POC TB testing: Opportunities and Challenges

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Disclosure

• No financial/industry conflicts

• I consult for the Bill & Melinda Gates Foundation (views expressed are my own)

• I also receive grant funding from BMGF
Everyone agrees that we need POC TB testing, but we need to first agree on what POC testing is!

**Popular view: product oriented**

- **ASSURED** (保证)
- **Affordable** (价格适宜)
- **Sensitive** (灵敏)
- **Specific** (特异)
- **User-friendly** (容易使用)
- **Rapid/Robust** (快速/可靠)
- **Equipment-free** (无仪器)
- **Deliverable** (易储运)

- Dipstick or “pregnancy test”
- Cheap
- Rapid
- No instrument
- No lab
- No trained lab personnel
- Used by community health workers in remote areas
Since it is so product-oriented, the dominant view: there is no POC test for TB

This is because of the focus on product rather than what ‘job needs to be done’

Point-of-care tuberculosis diagnosis: are we there yet?

“...absence of a dipstick-type point-of-care test continues to be a gaping hole in the pipeline.”

Denkinger & Pai. LID 2011

“...absence of a dipstick-type point-of-care test continues to be a gaping hole in the pipeline.”

Denkinger & Pai. LID 2011

This is because of the focus on product rather than what ‘job needs to be done’

Opportunities and Challenges for Cost-Efficient Implementation of New Point-of-Care Diagnostics for HIV and Tuberculosis

“For TB, several new diagnostic tests have recently been endorsed by the WHO, but a POC test remains elusive”
A less restrictive, more realistic and goal-oriented view

Started with treatment (the goal) and worked our way backwards

*Treatment* is what really matters – it will have a clinical impact and hence a public health impact on reducing transmission...

- Rapid, clinically actionable results
- Change in provider’s decisions
- Correct treatment or management choices
- Improved patient outcomes or public health benefits

*on the spot; in the same clinical encounter; while the patient waits; at least on the same day*
Rapid completion of the “test and treat” loop in the same clinical encounter is the ‘job-to-be-done’

- Test is ordered
- Test is done
- Results are reported
- Treatment decision
- Patient is seen

*Treatment can be: start drugs, stop drugs, modify drugs, refer, order more tests, discharge, admit, etc.
“Testing that will result in a clear, actionable, management decision (e.g. referral, initiation of confirmatory test, start of treatment), within the same clinical encounter (e.g. day).”

TB MAC meeting Amsterdam
POCT is a “spectrum” which covers a variety of settings, users, products (i.e. TPPs)

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001306
POC testing is a spectrum (dipstick in the community is just one TPP)

POCT program = technology + enabling healthcare system

or

POCT program = test + business model*

• Technology does not define a POC test nor determine its use at the POC.
• It is the successful use at the point-of-care that defines a diagnostic process as POC testing.
• So, we need POC testing programs, rather than POC tests.
Test developers seem to believe that smallness of the device or portability = POC technology

Smallness/portability may help, but they do not guarantee POCT implementation.

It is not the size or portability, but whether the technology can actually be implemented in a manner that allows rapid completion of the test and treat loop in any one of the 5 TPPs.
Smear microscopy is not a dipstick, but is it amenable to a POCT program?

It is, but most healthcare systems are unable or unwilling to make it work as a POCT program
In India, for example, it can take 8 days before TB treatment is started after sputum smear is read +ve
In S Africa, one in four smear-positive TB patients were not started on treatment within 1 month of diagnosis...

Tuberculosis patients in primary care do not start treatment. What role do health system delays play?

M. M. Claassens,*† E. du Toit,* R. Dunbar,* C. Lombard,† D. A. Enarson,§ N. Beyers,* M. W. Borgdorff†

*Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; †University of Amsterdam, Amsterdam, The Netherlands; ‡Biostatistics Unit, Medical Research Council, Cape Town, South Africa; §International Union Against Tuberculosis and Lung Disease, Paris, France

SUMMARY

SETTING: Primary health care facilities in five provinces of South Africa.

OBJECTIVE: To investigate the association between the proportion of sputum results with a prolonged smear turnaround time and the proportion of smear-positive tuberculosis (TB) cases initially lost to follow-up.

