Implementation and scale-up of the Xpert MTB/RIF system for rapid diagnosis of tuberculosis and multidrug-resistance

GLOBAL CONSULTATION

Date and time: 30 November - 2 December 2010
Venue: Centre International de Conférences de Gèneve (CICG)
17, Rue de Varembé, Geneva, Switzerland

BACKGROUND

Earlier and improved tuberculosis (TB) case detection - including smear-negative disease - as well as expanded capacity to diagnose multidrug-resistant tuberculosis (MDR-TB) are global priorities for TB control. MDR-TB poses formidable challenges due to its complex diagnostic and treatment challenges, while HIV-associated TB largely goes undetected due to the limitations of current diagnostic techniques. Alarming increases in MDR-TB, the global emergence of extensively drug-resistant TB (XDR-TB), documented institutional transmission, and rapid mortality in MDR-TB and XDR-TB patients with HIV co-infection have highlighted the urgency for rapid diagnostic methods.

No single test currently satisfies all the demands of 'quick', 'cheap', and 'easy'. Commercially available liquid culture systems and molecular line probe assays for rapid detection of MDR-TB have been endorsed by WHO; however, due to their complexity and cost, as well as the need for sophisticated laboratory infrastructure, uptake has been limited in many resource-constrained settings.

Genotypic (molecular) methods have considerable advantages for scaling up programmatic management and surveillance of drug-resistant TB, offering speed of diagnosis, standardised testing, potential for high through-put, and fewer requirements for laboratory biosafety. Since the development in the early 1980s of the polymerase chain reaction (PCR), the first and most familiar method to amplify nucleic acid sequences, molecular diagnostics have been widely expected to have a major impact on clinical medicine. However, despite several theoretical advantages, the use of molecular tests for TB has been limited, largely due to the complexities of DNA extraction, amplification and detection, and the biosafety concerns related to manipulating Mycobacterium tuberculosis organisms. In addition, commercial nucleic acid amplification tests (NAAT) proved to be significantly less sensitive than microbiological culture, especially for smear-negative TB. Moreover, culture largely remained necessary as a precursor to drug-susceptibility testing, while scale-up of conventional culture and drug-susceptibility services remained slow and expensive, compounded by huge demands on laboratory infrastructure and human resources.

Over the past five years, and with support from NIH, the Foundation for Innovative New Diagnostics (FIND) has partnered with Cepheid, Inc. (Sunnyvale, CA) and the University of Medicine and Dentistry of New Jersey (UMDNJ, Newark, NY) to develop an automated, cartridge-based NAAT for TB based on the GeneXpert multi-disease platform. The GeneXpert system was launched in 2004 and simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing. The GeneXpert platform is currently the only one of its kind and uses a cartridge containing lyophilised reagents, buffers and washes. Target detection and characterization is performed in real time using a six-colour laser detection device.

WORLD HEALTH ORGANIZATION: EVIDENCE-BASED POLICIES FOR TB DIAGNOSIS

In order to facilitate rapid policy guidance on the use of new diagnostic tools, new methods, and/or novel approaches using existing tools, WHO/STB has developed a systematic, structured, evidence-based process: The first step involves a systematic review and meta-analysis of available data (where feasible), 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 logistical considerations for mainstreaming such tools/approaches into national TB control programmes, and/or identify gaps to be addressed in future research. The third step involves WHO policy guidance on the use of these tools/approaches, presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) for endorsement and subsequent dissemination to Member States for implementation.

An **Expert Group** meeting convened by WHO in September 2010 reviewed data from four published papers on Xpert-MTB/RIF, large multi-centre laboratory validation and demonstration studies coordinated by FIND, and unpublished data from 12 investigator-driven, single-centre studies, using the GRADE process. The evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB-RIF for detection of TB and rifampicin resistance. The Expert Group therefore recommended that:

- Xpert MTB/RIF should be used *as the initial diagnostic test* in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation);

- Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications).

- Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

- Several operational conditions need to be met for successful implementation of Xpert MTB/RIF - stable electrical supply, security against theft, trained personnel, adequate storage space, annual calibration of the instrument by a commercial supplier, and biosafety precautions similar to those for direct sputum microscopy should all be in place.

