Importance of evidence synthesis in TB and HIV control

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Evidence-based medicine

- The evidence-based medicine movement has emphasized the need for making decisions about interventions based on the best available evidence from strong scientific research.
Report prepared for the Dutch Health Care Insurance Board.

EVIDENCE-BASED MEDICAL TESTING
Developing evidence-based reimbursement recommendations for tests and markers.

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Systematic Reviews in Tuberculosis

Relationship between Bacille Calmette-Guerin (BCG) strains and the efficacy of BCG vaccination in the prevention of tuberculosis.

Brewer TF, Colditz GA.
Clin Infect Dis. 1995
Systematic Reviews in Tuberculosis

- A large number in the past 5 – 10 years
- Over 250 SRs focused on TB
- Used by many bodies for policy and guideline development in TB

The Grading of Recommendations Assessment, Development and Evaluation

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide.
Systematic Reviews on TB Diagnostics

- Over 40 SRs on TB diagnostics
- Used for policy and guideline development (with or without GRADE)
- More than 10 new WHO recommendations on TB diagnostics since 2007 (with GRADE since 2009)
Systematic Reviews on TB Diagnostics

"Current methods focus mostly on diagnostic accuracy, based on comparisons between a test and the clinical reference standard, and grade the level of evidence based on the design of diagnostic test accuracy studies."

Systematic Reviews on TB Diagnostics

"There is a growing awareness that tests should be evaluated not on their intrinsic qualities (essentialism) but based on their consequences for patients’ health and the use of health care resources (consequentialism)."

"Acceptable diagnostic accuracy, though usually desired, is generally not sufficient for demonstrating benefits from testing."
Evidence Synthesis on Tuberculosis Diagnostics

- New Diagnostics Working Group (Stop TB Partnership)
- Subgroup dedicated to Evidence Synthesis (Karen Steingart and Rick O'Brien)
- Setting rational policy-relevant research agendas
- Research into evidence
- Evidence into policy

Example 1: Optimizing ZN Microscopy

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

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Example 1: Optimizing ZN Microscopy

Improving the Diagnosis of Tuberculosis through Optimization of Sputum Microscopy

Expert Consultation, WHO Headquarters
Geneva 1-2 September 2005

Participants: Mohamed A Arif, WHO STR, Switzerland;
Irina F. Gurfinkel, ICFM, UK;
Jean-Claude Hauw, WHO STR, Switzerland;
Jana Vogen, WHO STR, Switzerland;
Anita B. Wiersema, University of California, USA;
Madhusudan Pati, University of California, USA;
Mark D. Perkins, FIND, Switzerland;
Krzysztof Ryszewski, WHO STR, Switzerland;
S. Berrie Spurr, LSTM, UK;
Karen Stringer, University of California, USA;
Veronique Vincent, Institut Pasteur, France;
Kann Wuyt, MIRU, South Africa;
Mohammed A. Yassen, LSTM, UK

Chair: John Riddelhof, CDC, USA
Rapporteur: Andy Rensburg, TDR, Switzerland

Example 1: Optimizing ZN Microscopy

Recommendations:

i. There is strong evidence that the mean incremental yield of the 3rd sputum smear is only 2-5%. However, evidence on incremental yield is derived from an analysis in which one positive smear would define a smear positive TB case. This differs from the currently internationally recommended requirement for at least 2 positive smears to define a smear positive case. A separate analysis would be required to evaluate the evidence base for the current international case definition.

ii. The advantages which could accrue from omitting the third specimen in serial sputum examinations are pre-empted by the requirement for 2 positive smears to define a smear positive case as described in (i).

iv. Because of the limitations imposed by the standard case definition, countries should not consider the introduction of a 2 sputa strategy until the key research questions laid out in (vi) below are addressed.
Example 1: Optimizing ZN Microscopy

vii. Multi-centre studies, which should follow one or more internationally-coordinated well-designed protocols, are required to:

- Determine the sensitivity and specificity (compared with culture) of a revised case definition with one positive smear result;
- Prospectively evaluate the relative yield of serial sputum specimens;
- Define the optimal timing of specimen collection that minimizes delay in the diagnostic pathway.

