

APPROACHES TO IMPROVE SPUTUM SMEAR MICROSCOPY FOR TUBERCULOSIS DIAGNOSIS

- EXPERT GROUP MEETING -

Date and time: 7 September 2009, 08:30 – 18:00
Venue: Crowne Plaza Hotel, Geneva, Switzerland

BACKGROUND

Direct sputum smear microscopy is the most widely used test for the diagnosis of pulmonary tuberculosis (TB), available in most primary health care laboratories at health centre level. The majority of laboratories use conventional light microscopy to examine Ziehl-Neelsen stained direct smears, documented to be highly specific in areas with a high prevalence of TB but with varying sensitivity (20-80%). Besides being labour-intensive, direct sputum smear microscopy may have considerable patient costs and inconvenience associated with the need to submit multiple sputum specimens over a period of up to three days. A number of TB control programmes have reported high rates of initial patient default as a result.

Simple rapid diagnostics that can replace direct smear microscopy at the lower levels of health services are urgently needed; however, it is also recognized that these are unlikely to become available in the short to medium term. Considerable recent research has therefore focused on ways to improve smear microscopy and its yield for TB case-finding. A series of systematic reviews commissioned in 2005 by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) covered three ways of improving sputum microscopy: sputum processing methods, fluorescence microscopy, and more efficient direct examination of specimens. An Expert Consultation by WHO was subsequently convened in September 2005 to consider the evidence in these reviews, with the following findings and recommendations:

Sputum processing methods

The systematic review on sputum processing methods reported that chemical processing (by bleach) prior to concentration by centrifugation or overnight sedimentation improved the sensitivity of smear microscopy by 18% and 23%, respectively. In all studies reported, sensitivity for processed smears was higher than for direct smears, including one study involving HIV-infected individuals (with mycobacterial culture as gold standard) where sensitivity was increased by 11%. The Expert Consultation did, however, not recommend the use of bleach with centrifugation or sedimentation at that time because of large variations in study methodology and inconsistencies in the results reported. Additionally, concerns were raised about the safety of centrifugation-based methods at peripheral laboratory level, and the feasibility of implementing such methods on a large-scale.

The Expert Consultation called for research to develop standardized methods and understand the basis of the wide variability in performance reported. A number of research groups have addressed this in studies since 2005.

Fluorescence microscopy

The systematic review of fluorescence microscopy (FM) reported sensitivity to be 10% higher than conventional ZN microscopy, and noted that examination of fluorochrome-stained smears took 25% of the time taken to examine ZN-stained smears. The Expert Consultation in 2005 recommended that FM be considered at all levels of the health system, particularly in high HIV prevalence settings and in settings with high laboratory workload. However, it was also acknowledged that FM based on the technology available in 2005 (expensive microscopes with

mercury vapour light sources) would be difficult to implement in resource-poor settings. In addition, concern was expressed about the lack of internationally-agreed methods for external quality assessment of FM.

The Expert Consultation called for research to develop fluorescence microscopes that could overcome the limitations of existing equipment, particularly those related to capital costs and maintenance needs. Since then it has been shown that low-cost ultra-bright light-emitting diodes (LEDs) with a long lifespan could replace expensive mercury vapour lamps and enable the development of microscopy systems that are substantially less expensive than conventional FM, offering the possibility for widespread use of LED-based FM in resource-limited settings. In view of these potential advantages, several companies have developed inexpensive, robust LED microscopes or LED attachments for routine use in high-burden countries. Preliminary data suggest that LED microscopy is feasible and as accurate as standard FM and field evaluation studies have been completed in several countries.

Serial sputum specimen examination ('front-loading')

A systematic review of the yield of serial sputum specimen examinations for the diagnosis of TB confirmed that the majority of TB cases were detected with the first sputum specimen (85.8%), while the average incremental yield of the second and third sputum specimen was 11.9% and 3.1% respectively. The Expert Consultation in 2005 concluded that, although the evidence was compelling, the examination of three specimens would be necessary as long as the definition of a smear-positive case required two positive smears.

