Evidence-based TB Diagnosis: how evidence informs practice and policy

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Stop TB Partnership

Working Group on New Diagnostics

ANNUAL MEETING

Disclosure of conflicts

- No financial conflicts
  - No stocks, no advisory boards, no speaker fees, no funds for research

- I consult for Foundation for Innovative New Diagnostics, a non-profit agency
  - FIND partners with several industries to develop new diagnostics for neglected diseases

The need for evidence in clinical and policy decision making

- While new tools offer great promise, limited resources and the movement toward evidence-based guidelines and policies require careful validation of new tools prior to their introduction for routine use
- The world spends an estimated US$1 billion per year on diagnostics for TB [FIND/TDR 2006]
- Such expenditure must be backed by strong evidence.

The need for evidence in clinical and policy decision making

- Ideally, clinical and policy decisions must be guided by the totality of evidence on a given topic
- Concerns have been raised about the lack of emphasis on evidence in some of the existing TB guidelines [Oxman et al]:
  - "Systematic reviews and concise summaries of findings are rarely used for developing recommendations.
  - Instead, processes usually rely heavily on experts in a particular specialty…."

Use of evidence in WHO recommendations

Andrew D Oxman, John N Lavis, Atle Fretheim

Summary

Background WHO regulations, dating back to 1951, emphasise the role of expert opinion in the development of recommendations. However, the organisation's guidelines, approved in 2003, emphasise the use of systematic reviews for evidence of effects, processes that allow for the explicit incorporation of other types of information (including values), and evidence-informed dissemination and implementation strategies. We examined the use of evidence, particularly evidence of effects, in recommendations developed by WHO departments.

Methods We interviewed department directors (or their delegates) at WHO headquarters in Geneva, Switzerland, and reviewed a sample of the recommendation-containing reports that were discussed in the interviews (as well as related background documentation). Two individuals independently analysed the interviews and reviewed key features of the reports and background documentation.

Findings Systematic reviews and concise summaries of findings are rarely used for developing recommendations. Instead, processes usually rely heavily on experts in a particular specialty, rather than representatives of those who will have to live with the recommendations or on experts in particular methodological areas.

Interpretation Progress in the development, adaptation, dissemination, and implementation of recommendations for member states will need leadership, the resources necessary for WHO to undertake these processes in a transparent and defensible way, and close attention to the current and emerging research literature related to these processes.

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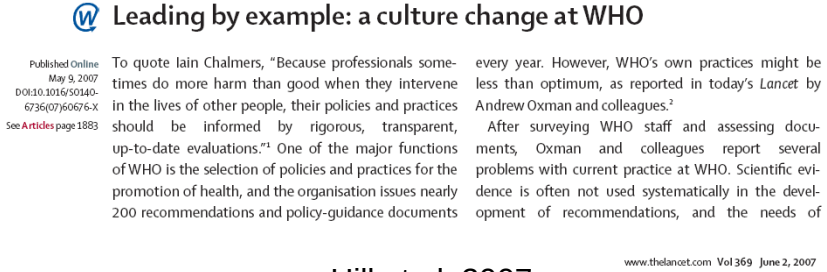
Oxman et al. 2007

The need for evidence in clinical and policy decision making

- These concerns are being taken seriously and the outcome should be evident in upcoming TB guidelines and policies.
- WHO recently announced its approach for developing new policies on TB in a document entitled "Moving Research Findings into New WHO Policies [2008]"



Leading by example: a culture change at WHO

Published Online May 9, 2007 DOI:10.1016/S0140-6736(07)60676-X See Articles page 1883

To quote Iain Chalmers, "Because professionals sometimes do more harm than good when they intervene in the lives of other people, their policies and practices should be informed by rigorous, transparent, up-to-date evaluations."[1] One of the major functions of WHO is the selection of policies and practices for the promotion of health, and the organisation issues nearly 200 recommendations and policy-guidance documents every year. However, WHO's own practices might be less than optimum, as reported in today's *Lancet* by Andrew Oxman and colleagues.[2]

After surveying WHO staff and assessing documents, Oxman and colleagues report several problems with current practice at WHO. Scientific evidence is often not used systematically in the development of recommendations, and the needs of

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Hill et al. 2007

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Publications
Data and statistics
Programmes and projects
Tuberculosis
Stop TB Strategy
DOTS expansion
TB/HIV MDR/XDR-TB
Health systems
Public-Private Mix
Affected people
TB research
TB data
TB publications
Topics index
About us

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WHO > Programmes and projects > Tuberculosis (TB) > Pursue high-quality DOTS expansion and enhancement > Strengthening tuberculosis laboratories

printable version

New WHO policies: Previous page | 1,2,3,4,5

Moving research findings into new WHO policies

Introduction

Today's technologies for tuberculosis (TB) control—medicines, diagnostics, and vaccines—are decades old, and improvements in these technologies or new technologies altogether would accelerate TB control efforts worldwide. "Retooling" TB control is the process for adopting and introducing new and improved health technologies with the goal of maximizing their widespread use, while minimizing delays. A pivotal point in retooling is when a global policy is revised or created to encompass a new technology or strategy.

