts excluded: Not original study
101 (3%)

1. Underpinning Research
   - Biological
     - 272 (91%)
     - 319 (31%)
   - Aetiology
     - 1028 (33%)
     - 195 (19%)
   - Prevention of Disease and Conditions, and Promotion of Well-Being
     - 120 (4%)

2. Aetiology
   - 1028 (33%)
   - Biological
     - 319 (31%)
   - Environmental
     - 402 (39%)
   - Psychological, social, economic
     - 65 (6%)
   - Distribution
     - 11 (9%)
   - Methodology
     - 49 (5%)
   - Resources
     - 2 (0.2%)

3. Prevention of Disease and Conditions, and Promotion of Well-Being
   - Behaviour
     - 0 (0%)
   - Environmental
     - 11 (9%)
   - Nutrition, Chemoprevention
     - 0 (0%)
   - Vaccines
     - 109 (91%)
   - Resources
     - 0 (0%)

4. Detection, Screening and Diagnosis
   - 420 (13%)
   - Preclinical
     - 32 (8%)
   - Evaluation
     - 372 (89%)
   - Impact
     - 4 (1%)
   - Population Screening
     - 2 (0.5%)
   - Resources
     - 2 (0.5%)
   - Cost
     - 8 (2%)

5. Development of Treatments and Therapeutic Interventions
   - 202 (7%)

6. Evaluation of Treatments and Therapeutic Interventions
   - 162 (5%)

7. Management Of Diseases and Conditions
   - 232 (7%)
   - Individual care needs
     - 96 (41%)
   - End of life Care
     - 1 (1%)
   - Management
     - 133 (57%)
   - Resources
     - 2 (1%)

8. Health and Social Care Services Research
   - 104 (3%)
   - Organisation Delivery of Services
     - 54 (52%)
   - Health, welfare Economics
     - 15 (14%)
   - Policy, ethics Research Governance
     - 34 (33%)
   - Methodology
     - 1 (1%)
   - Resources
     - 0 (0%)

9. Case Reports or Case Series
   - 559 (18%)
In conclusion, much progress has been made in improving diagnosis but...
Are we close to the big goal of a simple point of care test?
What specifications should a POC test for TB have?

<table>
<thead>
<tr>
<th>Test Specification</th>
<th>Minimum Required Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical decision</td>
<td>Treatment initiation</td>
</tr>
</tbody>
</table>
| Sensitivity – Adults (for pulmonary TB only; regardless of HIV status) | Pulmonary TB:  
- 95% for smear positive, culture positive  
- (60-70)% for smear negative, culture positive  
[Detection of EP-TB being a preferred but not minimal requirement] |
| Sensitivity – Children (including EP-TB; regardless of HIV status) |  
- 80% compared to culture of any specimen  
- 60% of probable TB (noting problem of lack of a gold standard) |
| Specificity – adults | 95% compared to culture |
| Specificity – children | 95% compared to culture  
- 90% for culture-negative probable TB (noting problem of lack of a gold standard) |
| Time to results | 3 hours max. (patient must receive results the same day)  
[Depletable would be a solution] |
| Throughput | 20 tests/day, minimum, by 1 lab staff |
| Specimen type | Adult: urine, oral, breath, venous blood, sputum  
[Recommended: NSG/rapid-spot sample type and use of finger prick instead of venous blood]  
Children: urine, oral, capillary blood (finger/heel prick) |
| Sample preparation | 3 steps max.  
- Safe: biosafety level 1  
- Ability to use approximate volumes (i.e., no need for precise pipetting)  
- Preparation that is not highly time sensitive |
| Number of samples | One sample per test |
| Readout | Easy-to-read, unambiguous, simple “yes”, “no”, or “invalid” answer  
- Readable for at least 1 hour |
| Waste disposal | Simple burning or sharps disposal; no glass component  
- Environmentally acceptable disposal |
| Controls | Positive control included in test kit  
- Quality control simpler and easier than with SSM |
| Reagents | All reagents in self-contained kit  
- Kit contains sample collection device and water (if needed) |
| Storage/stability | Shelf life of 24 months, including reagents  
- Stable at 30°C, and at higher temperatures for shorter time periods (to be defined)  
- Stable in high humidity environments |
| Instrumentation | If instrument needed, no maintenance required  
- Instrument works in tropical conditions  
- Acceptable replacement cost  
- Fits in backpack  
- Shock resistant |
| Power requirement | Can work on battery |
| Training | 1 day max. training time  
- Can be performed by any health worker |
| Cost | <US$10 per test after scale-up  
*Consensus could not be reached on a definite minimum value.*
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SpaceShipOne wins $10 million X Prize
Flight also bests X-15 altitude record

Google Lunar X PRIZE

Archon X PRIZE for Genomics

Progressive Automotive X PRIZE
X Prize May be Announced for a TB Diagnostic Test!

X PRIZE Foundation to Help Fight Tuberculosis Worldwide with Gates Foundation Support

Gates Foundation providing grant to explore prize for innovative breakthroughs in TB Diagnostics

OCTOBER 16, 2008, PLAYA VISTA, Calif. – The X PRIZE Foundation has received a planning grant from the Bill & Melinda Gates Foundation to develop an X PRIZE for effective diagnosis of tuberculosis in the developing world. The overall goal of the prize will be to promote better management of the world’s second most lethal infectious disease. Innovation will need to be tailored for the use in underdeveloped regions, where over 50% of tuberculosis patients have access to only primitive, peripheral health clinics with scarce resources.

The most commonly used diagnostic method (smear microscopy) used in these under-developed regions fails to efficiently and accurately diagnose tuberculosis. Patients must travel at great cost and time to microscopy centers to receive insensitive tests requiring trained technicians and repeated clinic visits. This current “state of the art” has a sensitivity of approximately 40%. As a result of these challenges, many people, especially those who have latent TB, are in the early stages of infection, are co-infected with HIV, or suffer from extrapulmonary TB, are under-diagnosed and treated, resulting in significant death, suffering, and the continued spread of disease.

“Tuberculosis is the second most deadly infectious disease in the world and primarily afflicts developing countries with limited resources to manage the disease and prevent its spread,” said Bard J. Geesaman MD PhD, Executive Director of the X PRIZE Foundation Life Sciences Group. “The great unmet need is effective tools and practices for determining who is infected and needs to be treated. Because of the existing lack of adequate financial incentives to develop such tests, a prize is an ideal tool to incentivize innovation in this important area.”
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