DESIGN: The unit of investigation was a primary health care facility and the outcome was the initial loss to follow-up rate per facility, which was calculated by comparing the sputum register with the TB treatment register. A prolonged turnaround time was defined as more than 48 h from when the sputum sample was documented in the sputum register to receipt of the result at the facility.

RESULTS: The mean initial loss to follow-up rate was 25% (95% CI 22–28). Smear turnaround time overall was inversely associated with initial loss to follow-up ($P = 0.008$), when comparing Category 2 (33–66% turnaround time within 48 h) with Category 1 (0–32%) (OR 0.73, 95% CI 0.48–1.13, $P = 0.163$) and when comparing Category 3 (67–100%) with Category 1 (OR 0.62, 95% CI 0.39–0.99, $P = 0.045$). The population preventable fraction of initial loss to follow-up (when turnaround time was <48 h in ≥67% of smear results) was 21%.

CONCLUSION: Initial loss to follow-up should be reported as part of the TB programme to ensure that patients are initiated on treatment to prevent transmission within communities.

KEY WORDS: tuberculosis; initial loss to follow-up; turnaround time.
Same-day diagnosis of tuberculosis by microscopy

Policy statement

Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis

J Lucian Davis, Adithya Cattamanchi, Luis E Cuevas, Philip C Hopewell, Karen R Steingart

OPEN ACCESS Freely available online

A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis

Luis Eduardo Cuevas1,2, Mohammad Al-Saleh3, Najla Al-Senobri2, Lovett Lawson2, Isabel Arbo1, Nasheer Al-Aghbari4, Jeevan Bahadur Shershand5, Amin Al-Abi6, Emmanuel Nnamdi Emenyonye7, Yared Merid8, Moses Ifeniy Okobi9, Juliana Okubumi Onuoha9, Melkamew Aschalew9, Ibrahim Aseffa9, Greg Harper10, Rachel Mary Anderson de Cuevas1, Kristin Kremer11, Dick van Soolingen11, Carl-Michael Nathanson9, Jean Joby9, Brian Faragher1, Stephen Bertel Squire1, Andrew Ramsay9

Test and Treat: A New Standard for Smear-Positive Tuberculosis

J. Lucian Davis, MD, MAS*†
David W. Dowdy, MD, PhD, ScM‡
Saskia den Boon, MSc, PhD†
Nicholas D. Walter, MD†§
Achilles Katamba, MBChB, PhD†||
Adithya Cattamanchi, MD, MAS*†

JAIIDS 2012

“same-day reporting of results is more likely to result in successful treatment initiation than either same-day or 2-day collection with delayed reporting”
Can GeneXpert work as a POCT program for TB?
Ultimately, the diagnosis-treatment gap will only be closed by rapid point-of-care diagnostic assays that can be used during the patient’s first clinic visit to permit immediate treatment decisions...

Lawn S et al.

“Providing Xpert at point of care had important advantages. Results were available the day of the clinic visit, allowing immediate treatment initiation and eliminating the need for a return visit. This reduced the cost borne by patients...”

[Van Rie et al. IJTLD 2013]
India

Xpert implemented in upgraded microscopy centers (CB-NAAT demonstration study)
But a system is currently not in place that allows providers to start TB Rx on the same day
Even if Xpert can be made to work as a POCT program, it was designed for district/sub-district labs.

- More decentralized
- Closer to patients
- May help detect TB earlier
### Why are microscopy centers important?

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of microscopy centres</th>
<th>Annual smear volumes in public sector (millions)</th>
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<tbody>
<tr>
<td>Afghanistan</td>
<td>Pending</td>
<td>0.46</td>
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<tr>
<td>Bangladesh</td>
<td>1059</td>
<td>4.00</td>
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<tr>
<td>Brazil</td>
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<tr>
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<tr>
<td>China</td>
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<tr>
<td>Congo (DRC)</td>
<td>1,522</td>
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<td>Ethiopia</td>
<td>2,497</td>
<td>6.04</td>
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<td>India</td>
<td>13,000</td>
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<td>Indonesia</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>32,707</strong></td>
<td><strong>40.9</strong></td>
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</tbody>
</table>

- Millions of patients are tested at this level
- TB drugs are usually available
- This is the most decentralized level where Rx can be initiated

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Sputum smear volumes in 22 highest TB burden countries: Preliminary results of ongoing survey
Sandra Kik, Madhukar Pai et al.
Enter “POC NAATs” ['fast-followers']