- A key consideration is the need for rapid access to appropriate treatment and care for all TB and MDR-TB patients who will be rapidly identified by the introduction of Xpert MTB/RIF in diagnostic and screening algorithms.

STAG-TB endorsed the Expert Group recommendations and advised that implementation of Xpert MTB/RIF technology be phased in within the context of comprehensive national TB and MDR-TB strategic plans. STAG-TB therefore recommended that WHO:

- Develop a global strategy for rapid uptake of Xpert MTB/RIF in a systematic and phased approach, including mechanisms to monitor and assess the roll-out of Xpert MTB-RIF, with a clear plan to document the impact on case detection, MDR response scale-up and cost-effectiveness.

- Proceed with a Global Consultation on the implementation considerations for scale-up of Xpert MTB/RIF under routine programme conditions (including diagnostic algorithms, logistics, procurement and distribution, quality assurance, and waste disposal).

- Assist countries with technical support and planning for inclusion of Xpert MTB/RIF in revised diagnostic algorithms.

MEETING OBJECTIVES

- To discuss the positioning of Xpert MTB/RIF technology in existing TB diagnostic algorithms for risk groups (eg. MDR-TB, TB-HIV) at different tiers of health services;
- To discuss implementation considerations for scale-up of Xpert MTB/RIF under routine programme conditions (including logistics, procurement and distribution, quality assurance, and waste disposal);
- To discuss a global strategy for rapid uptake of Xpert MTB/RIF in a systematic and phased approach, including mechanisms to monitor the roll-out of Xpert MTB-RIF and document the impact on case detection, MDR response scale-up and cost-effectiveness.

EXPECTED OUTCOMES

- Agreement on the positioning of Xpert MTB/RIF in TB diagnostic algorithms for risk groups at different levels of health services;
- Agreement on key implementation considerations for programmatic roll-out of Xpert MTB/RIF;
- Agreement on a global framework for rapid uptake of Xpert MTB/RIF within national TB and MDR strategic plans.

Provisional Agenda

TUESDAY, 30 NOVEMBER 2010 VENUE: CICG ROOM 3		
08:00 - 09:00	**Registration**	
Session 1: Setting the scene		**Chair: M Raviglione**
09:00 - 9:15	**Welcome**	M Raviglione
09:15 - 09:30	**Meeting scope and objectives**	K Weyer
09:30 - 10:00	**New frontiers changing diagnostic paradigms**	G Roscigno
10:00 - 10:30	**Responding to change: Rapid policy development by WHO**	M Raviglione & K Weyer
10:30 - 11:00	*Coffee break*	
Session 2: From development to evidence to implementation		**Chair: D Cirillo**
11:00 - 11:30	**Xpert MTB/RIF: development and analytical performance** I *Questions & discussion*	M Perkins
11:30 - 12:15	**Xpert MTB/RIF: evidence and operational considerations** I *Questions & discussion*	C Boehme
12:15 - 12:45	**Xpert MTB/RIF: update on price negotiations and market dynamics** I *Questions & discussion*	G Roscigno
12:45 - 14:00	*Lunch break*	
Session 3: Making it work – cost, capacity and resources		**Chair: M Iademarco**
14:00 - 14:25	**Xpert MTB/RIF in the Global Plan 2011-2015 – what will it cost?** I *Questions & discussion*	K Floyd
14:25 - 14:50	**Xpert MTB/RIF: Scenarios for cost-effectiveness** I *Questions & discussion*	A Vassall
14:50 - 15:15	**From diagnosis to treatment & care: the missing links** I *Questions & discussion*	P Nunn
15:15 - 15:30	**An ethical dilemma: diagnosis without treatment** I *Questions & discussion*	A Reis
15:30 - 15:45	**Xpert MTB/RIF: opportunity to enhance private sector** engagement I *Questions & discussion*	M Uplekar
15:45 - 16:10	*Coffee break*	
Session 4: Reality check – country, civil society and patient perspectives		**Chair: J Chakaya**
16:10 - 16:30	**Use of Xpert MTB/RIF in resource-limited settings: Tanzania** **Use of Xpert MTB/RIF in the private sector: Pakistan**	S Egwaga A Khan
16.30 - 16:50	**Patient perspectives:** 10 min each	L Cheshire, T Otwoma
16:50 – 17:10	**Civil society perspectives:** 10 min each	J Syed, F Varaine
17:10 – 17:30	*Questions & discussion*	
Session 5: Preparation for Day 2 Group Work		**Chair: K Weyer**
17:30 - 18:15	**Presentation of draft diagnostic algorithms and key principles** Group 1: MDR-TB Group 2: TB-HIV Group 3: DOTS expansion and enhancement	E Jaramillo H Getahun K Lonnroth
18:30 Cocktail reception		