A primary source of global health policy is the World Health Organization (WHO). As WHO is governed by Member States, WHO policy is commonly the foundation for country-level technical decisions. The majority of countries may not take up new tools or strategies that are not endorsed by the WHO, even when they are effective. WHO strongly supports TB retooling efforts and works towards the rapid and widespread dissemination and use of new technologies to combat TB and eliminate the disease. In addition to its role in policy setting, WHO can facilitate the translation of policy into practice through its normative, technical assistance, and monitoring functions at the country level.

A widespread and common understanding of the process that WHO utilizes to move research evidence into policy is critical to ensure that all product developers or researchers have similar access to the policy-making process, and to enable countries to access objective information on all new, improved and existing technologies.

More information

1. Background documentation
2. Definition of a new sputum smear-positive TB case
3. Reduction of number of smears for the diagnosis of pulmonary TB
4. The use of liquid medium for culture and DST
5. Moving research findings into new WHO policies

http://www.who.int/tb/dots/laboratory/policy/en/index4.html

The need for evidence in clinical and policy decision making

- According to WHO, in order to consider a global policy change, WHO must have solid evidence, including clinical trials or field evaluations in high TB prevalence settings.
- Policy process includes a comprehensive review of the evidence, as well as expert opinion and judgment
- All WHO guidelines will be approved by a Guideline Review Committee
- All guidelines and policies will explicitly incorporate evidence using the GRADE approach

Box 1. WHO Policy Process for Tuberculosis

1. Identifying the Need for a Policy Change

The need to formulate new or revised policies may arise from WHO's ongoing monitoring of technical developments or from interested parties submitting requests with supporting documentation for policy or guideline development. WHO receives information about a new technology or approach via many channels, with the most direct lines coming from national TB programs and researchers themselves. To consider a global policy change, WHO must have solid evidence, including clinical trials or field evaluations in high TB prevalence settings.

2. Reviewing the Evidence

WHO may carry out or commission a review of the documentation of the technology's clinical or programmatic performance, including newly published and "grey" research or reviews, "proof of principle" reports, large-scale field trials, and demonstration projects in different resource settings. Standardized evaluation criteria have been and are being developed by the New Diagnostics, New Drugs, and New Vaccines Working Groups of the Stop TB Partnership.

3. Convening an Expert Panel

If the evidence base is compelling, WHO will convene an external panel of experts, excluding all original principal investigators from the studies. The panel will review the evidence and make a recommendation or propose draft policies or guidelines to WHO's Strategic and Technical Advisory Group for Tuberculosis (STAG-TB).

4. Assessing Draft Policies and Guidelines

STAG-TB provides objective, ongoing technical and strategic advice to WHO on TB care and control. STAG-TB's objectives are to provide the Director-General, through the Stop TB Department, with an independent evaluation of the strategic, scientific, and technical aspects of WHO's TB activities; review progress and challenges in WHO's TB-related core functions; review and make recommendations on committees and working groups; and make recommendations on WHO's TB activity priorities. STAG-TB reviews the policy drafts and supporting documentation during its annual meeting. STAG-TB may endorse the policy recommendation with or without revisions, request additional information and re-review the evidence in subsequent years, or reject the recommendation.

5. Formulating and Disseminating Policy

New WHO policies and guidelines will be disseminated through different channels to Member States, including through the World Health Assembly, WHO Web site, listservs, and journal publications. WHO also disseminates its recommendations to other agencies and donors engaged in TB control activities.

Source: World Health Organization [7]

http://www.who.int/tb/dots/laboratory/policy/en/index4.html

Guidelines and recommendations: GRADE

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

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

Box 2 | Quality of evidence and definitions

High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— Any estimate of effect is very uncertain

Quality of evidence

High quality	⊕⊕⊕⊕	or A
Moderate quality	⊕⊕⊕◯	or B
Low quality	⊕⊕◯◯	or C
Very low quality	⊕◯◯◯	or D

Strength of recommendation

Strong recommendation for using an intervention	↑ ↑	or 1
Weak recommendation for using an intervention	↑ ?	or 2
Weak recommendation against using an intervention	↓ ?	or 2
Strong recommendation against using an intervention	↓ ↓	or 1

Fig 2 Representations of quality of evidence and strength of recommendations

http://www.gradeworkinggroup.org/

Evidence-based diagnosis ("EBD")

- Evidence-based medicine (EBM) includes evidence based diagnosis
- EBD, in turn, requires synthesis of evidence on various diagnostic tests and algorithms (i.e. systematic reviews)
- Although diagnostic studies are very common, systematic reviews and meta-analyses of diagnostic studies are uncommon
  - First Cochrane diagnostic review was published in October 2008
  - For example, until early 2000, no systematic reviews had been published on TB diagnostics
  - In 2008, we have 31 systematic reviews on TB diagnostics!

Latent TB

The end of tuberculin skin testing?

A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements

L Wang, M O Turner, R K Elwood, M Schulzer, J M FitzGerald

Thorax 2002;57:804–809

See end of article for authors' affiliations

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Accepted for publication 22 March 2002

Background: The accurate diagnosis of latent tuberculosis infection (LTBI) is an important component of any tuberculosis control programme and depends largely on tuberculin skin testing. The appropriate interpretation of skin test results requires knowledge of the possible confounding factors such as previous BCG vaccination. Uncertainty about the effect of BCG vaccination on tuberculin skin testing and the strength with which recommendations are made to individual patients regarding treatment of LTBI have identified a need to analyse the available data on the effect of BCG on skin testing. A meta-analysis of the evidence for the effect of BCG vaccination on tuberculin skin testing in subjects without active tuberculosis was therefore performed.