The Expert Consultation called for further research on the sensitivity and specificity of a revised case definition based on one positive smear. This research was subsequently undertaken by a number of international partners and presented to the WHO Strategic and Technical Advisory group for TB (STAG-TB). In 2007, the definition of a smear-positive case was revised and the minimum number of sputum specimens to be examined reduced from three to two in settings where a well-functioning external quality assurance system exists, the workload is high, and human resources are limited. This approach greatly reduces the workload in laboratories, a considerable advantage in countries with high HIV prevalence.

The Expert Consultation in 2005 also called for research on the optimal timing of specimen collection to minimise delays in the patient diagnostic pathway. Currently, most sputum specimens - following the spot-morning-spot system - are examined on the second day that the patient presents. Alternatively, frontloaded microscopy (also called 'same day' or 'one-stop' microscopy) involves sputum smear microscopy approaches that entails the majority (or all) of the specimens being examined on the first day. Studies to determine whether the number of patient visits required for standard TB diagnosis can be reduced, and whether the delay in diagnosis can be cut from three days to one day, have subsequently been conducted, also investigating the possibility that drop-out from the diagnostic pathway can be significantly reduced.

WORLD HEALTH ORGANIZATION: EVIDENCE-BASED PROCESS FOR POLICY GUIDANCE

In order to facilitate rapid policy guidance on the use of new diagnostic tools or novel approaches using existing tools, WHO has recently developed a systematic, structured, evidence-based process. The first step constitutes a systematic review and meta-analysis of available data, using standard methods appropriate for diagnostic accuracy studies. The second step involves the convening of an Expert Group to evaluate the strength of the evidence base and recommend operational and logistic considerations for mainstreaming such tools/approaches into national TB control programmes, and/or identify gaps to be addressed in future research. The third and final step involves WHO policy guidance on the use of these tools/approaches, presented to STAG-TB for endorsement and subsequent dissemination to member states for implementation.

MEETING OBJECTIVES

- To review the evidence base and evaluate data from systematic reviews (including updates to the 2005 systematic reviews) commissioned by WHO on sputum processing methods, frontloaded microscopy and LED microscopy;
- To identify the implications of adopting such methods/approaches for laboratory infrastructure development, human resource requirements, and research gaps needed for programmatic implementation of these tools/approaches;
- To outline potential issues to be addressed by WHO in subsequent policy recommendations.

EXPECTED OUTCOMES

- Evidence-based recommendations on the use of sputum processing methods, frontloaded microscopy and LED microscopy to improve sputum smear microscopy for TB diagnosis;
- Consensus on laboratory infrastructure, human resource requirements and further operational research data needed for programmatic implementation of sputum processing methods, frontloaded microscopy and LED microscopy;
- Development of WHO policy guidance on the use of sputum processing methods, frontloaded microscopy and LED microscopy to improve sputum smear microscopy for TB diagnosis.

PROVISIONAL AGENDA

Chair: P Nunn & K Weyer, WHO
 Rapporteur: B Squire

08:30 - 08:40	Welcome	M Raviglione/R Ridley
08:40 - 08:50	Introduction Meeting objectives and expected outcomes	K Weyer
08:50 - 09:00	Declaration of interest by Expert Group members	Chair
09:00 - 09:20	Grading quality of evidence and strength of recommendations: Brief overview of GRADE	K Steingart
09:20 - 09:30	Background to current systematic reviews and methods used	K Steingart
09:30 - 10:00	Systematic review: Frontloaded sputum microscopy for the diagnosis of pulmonary TB	A Cattamanchi
10:00 - 10:30	Discussion	All
10:30 - 11:00	Draft recommendations	All
BREAK 11:00 - 11:15		
11:30 - 12:00	Systematic review: Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis	A Cattamanchi
12:00 - 12:30	Discussion	All
12:30 - 13:00	Draft recommendations	All
LUNCH 13:00 - 14:00		
14:00 - 14:30	Systematic review: Light emitting diode (LED) fluorescence microscopy for TB diagnosis	J Minion/M Pai
14:30 - 15:00	Laboratory infrastructure and human resource requirements needed for implementation of LED microscopy	C Boehme
15:00 - 16:00	Discussion	All
BREAK 16:00 - 16:15		
16:15 - 16:30	GRADE summary	K Steingart
16:30 - 17:30	Final recommendations	Chair
17:30 - 18:00	Next steps and closing	Chair

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