Serological tests for tuberculosis: the evidence is reviewed

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Chennai, December 13 2010

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Disclosure

▸ I serve as co-chair of the Evidence Synthesis subgroup of Stop TB Partnership's New Diagnostics Working Group

Overview

- WHO recommendations on the use of serological tests
- Review of the evidence
    - Background
    - Serological tests: An updated systematic review and meta-analysis
    - Cost effectiveness model of serological tests in India

WHO issues a strong recommendation *against* the use of serological tests

- WHO Expert Group recommended that serological tests should not be used in individuals suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status (22 July 2010)

- The WHO Strategic and Technical Advisory Group for TB (STAG-TB, highest policy making body for TB at WHO) endorsed the Expert Group recommendations (27 September 2010) http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf

- A negative WHO policy on TB serology is expected in early 2011

BACKGROUND

Serological (antibody-detection) tests for TB…

…have been around for a long time

…are attractive, especially if made into point of care tests

▸ But existing serological tests have variable accuracies and a limited clinical role (based on 3 systematic reviews)

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[6,9*]

CLINICAL AND VACCINE IMMUNOLOGY, Feb. 2009, p. 260–276
1556-6811/09/$08.00+0   doi:10.1128/CVI.00355-08
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Vol. 16, No. 2

Performance of Purified Antigens for Serodiagnosis of Pulmonary Tuberculosis: a Meta-Analysis[▽†]

Karen R. Steingart,[1*] Nandini Dendukuri,[2] Megan Henry,[3]‡ Ian Schiller,[2] Payam Nahid,[4] Philip C. Hopewell,[1,4] Andrew Ramsay,[5] Madhukar Pai,[2] and Suman Laal[6,7,8]

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

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WHO/TDR Laboratory-based…2008

- Rapid - test result (< 15 mins)
- Simple - 1 or 2 steps, minimal training and no equipment
- Easy to interpret - card or strip format with visual readout
- Gold standard - culture plus clinical follow-up
- Archived specimens

World Health Organization

Diagnostics Evaluation Series No.2

Laboratory-based evaluation of 19 commercially available rapid diagnostic tests for tuberculosis

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Table 4. Performance of 19 rapid tests for pulmonary tuberculosis

	Manufacturer	Rapid Test	Sensitivity % (95% CI)	Specificity % (95% CI)
1	ABP Diagnostics	Focus Sure Check TB	8 (4-11)	95 (92-99)
2	Advanced Diagnostics	Tuberculosis Rapid Test	40 (33-46)	53 (45-61)
3	American Bionostica	Rapid Test for TB	20 (15-26)	80 (73-86)
4	Ameritek dBest	One Step TB Test	34 (27-40)	68 (61-76)
5	BioMedical Products Corp	TB Rapid Screen Test	49 (42-56)	57 (49-65)
6	Chembio	TB Stat-Pak II	32 (25-38)	83 (76-89)
7	CTK Biotech TB Antibody	Onsite Rapid Screening Test	27 (21-33)	69 (62-77)
8	Hema Diagnostic	Rapid 1-2-3 TB Test	36 (29-42)	72 (65-80)
9	Laboratorio Silanes	TB-Instantest	38 (31-44)	70 (62-77)
10	Millenium Biotechnology	Immuno-Sure TB Plus	2 (0-5)	99 (97-100)
11	Minerva Biotech	V Scan	21 (16-27)	89 (84-94)
12	Mossman Associates	MycoDot	36 (30-42)	87 (81-92)
13	Pacific Biotech	Bioline TB	19 (14-25)	95 (91-98)
14	Premier Medical Corporation	First Response Rapid TB	21 (16-27)	95 (92-99)
15	Princeton BioMeditech	BioSign M tuberculosis	1 (0-2)	99 (97-100)
16	Span Diagnostics	TB Spot ver 2.0	38 (32-45)	78 (71-85)
17	Standard Diagnostics	SD Rapid TB	21 (15-26)	96 (93-99)
18	UniMED International Inc	FirstSign MTB Card Test	60 (53-66)	58 (50-66)
19	Veda Lab	TB Rapid Test	13 (8-17)	98 (96-100)