Methods: Medline was searched for English language articles published from 1966 to 1999 using the key words "BCG vaccine", "tuberculin test/PPD", and "skin testing". Bibliographies of relevant articles were reviewed for additional studies that may have been missed in the Medline search. Articles were considered for inclusion in the meta-analysis if they had recorded tuberculin skin test results in subjects who had received BCG vaccination more than 5 years previously and had a concurrent control group. Only prospective studies were considered. The geographical location, number of participants, type of BCG vaccine used, type of tuberculin skin test performed, and the results of the tuberculin skin test were extracted.

Results: The abstracts and titles of 980 articles were identified, 370 full text articles were reviewed, and 26 articles were included in the final analysis. Patients who had received BCG vaccination were more likely to have a positive skin test (5 TU PPD: relative risk (RR) 2.12 (95% confidence interval (CI)1.50 to 3.00); 2 TU RT23: 26.50 (95% CI 1.83 to 3.85). The effect of BCG vaccination on PPD skin test results was less after 15 years. Positive skin tests with indurations of >15 mm are more likely to be the result of tuberculous infection than of BCG vaccination.

Conclusions: In subjects without active tuberculosis, immunisation with BCG significantly increases the likelihood of a positive tuberculin skin test. The interpretation of the skin test therefore needs to be made in the individual clinical context and with evaluation of other risk factors for infection. The size of the induration should also be considered when making recommendations for treatment of latent infection.

TST

INT J TUBERC LUNG DIS 10(11):1192–1204

REVIEW ARTICLE

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

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SUMMARY

BACKGROUND: Despite certain drawbacks, the tuberculin skin test (TST) remains in widespread use. Important advantages of the TST are its low cost, simplicity and interpretation based on extensive published literature. However, TST specificity is reduced by bacille Calmette-Guérin (BCG) vaccination and exposure to non-tuberculous mycobacteria (NTM).

METHODS: To estimate TST specificity, we reviewed the published literature since 1966 regarding the effect of BCG vaccination and NTM infection on TST. Studies selected included healthy subjects with documented BCG vaccination status, including age at vaccination. Studies of NTM effect had used standardised NTM antigens in healthy subjects.

RESULTS: In 24 studies involving 240 203 subjects BCG-vaccinated as infants, 20 406 (8.5%) had a TST of 10+ mm attributable to BCG, but only 56/5639 (1%) were TST-positive if tested ⩾10 years after BCG. In 12 studies of 12 728 subjects vaccinated after their first birthday, 5314 (41.8%) had a false-positive TST of 10+ mm, and 191/898 (21.2%) after 10 years. Type of tuberculin test did not modify these results. In 18 studies involving 1 169 105 subjects, the absolute prevalence of false-positive TST from NTM cross-reactivity ranged from 0.1% to 2.3% in different regions.

CONCLUSIONS: The effect on TST of BCG received in infancy is minimal, especially ⩾10 years after vaccination. BCG received after infancy produces more frequent, more persistent and larger TST reactions. NTM is not a clinically important cause of false-positive TST, except in populations with a high prevalence of NTM sensitisation and a very low prevalence of TB infection.

KEY WORDS: tuberculin skin test; latent TB infection; atypical mycobacteria; environmental mycobacteria; non-tuberculous mycobacteria; BCG vaccination

IGRAs

Interferon-γ assays in the immunodiagnosis of tuberculosis: a systematic review

Madhukar Pai, Lee W Riley, and John M Colford Jr

A major challenge in tuberculosis control is the diagnosis and treatment of latent tuberculosis infection. Until recently, there were no alternatives to the tuberculin skin test (TST) for diagnosing latent tuberculosis. However, an alternative has now emerged in the form of a new in-vitro test: the interferon-γ assay. We did a systematic review to assess the performance of interferon-γ assays in the immunodiagnosis of tuberculosis. By searching databases, contacting experts and test manufacturers, we identified 75 relevant studies. The results suggest that interferon-γ assays that use *Mycobacterium tuberculosis*-specific region of difference 1 (RD1) antigens (such as early secretory antigenic target 6 and culture filtrate protein 10) may have advantages over the TST, in terms of higher specificity, better correlation with exposure to *M tuberculosis*, and less cross-reactivity due to BCG vaccination and non-tuberculous

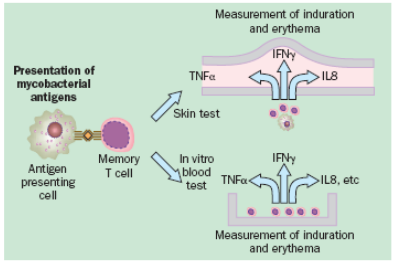

Figure 1. Biological basis of the tuberculin skin test and interferon-γ assay. TNFα=tumour necrosis factor α; IFNγ=interferon γ; IL8=Interleukin 8. Reproduced with permission from Elsevier.[9]

Annals of Internal Medicine | ARTICLE

Meta-analysis: New Tests for the Diagnosis of Latent Tuberculosis Infection: Areas of Uncertainty and Recommendations for Research

Dick Menzies, MD, MSc; Madhukar Pai, MD, PhD; and George Comstock, MD, DrPH

Background: Until recently, the tuberculin skin test was the only test for detecting latent tuberculosis (TB) infection, but 2 ex vivo interferon-γ release assays (IGRAs) are now commercially licensed.