**Nucleic acid testing for tuberculosis at the point-of-care in high-burden countries**

Angelika Niemz* and David S Boyle†

Early diagnosis of tuberculosis (TB) facilitates appropriate treatment initiation and can limit the spread of this highly contagious disease. However, commonly used TB diagnostic methods are

# Commercialization of microfluidic point-of-care diagnostic devices†

Curtis D. Chin, a Vincent Linder, b and Samuel K. Sia, a

Received 5th December 2011, Accepted 25th January 2012
DOI: 10.1039/c2lc21204h

A large part of the excitement behind microfluidics is in its potential for producing practical devices, but surprisingly few lab-on-a-chip based technologies have been successfully introduced into the market. Here, we review current work in commercializing microfluidic technologies, with a focus on point-of-care diagnostics applications. We will also identify challenges to commercialization, including lessons drawn from our experience in Clarus Diagnostics. Moving forward, we discuss the need to strike a balance between achieving real-world impact with integrated devices versus design of novel single microfluidic components.

**Alere to Develop Simple, Affordable Point-of-Care Nucleic Acid Test for Tuberculosis & Expand Manufacturing for POC HIV Viral Load Platform**

Waltham, MA — March 1, 2013 — Alere Inc. (NYSE: ALE) announced today that it has been awarded a grant of up to $21.6 million and debt financing of up to $20.6 million from the Bill & Melinda Gates Foundation. The $21.6 million grant will fund the development of a tuberculosis assay, which will be designed for use in both resource-constrained and well-resourced settings. It will also support the company’s efforts to incorporate one of its isothermal amplification technologies for TB detection onto the Alere™ Q, a compact, portable, and robust device intended for molecular testing at the point of care. In addition, the Gates Foundation will provide below-market loans of up to $20.6 million for the expansion and scale up of Alere’s manufacturing facilities in Jena, Germany for both the POC TB Nucleic Acid Test and the POC HIV Viral Load Test currently in the final stages of development. The Gates Foundation will provide these loans in exchange for commitments from Alere to make these diagnostics available at an affordable price to people in need in developing countries.
“POC NAATs” for TB
Can they be deployed at microscopy centers?
Will manual sample prep be a challenge?
Will health systems allow them to be implemented for same-day Rx?

Loopamp® by Eiken, Japan

TrueLab® by Molbio, India

GeneDrive® by Epistem, UK

NATeasy® by Ustar, China
Are peripheral microscopy centres ready for next generation molecular tuberculosis diagnostics?

Claudia M. Denkinger1,2, Ioana Nicolau2, Andrew Ramsay3, Pamela Chedore4 and Madhukar Pai2,4
1Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA. 2McGill International TB Centre and Dept of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, and 4Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Montreal, QC, Canada. 3Bute School of Medicine, St Andrews University, Fife, UK.
## Characteristics of peripheral microscopy centers in 22 HBCs

<table>
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<th>Country</th>
<th>Environment</th>
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**Legend:**
- BAD: Poor conditions
- GOOD: Adequate conditions
- MAYBE: Questionable conditions
- UNSURE/no answer
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<tr>
<th>Country</th>
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Even if we can deploy NAATs in microscopy centers, which problem will it fix?

<table>
<thead>
<tr>
<th>Total delay</th>
<th>Health system delay</th>
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<tr>
<td>Patient delay</td>
<td>diagnostic delay</td>
</tr>
<tr>
<td>Onset of symptom</td>
<td>Confirmation of diagnosis</td>
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<tr>
<td>First consultation with a HCP</td>
<td>Start of treatment</td>
</tr>
</tbody>
</table>

Health system delay can be reduced via POCT
Patient delays can be considerable, as shown by systematic reviews

Research article

**Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature**
Chandrashekhar T Sreeramareddy*1,5, Kishore V Panduru2,6, Joris Menten3 and J Van den Ende4

Research article

**A systematic review of delay in the diagnosis and treatment of tuberculosis**
Dag Gundersen Storla*1,2, Solomon Yimer1 and Gunnar Aksel Bjune1

Address: 1Department of International Health, Institute of General Practice and Community Medicine, University of Oslo, PO Box 1130 Blindern, N-0318 Oslo, Norway and 2Competence Centre for Imported and Tropical Diseases, Ullevål University Hospital, Oslo, Norway

Average patient delay ~ 1 month
Total delay of 2 – 3 months
If much of the transmission occurs early, then new POCT diagnostics may have little impact on TB incidence...
Are patients not seeking care, or are they seeking care from informal, ‘invisible’ sectors?