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


Reducing the number of sputum samples examined and thresholds for positivity: an opportunity to optimise smear microscopy

M. Bonnet, A. Ramsay, L. Gagnidze, W. Githui, P. J. Guérin, F. Varaine

Sputum, sex and scanty smears: new case definition may reduce sex disparities in smear-positive tuberculosis

A. Ramsay, M. Bonnet, L. Gagnidze, W. Githui, F. Varaine, P. J. Guérin

*Liverpool School of Tropical Medicine, Liverpool, UK; †Epicentre, Paris, France; ‡Kenya Medical Research Institute, Nairobi, Kenya; ′Médecins Sans Frontières, Paris, France
Define the optimal timing of specimen collection


Research Article

Front-Loading Sputum Microscopy Services: An Opportunity to Optimise Smear-Based Case Detection of Tuberculosis in High Prevalence Countries

Andy Rimasy,1,2 Mohammed Ahmed Yassin,3,4 Alexis Lambis,4 Susume Hirots,1 Ahmad Amiratwa,1 Mohamed Gamm,1 Lovett Lovson,4 Izbel Arbide,2 Nasser Al-Aghbari,6 Najla Al-Senbell,7 Tevun Bahadur Sherchand,7 Punita Gauchan,8 and Luis Eduardo Cuevas9
SAME-DAY-DIAGNOSIS OF TUBERCULOSIS BY MICROSCOPY

POLICY STATEMENT

WHO recommends that:

- Countries that have successfully implemented the current WHO policy for a two-specimen case-finding strategy consider a switch to the same-day-diagnosis approach, especially in settings where patients are likely to default from the diagnostic process;
- Countries that are still using the three-specimen case-finding strategy consider a gradual change to the same-day-diagnosis approach, once WHO-recommended external microscopy quality assurance systems are in place and good quality microscopy results have been documented;

Example 2: Fluorescence Microscopy

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

Karen F. Steingart, Megan Henry, Vivienne Ng, Philip C. Hopkins, Andrew Burns, Jane Cunningham, Richard Usczenski, Mark Perkins, Mohamed Abdel Aziz, Keshuvar Vai
Example 2: Fluorescence Microscopy

Assessment of evidence on performance of FM

There is strong evidence, presented in the systematic review, that:

a) fluorescence microscopy is on average 10% more sensitive for the detection of pulmonary tuberculosis than conventional light microscopy (LM);

b) the specificity of FM for detection of acid fast organisms in sputum is comparable to that of LM.

c) the increased sensitivity of FM is greatest in low grade positives. The proportion of low grade positives in the population served may thus determine the relative sensitivity of the method over LM in any particular setting;

d) Fluorochrome-stained smears take less time to examine than those stained with the Ziehl-Neelsen (ZN) method (25% of the time taken to examine ZN-stained smears).
Example 2: Fluorescence Microscopy

Recommendations:

i. FM may be considered at all levels of the health system in high HIV prevalence countries seeking to improve the sensitivity of sputum microscopy, shorten time to diagnosis and reduce laboratory workload;

ii. This technology has been demonstrated to be effective in high volume settings. Countries wishing to implement FM at the peripheral level, in lower volume settings, should do so within the context of operational research to best determine models for implementation and to explore issues of cost, feasibility and sustainability.

iii. Research in this area should follow a coordinated and standardized approach\(^2\), both to strengthen the country-specific evidence base and to permit comparison with data from different settings.

iv. NTPs may consider building operational research on fluorescence microscopy into their planning and applications for financial support.

v. The feasibility of developing fluorescent microscopes that overcome the limitations of existing equipment, particularly capital cost and maintenance needs, should be investigated

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WHO therefore recommends that:

- Conventional fluorescence microscopy be replaced by LED microscopy using amine staining in all settings where fluorescence microscopy is currently used;
- LED microscopy be phased in as an alternative for conventional ZN light microscopy in both high and low volume laboratories;
- The switch to LED microscopy be carried out through a carefully phased implementation plan, using LED technologies that meet WHO specifications;
Example 3: Serodiagnostics

Commercial serological tests for the diagnosis of tuberculosis: An updated systematic review and meta-analysis

Example 3: Serodiagnostics

Future needs

- Setting rational policy-relevant research agendas
- Research into evidence
- Evidence into policy

- **Policy into practice**
  - Implementation research
  - Impact assessment
  - Evidence synthesis
  - Challenges
Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools

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A Framework for Impact Assessment for New Diagnostics

1. Clinical utility
   - How will the new test work in terms of accuracy?
   - How many additional cases will be identified if the new test is used?
   - How many additional cases will actually be treated as a result of using the new test?

2. Cost
   - What are the direct costs of introducing the new test (e.g., labor, equipment, supplies, etc.)?
   - What are the indirect costs of introducing the new test (e.g., training, implementation, etc.)?

3. Impact on healthcare system
   - What are the potential impacts on healthcare delivery at the national level?
   - What are the potential impacts on healthcare delivery at the regional level?

4. Cost-effectiveness
   - What are the cost-effectiveness analyses of the new test compared to current tests?
   - What are the cost-effectiveness analyses of the new test compared to other interventions?

5. Policy and politics
   - What are the potential policy implications of introducing the new test?
   - What are the potential political implications of introducing the new test?
TREAT TB Symposium

INNOVATIONS IN RESEARCH

- Sunday 14 November
- 14.00 – 16.15hrs
- Hall 4/5

IMPACT ASSESSMENT FRAMEWORK