Purpose: To estimate sensitivity, specificity, and reproducibility of IGRAs (commercial or research versions of QuantiFERON [QFT] and Elispot) for diagnosing latent TB infection in healthy and immune-suppressed persons.

Data Sources: The authors searched MEDLINE and reviewed citations of all original articles and reviews for studies published in English.

Study Selection: Studies had evaluated IGRAs using *Mycobacterium tuberculosis*–specific antigens (RD1 antigens) and overnight (16- to 24-h) incubation times. Reference standards had to be clearly defined without knowledge of test results.

Data Extraction and Quality Assessment: Specific criteria for quality assessment were developed for sensitivity, specificity, and reproducibility.

Data Synthesis: When newly diagnosed active TB was used as a surrogate for latent TB infection, sensitivity of all tests was suboptimal, although it was higher with Elispot. No test distinguishes active TB from latent TB. Sensitivity of the tuberculin skin test and IGRAs was similar in persons who were categorized into clinical gradients of exposure. Pooled specificity was 97.7% (95% CI, 96% to 99%) and 92.5% (CI, 86% to 99%) for QFT and for Elispot, respectively. Both assays were more specific than the tuberculin skin test in samples vaccinated with bacille Calmette–Guérin. Elispot was more sensitive than the tuberculin skin test in 3 studies of immune-compromised samples. Discordant tuberculin skin test and IGRA reactions were frequent and largely unexplained, although some may be related to varied definitions of positive test results. Reversion of IGRA results from positive to negative was common in 2 studies in which it was assessed.

Limitations: Most studies used cross-sectional designs with the inherent limitation of no gold standard for latent TB infection, and most involved small samples with a widely varying likelihood of true-positive and false-positive test results. There is insufficient evidence on IGRA performance in children, immune-compromised persons, and the elderly.

Conclusions: New IGRAs show considerable promise and have excellent specificity. Additional studies are needed to better define their performance in high-risk populations and in serial testing. Longitudinal studies are needed to define the predictive value of IGRAs.

Ann Intern Med. 2007;146:340-354. www.annals.org
For author affiliations, see end of text.

Annals of Internal Medicine | REVIEW

Systematic Review: T-Cell–based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update

Madhukar Pai, MD, PhD; Alice Zwerling, MSc; and Dick Menzies, MD, MSc

Background: Interferon-γ–release assays (IGRAs) are alternatives to the tuberculin skin test (TST). A recent meta-analysis showed that IGRAs have high specificity, even among populations that have received bacille Calmette–Guérin (BCG) vaccination. Sensitivity was suboptimal for TST and IGRAs.

Purpose: To incorporate new evidence into an updated meta-analysis on the sensitivity and specificity of IGRAs.

Data Sources: PubMed was searched through 31 March 2008, and citations of all original articles, guidelines, and reviews for studies published in English were reviewed.

Study Selection: Studies that evaluated QuantiFERON-TB Gold, QuantiFERON-TB Gold In-Tube (both from Cellestis, Victoria, Australia), and T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) or its precommercial ELISpot version, when data on the commercial version were lacking. For assessing sensitivity, the study sample had to have microbiologically confirmed active tuberculosis. For assessing specificity, the sample had to comprise healthy, low-risk individuals without known exposure to tuberculosis. Studies with fewer than 10 participants and those that included only immunocompromised participants were excluded.

Data Extraction: One reviewer abstracted data on participant characteristics, test characteristics, and test performance from 38 studies; these data were double-checked by a second reviewer. The original investigators were contacted for additional information when necessary.

Data Synthesis: A fixed-effects meta-analysis with correction for overdispersion was done to pool data within prespecified subgroups. The pooled sensitivity was 78% (95% CI, 73% to 82%) for QuantiFERON-TB Gold, 70% (CI, 63% to 78%) for QuantiFERON-TB Gold In-Tube, and 90% (CI, 86% to 93%) for T-SPOT.TB. The pooled specificity for both QuantiFERON tests was 99% among non–BCG-vaccinated participants (CI, 98% to 100%) and 96% (CI, 94% to 98%) among BCG-vaccinated participants. The pooled specificity of T-SPOT.TB (including its precommercial ELISpot version) was 93% (CI, 86% to 100%). Tuberculin skin test results were heterogeneous, but specificity in non–BCG-vaccinated participants was consistently high (97% [CI, 95% to 99%]).

Limitation: Most studies were small and had limitations, including no gold standard for diagnosing latent tuberculosis and variable TST methods and cutoff values. Data on the specificity of the commercial T-SPOT.TB assay were limited.

Conclusion: The IGRAs, especially QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube, have excellent specificity that is unaffected by BCG vaccination. Tuberculin skin test specificity is high in non–BCG-vaccinated populations but low and variable in BCG-vaccinated populations. Sensitivity of IGRAs and TST is not consistent across tests and populations, but T-SPOT.TB appears to be more sensitive than both QuantiFERON tests and TST.