In many developing countries, there are huge numbers of:

– Unqualified healthcare providers
– Less than qualified providers
– Traditional healers
– Chemists and pharmacists
– Alternative health system practitioners
Informal providers make up a significant portion of the healthcare sector globally... Utilization estimates from 24 studies for healthcare services ranged from 9% to 90% of all healthcare interactions...."

‘First we go to the small doctor’: First contact for curative health care sought by rural communities in Andhra Pradesh & Orissa, India

Meenakshi Gautham*, Erika Binnendijk*, Ruth Koren** & David. M. Dror* -

A large number of people with TB are not seeking first-contact care in NTPs
India: TB patients often seek care from informal providers and chemists in the private sector

Long, broken pathway to care

On average, 3 providers are seen before TB diagnosis and treatment
So, to diagnose TB early, we need a strategy to engage providers who see TB patients first.

We modeled the population-level impact and resource implications of scaling-up a molecular diagnostic test (Xpert MTB/RIF) in different healthcare sectors over five years.

Salje H et al. Under review [confidential]
Transmission model that accounts for private/informal sector, movement between the sectors, and diagnostic delays
Key findings: it is not just the technology, but how it is deployed that matters

Transformative strategies require private/informal sector engagement, improved quality of care, and substantial resources.
Final thoughts...

• DOTS has saved lives, but has not reduced incidence as expected

• *Early diagnosis* will require two approaches:
  
  – New technologies, designed for decentralized settings
  
  – New delivery strategies
    
    • POCT programs to reduce health system delays
    • Large-scale engagement of informal, private and first-contact providers to reduce patient pathways to care
Both approaches are being pursued!

NAATs for microscopy centers

Innovative private-sector initiatives

Engaging the private sector to increase tuberculosis case detection: an impact evaluation study

Aamir Z Khan, Saima Khan, Faisal S Khan, Fakhar Qazi, Ismat Lobi, Ali Habibi, Shamsa Mohammed, Umme Khan, Fakhra Anamullah, Hamidah Hussain, Mercedes C Becerra, Jacob Creswell, Saiman Keshavarz

Summary

Background In many countries with a high burden of tuberculosis, most patients receive treatment in the private sector. We evaluated a multifaceted case-detection strategy in Karachi, Pakistan, targeting the private sector.

Methods A year-long communications campaign advised people with 2 weeks or more of productive cough to seek care at one of 54 private family medical clinics or a private hospital that was also a national tuberculosis programme (NTP) reporting centre. Community laypeople participated as screeners, using an interactive algorithm on mobile phones to assess patients and visitors in family-clinic waiting areas and the hospital’s outpatient department. Screeners received cash incentives for case detection. Patients with suspected tuberculosis also came directly to the hospital’s tuberculosis clinic (self-referrals) or were referred there (referrals). The primary outcome was the change (from 2010 to 2011) in tuberculosis notifications to the NTP in the intervention area compared with that in an adjacent control area.

Findings Screeners assessed 388,186 individuals at family clinics and 81,700 at Indus Hospital’s outpatient department from January–December, 2011. A total of 2416 tuberculosis cases were detected and notified via the NTP reporting centre at Indus Hospital: 603 through family clinics, 273 through the outpatient department, 1020 from self-referrals, and 520 from referrals. In the intervention area overall, tuberculosis case-notification to the NTP increased two times (from 1569 to 3140 cases) from 2010 to 2011—a 2.21 times increase (95% CI 1.93 to 2.55) relative to the change in number of case notifications in the control area. From 2010 to 2011, pulmonary tuberculosis notifications at Indus Hospital increased by 3.77 times for adults and 7.32 times for children.

Interpretation Novel approaches to tuberculosis case-finding involving the private sector and using laypeople, mobile phone software and incentives, and communication campaigns can substantially increase case notification in dense urban settings.
Thank you!

We acknowledge useful input from:

- Claudia Denkinger
- Sandra Kik
- David Dowdy
- Henrik Salje

Our work is supported by a grant from the Bill & Melinda Gates Foundation