WEDNESDAY, 1 DECEMBER 2010		Chair: K Castro
Session 6: From the WHAT to the HOW - Break-out group discussions (Structured format, facilitated by WG chairs/secretariats, rapporteurs to report back at plenary)		
9:00 - 12:00 Including Coffee break	**Each group to address three questions:** 1. Where does Xpert MTB/RIF fit into diagnostic algorithms? 2. How will we make it work in tiered health/laboratory services? 3. Where are the gaps and what are the needs for scale-up? **Expected outcomes:** 1. Consensus on diagnostic algorithms 2. Consensus on positioning of Xpert MTB/RIF in tiered services 3. Consensus on priorities for scale-up **Group 1: MDR-TB**: ***Venue: CICG Room 7-8*** Facilitator: A Khan Rapporteur: D Falzon — WHO back-up: E Jaramillo & F Wares **Group 2: TB-HIV: *Venue: CICG Room 13*** Facilitator: J Varma Rapporteur: D Sculier — WHO back-up: H Getahun **Group 3: DOTS expansion & enhancement: *Venue: CICG Room 14*** Facilitator: J Chakaya Rapporteur: S Sahu — WHO back-up: K Lonnroth & M Uplekar	
Session 7: Report-back from break-out group discussions, identifying consensus and controversies		**VENUE: CICG ROOM 3**
12:00 - 13:00	**10-minute presentations by Rapporteurs from each Group** Discussion	
13:00 – 14:00	*Lunch Break*	
Session 8: Consensus building: Break-out group discussions on consensus and controversies (Participants re-allocated to Groups, structured format, facilitated by WG chairs/secretariats, feedback to plenary)		
14:00 - 16:00 Including Coffee break	**Group 1: MDR-TB**: ***Venue: CICG Room 7-8*** Facilitator: A Khan Rapporteur: D Falzon — WHO back-up: E Jaramillo & F Wares **Group 2: TB-HIV: *Venue: CICG Room 13*** Facilitator: J Varma Rapporteur: D Sculier — WHO back-up: H Getahun **Group 3: DOTS expansion & enhancement: *Venue: CICG Room 14*** Facilitator: J Chakaya Rapporteur: S Sahu — WHO back-up: K Lonnroth & M Uplekar	
16:00 - 16:30	*Coffee break*	
Session 9: Report-back from break-out group discussions, presenting consensus decisions		**VENUE: CICG ROOM 3**
16:30 - 17:30	**10-minute presentations by Rapporteurs from each Group** Discussion	
17:30 - 18:00	Summary of Day 2	K Castro

THURSDAY, 2 DECEMBER 2010 VENUE: CICG ROOM 18		Chair : T Shinnick
Session 10: Moving forward with Xpert MTB/RIF implementation and scale-up		
09:00 - 9:30	**Learning by doing through EXPAND-TB** Discussion	E Adam
09:30 - 10:00	**Increasing access to vulnerable groups through TBREACH** Discussion	L Ditiu
10:00 - 10:30	**Mobilising country capacity through TBCARE** Discussion	A Piatek
10:30 - 11:00	**Targeting HIV settings through PEPFAR** Discussion	B Coggin
11:00 - 11:30	*Coffee break*	
11:30 - 12:00	**Country plan for scaling up Xpert MTB/RIF: South Africa** Discussion	G Coetzee & L Mvusi
12:00 - 12:45	**Global Roadmap for scaling up Xpert MTB/RIF** Discussion	K Weyer
12:45 – 13:00	**Next steps and closing**	H Nakatani
13:00 – 14:00	*Lunch break*	