Ann Intern Med. 2008;149. www.annals.org
For author affiliations, see end of text.

Active TB

Can microscopy be optimized?

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 Pai

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 Pai

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 policy developments (2007)

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.

Detailed background information [pdf 144kb]

Proposal for a revision of the case definition of "Sputum Smear-Positiove Tuberculosis" [pdf 1.99Mb]
Background document prepared by Hans L. Rieder and Armand Van Deun

More information

1. Background documentation
2. Definition of a new sputum smear-positive TB case
3. Reduction of number of smears for the diagnosis of pulmonary TB
4. The use of liquid medium for culture and DST
5. Moving research findings into new WHO policies

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.

Detailed background information [pdf 144kb]

BACKGROUND

The WHO Stop TB Strategy and the Global Plan to Stop TB, 2006-2015 recognizes the weakness of the health system as one of the greatest challenges to TB control and indeed to the achievement of the Millenium Development Goals (MDGs) in general. The Global Plan also recognizes that patients, particularly poor patients, face economic barriers in accessing TB control services and that patients with TB in many resource-limited settings face long and sometimes costly pathways to diagnosis. In most of these countries, the laboratory services are often neglected and may be considered to be among the weakest components of the health system.

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•http://www.who.int/tb/dots/laboratory/policy/en/

Liquid Culture

- Liquid culture systems reduce delays in obtaining results to days rather than weeks
  - For DST, delay may be as little as 10 days vs. 28-42 days with solid media
- Liquid systems are more sensitive - increase the case yield by ~10% over solid media
- Liquid systems are, however, more prone to contamination by other micro-organisms.
  - In experienced laboratories, ~5-10% of specimens cannot yield results because of contamination

http://www.who.int/tb/dots/laboratory/policy/en/index3.html

New policy developments (2007)

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.**

More information

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Use of Liquid TB Culture and Drug Susceptibility Testing (DST) in Low and Medium Income Settings

Summary report of the

Expert Group Meeting on the use of liquid culture media,

Geneva, 26 March 2007

http://www.who.int/tb/dots/laboratory/policy/en/

Nucleic acid amplification tests (NAAT)

- NAATs have high specificity and PPV
- Sensitivity is lower and highly variable across studies
  - Sensitivity lower in extra-pulmonary and smear-neg pulmonary TB – thus, reducing applicability in HIV+
  - Negative test does not rule out TB
- Expensive; limited applicability in developing countries with high HIV prevalence

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

Research article

Open Access

Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis

Madhukar Pai[1], Laura L Flores[2], Alan Hubbard[3], Lee W Riley[2] and John M Colford Jr*[1]

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

Research article

Open Access

In-house nucleic acid amplification tests for the detection of *Mycobacterium tuberculosis* in sputum specimens: meta-analysis and meta-regression

Laura L Flores[1,2,3], Madhukar Pai[1,3], John M Colford Jr[1] and Lee W Riley*[1]

Current evidence on diagnostic accuracy of commercially based nucleic acid amplification tes for the diagnosis of pulmonary tuberculosis

S Greco, E Girardi, A Navarra, C Saltini

OPEN ACCESS Freely available online

PLoS one

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

Daphne I. Ling[1], Laura L. Flores[2], Lee W. Riley[1,3], Madhukar Pai[4]*

1 Division of Epidemiology, School of Public Health, University of California, Berkeley, California, 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, California, United States of America, 4 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Serological tests for TB

- Attractive, especially if made into point of care (POC)
- Have been around for a long time
- Existing serological tests have failed
  - But still sold by many companies and used in developing countries

OPEN ACCESS Freely available online PLOS MEDICINE

Commercial Serological Antibody Detection Tests for the Diagnosis of Pulmonary Tuberculosis: A Systematic Review

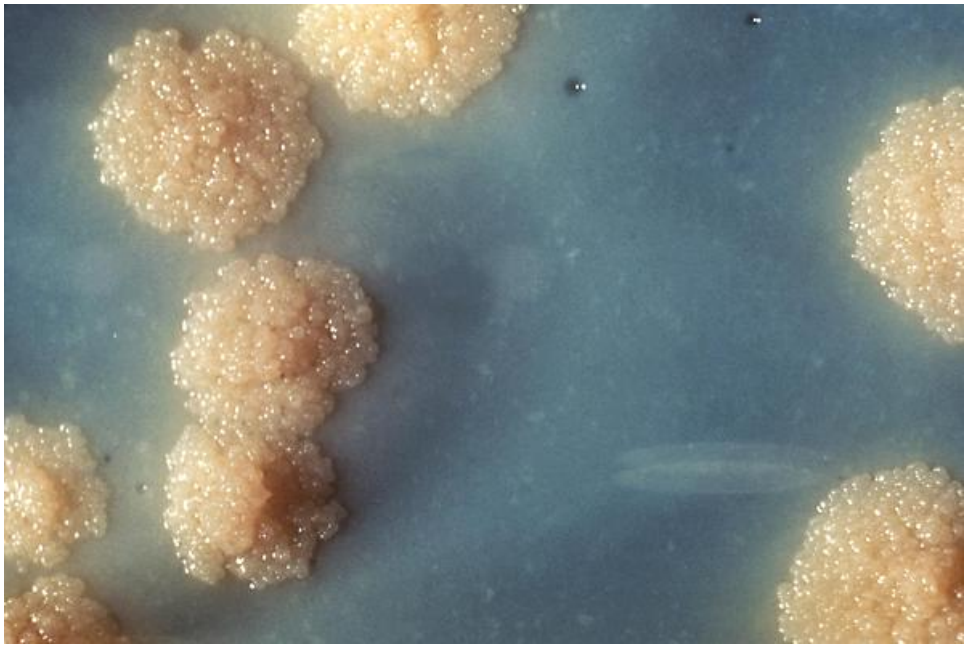
Karen R. Steingart[1,2], Megan Henry[3], Suman Laal[4,5,6], Philip C. Hopewell[1,2], Andrew Ramsay[7], Dick Menzies[8,9], Jane Cunningham[7], Karin Weldingh[10], Madhukar Pai[8,9*]

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;**62**:911–918. doi: 10.1136/thx.2006.075754

Detection of drug resistance

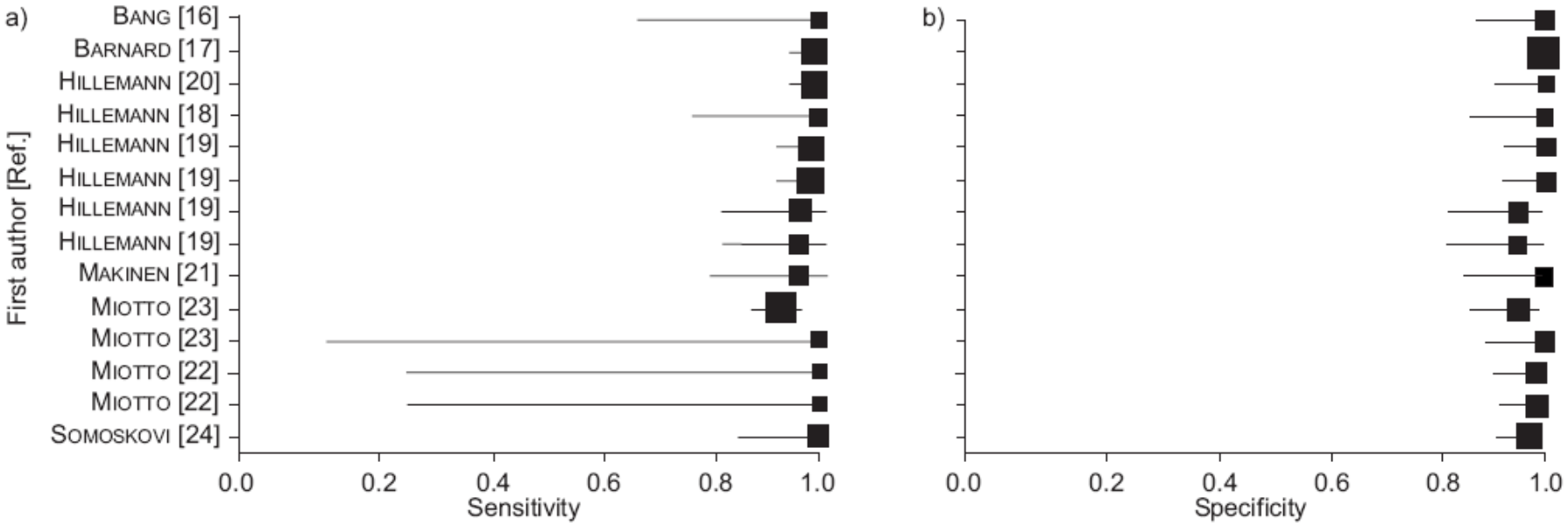


Meta-analysis of GenoType MTBDR studies: rifampicin resistance

Eur Respir J 2008; 32: 1–10
DOI: 10.1183/09031936.00061808

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

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

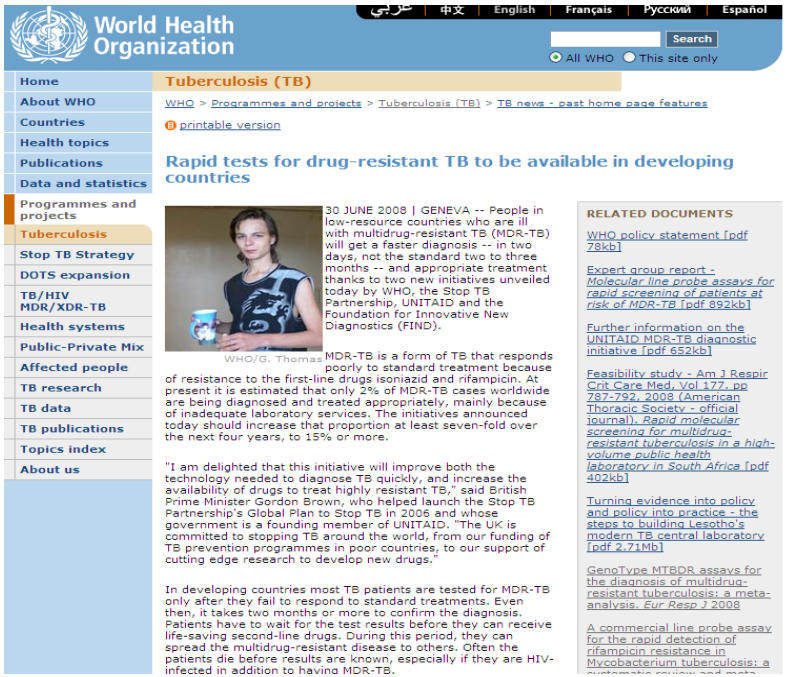


98% Sensitivity

99% Specificity

Ling, Zwerling & Pai. ERJ 2008

New WHO policy on line probe assays (2008)



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Tuberculosis (TB)

WHO > Programmes and projects > Tuberculosis (TB) > TB news - past home page features

printable version

Rapid tests for drug-resistant TB to be available in developing countries

WHO/G. Thomas

30 JUNE 2008 | GENEVA -- People in low-resource countries who are ill with multidrug-resistant TB (MDR-TB) will get a faster diagnosis -- in two days, not the standard two to three months -- and appropriate treatment thanks to two new initiatives unveiled today by WHO, the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND).

MDR-TB is a form of TB that responds poorly to standard treatment because of resistance to the first-line drugs isoniazid and rifampicin. At present it is estimated that only 2% of MDR-TB cases worldwide are being diagnosed and treated appropriately, mainly because of inadequate laboratory services. The initiatives announced today should increase that proportion at least seven-fold over the next four years, to 15% or more.

"I am delighted that this initiative will improve both the technology needed to diagnose TB quickly, and increase the availability of drugs to treat highly resistant TB," said British Prime Minister Gordon Brown, who helped launch the Stop TB Partnership's Global Plan to Stop TB in 2006 and whose government is a founding member of UNITAID. "The UK is committed to stopping TB around the world, from our funding of TB prevention programmes in poor countries, to our support of cutting edge research to develop new drugs."

In developing countries most TB patients are tested for MDR-TB only after they fail to respond to standard treatments. Even then, it takes two months or more to confirm the diagnosis. Patients have to wait for the test results before they can receive life-saving second-line drugs. During this period, they can spread the multidrug-resistant disease to others. Often the patients die before results are known, especially if they are HIV-infected in addition to having MDR-TB.

RELATED DOCUMENTS

WHO policy statement [pdf 78kb]

Expert group report - *Molecular line probe assays for rapid screening of patients at risk of MDR-TB* [pdf 892kb]

Further information on the UNITAID MDR-TB diagnostic initiative [pdf 652kb]

Feasibility study - Am J Respir Crit Care Med, Vol 177, pp 787-792, 2008 (American Thoracic Society - official journal). *Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa* [pdf 402kb]

Turning evidence into policy and policy into practice - the steps to building Lesotho's modern TB central laboratory [pdf 2.71Mb]

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. *Eur Resp J* 2008

A commercial line probe assay for the rapid detection of rifampicin resistance in Mycobacterium tuberculosis: a

http://www.who.int/tb/features_archive/mdrtb_rapid_tests/en/index.html

EXPERT REVIEWS

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

Expert Rev. Resp. Med. 2(5), 583–588 (2008)

Daphne I Ling, Alice A Zwerling and Madhukar Pai†

Growing concerns about the spread of multidrug-resistant tuberculosis (MDR-TB) and the emergence of extensively drug-resistant TB have triggered substantial interest in the development and application of rapid tests for the detection of drug-resistant TB. Molecular assays to detect

New initiatives by WHO, Stop TB Partnership, UNITAID and FIND

Rapid tests for drug-resistant TB to be made available in developing countries

The availability of rapid tests to detect MDR-TB in several developing countries was announced on 30 June 2008 during a press conference held at Palais des Nations. *From left to right:* Dr. Robert Matiru, General Manager, Global Drug Facility; Dr. Giorgio Roscigno, FIND CEO; Dr. Mario Raviglione, Director, WHO Stop TB Department; and Dr. Jorge Bermudez, Executive Secretary of UNITAID

Geneva -- People in low-resource countries who are ill with multidrug-resistant (MDR) TB will get a faster diagnosis -- in two days, not the standard two to three months -- and appropriate treatment thanks to two new initiatives unveiled today by the World Health Organization (WHO), the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND).

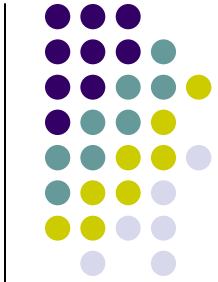
MDR-TB is a form of TB that responds poorly to standard treatment because of resistance to the first-line drugs isoniazid and rifampicin. At present it is estimated that only 2% of MDR-TB cases worldwide are being diagnosed and treated appropriately, mainly because of inadequate laboratory services. The initiatives announced today should increase that proportion at least seven-fold over the next four years, to 15% or more.

Countries that will receive MDR-TB diagnostics through this initiative:

Azerbaijan, Bangladesh, Côte d'Ivoire, the Democratic Republic of Congo, Ethiopia, Georgia, Indonesia, Kazakhstan, Kyrgyzstan, Lesotho, Republic of Moldova, Myanmar, Tajikistan, Ukraine, Uzbekistan, Viet Nam

http://www.finddiagnostics.org/

While the evidence-base has grown, there are several challenges…



- Lack of rigour in TB diagnostic studies
- Still focused on sensitivity and specificity
  - Lack of evidence on patient-centered outcomes and added value of new tests
- Difficult to keep the evidence up to date in rapidly evolving fields
- Evidence is not well used in policies and guidelines on diagnostics

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies

The GRADE system can be used to grade the quality of evidence and strength of recommendations for diagnostic tests or strategies. This article explains how patient-important outcomes are taken into account in this process

SUMMARY POINTS

As for other interventions, the GRADE approach to grading the quality of evidence and strength of recommendations for diagnostic tests or strategies provides a comprehensive and transparent approach for developing recommendations

Cross sectional or cohort studies can provide high quality evidence of test accuracy

However, test accuracy is a surrogate for patient-important outcomes, so such studies often provide low quality evidence for recommendations about diagnostic tests, even when the studies do not have serious limitations

Inferring from data on accuracy that a diagnostic test or strategy improves patient-important outcomes will require the availability of effective treatment, reduction of test related adverse effects or anxiety, or improvement of patients' wellbeing from prognostic information

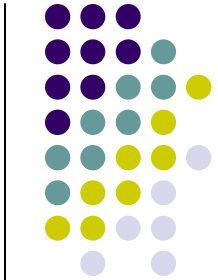
Judgments are thus needed to assess the directness of test results in relation to consequences of diagnostic recommendations that are important to patients

BMJ 2008

We need to move beyond sensitivity and specificity

- Need to study outcomes such as:
  - accuracy of diagnostic algorithms (rather than single tests) and their relative contributions to the health care system;
  - incremental or added value of new tests;
  - impact of new tests on clinical decision-making and therapeutic choices;
  - cost-effectiveness in routine programmatic settings;
  - impact on patient-centered outcomes; and societal impact of new tools.

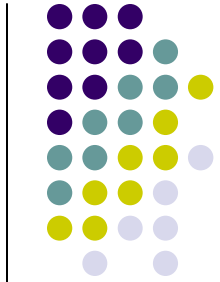
Promoting the use of evidence in policies and guidelines



- Promote transparency in guideline and policy development
  - E.g. GRADE is now used for all ATS policy statements and all WHO guidelines
- Include methodologists in guideline panels
  - E.g. Methodologists are co-chairs of guideline committees at WHO
- Stop TB Partnership's New Diagnostics Working Group has created a new subgroup on Evidence Synthesis for TB Diagnostics [Co-chairs: M Pai & R O'Brien]
  - To support the development of new systematic reviews, facilitate the development and dissemination of evidence summaries on new diagnostics, and actively promote their use in guideline and policy development processes, along the lines of the GRADE approach

http://www.stoptb.org/wg/new_diagnostics/

Acknowledgements:
Andy Ramsay & Rick O'Brien



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PLoS MEDICINE

Research in Translation

Evidence-Based Tuberculosis Diagnosis

Madhukar Pai*, Andrew Ramsay, Richard O'Brien

There is great excitement in the tuberculosis (TB) scientific community over the introduction of new tools into TB control activities. The development of new tools is an important component of the Global Plan to Stop TB and the World Health Organization's new global Stop TB Strategy [1,2]. Anticipating the introduction of new tools, the Stop TB Partnership has established a Retooling Task Force to develop a framework for engaging policy makers to foster accelerated adoption and implementation of new tools into TB control programs [3].

While new tools offer great promise in clinical medicine and in public health, limited resources and the movement toward evidence-based guidelines and policies require careful validation of new tools prior to their introduction for routine use. The world spends an estimated US$1 billion per year on diagnostics for TB [4]. It is important to ensure that steps involved in the policy process include a comprehensive review of the evidence, as well as expert opinion and judgment (Box 1).

High-quality evidence on TB diagnostics is critical for the development of evidence-based policies on TB diagnosis, and, ultimately, for effective control of the global TB epidemic. While primary diagnostic trials are needed to generate data on test accuracy and operational performance, systematic reviews provide the best synthesis of current evidence on any given diagnostic test [8]. Although a large number of trials on TB diagnostics have been published, surprisingly, no systematic reviews were published until recently. In the past few years, at least 30 systematic reviews and meta-analyses have been published on various TB tests [9–38]. These reviews have synthesized the results of more than 1,000 primary studies, providing valuable insights into the diagnostic accuracy of various tests (Table 1, Box 2).

in the latter setting. However, meta-analyses on IGRAs have highlighted the lack of evidence on the predictive ability of these assays in identifying those individuals with TB infection who are at highest risk for progressing to active disease. Several cohort studies are ongoing (reviewed elsewhere [39]), and these should provide useful evidence on this unresolved issue.

For active TB, serological tests have been attempted for decades. Two meta-analyses have convincingly shown that existing commercial antibody-based tests have poor accuracy and limited clinical utility [29,30]. Despite this evidence, dozens of commercial serological tests continue to be marketed, mostly in private sectors of countries that lack diagnostic regulatory bodies [4].

Nucleic acid amplification tests (NAATs) were considered to be a major breakthrough in TB diagnosis when they were first introduced. A series of meta-analyses have shown

Pai M, Ramsay A, O'Brien R (2008) Evidence-based tuberculosis diagnosis. PLoS Med 5(7): e156.