ROC curve, commercial rapid tests for the diagnosis of pulmonary TB (n=355)
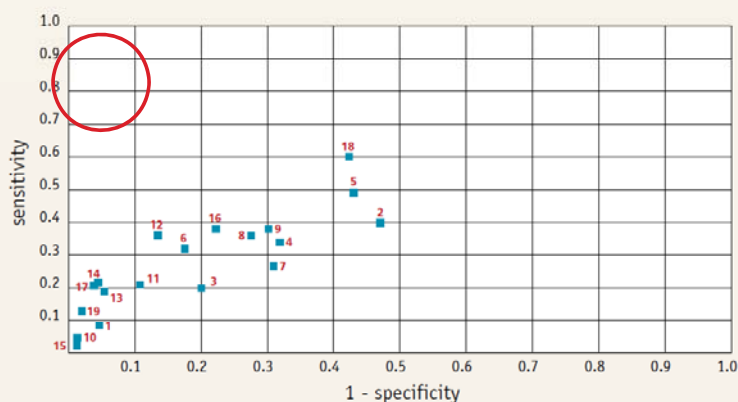
Sensitivity range: 1 to 60%
Specificity range: 53 to 99%

Current situation

▸ No serological TB test for clinical use is recommended by international guidelines nor approved by the US Food and Drug Administration

▸ Dozens of commercial serological tests based on detection of antibodies are marketed in many parts of the world, especially in developing countries with weak regulatory systems

Claims of high accuracy

▶ Package inserts are usually based on internal company data

SD STANDARD DIAGNOSTICS, INC.
156-68 Hagal-dong, Giheung-gu, Yongin-si, Kyonggi-do, Korea
Tel : 82-31-899-9700   Fax : 82-31-899-9740   http://www.standardia.com

2) Comparison SD Rapid TB vs. a commercial anti-TB ELISA
The SD Rapid TB have tested with positive and negative clinical samples tested by a leading commercial ELISA test. The result shows that the SD Rapid TB is very accurate to other commercial ELISA test.

		A Commercial PHA		Total Results
		Positive	Negative	
A commercial anti-M.tuberculosis ELISA kit	Positive	112	2	114
	Negative	1	350	351
Total Results		113	352	465

In a comparison of the SD Rapid TB versus a leading commercial ELISA test, results gave sensitivity of 98.2% (112/114), a specificity of 99.7 % (350/351), and a total agreement of 99.35% (462/465).

American Bionostica, Inc.

SUMMARY OF CLINICAL TEST RESULTS

Specimen no./origin	ABI Test Sensitivity	ABI Test Specificity
111 Mexico	64%	98%
100 Mexico	70%	100%
85 Russia	78%	91%
341 East Europe	89%	95%
321 Estonia Group 1	88%	97%
164 Estonia Group 2	93%	95%
73 Miami	92%	93%
200 Russia	86%	92%
95 Russia	85%	94%
19 Estonia	90%	89%
33 India (all positive)	91%	N/A
73 East Europe	72%	95%

TASHIMA Inc.

PERFOMANCE CHARACTERISTICS:

Sensitivity : Sera were collected from patients under anti TB treatment. Results of sputum examination were not available. Among 75 sera collected, samples were positive by the TB onsite Rapid screening Test Thus, the test sensitivity is 93%.

Specificity : In 53 sera derived from Northern America, all the samples were negative.

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## Based on a survey of more than 80 Indian laboratories, some preliminary estimates

• About 50 large and medium *private labs* alone are doing over 60,000 tests per month

• ~1.5 million TB serological (ELISA) tests every year

• @ $10 per test**, the market is worth at least $15 million (this is highly conservative)

**The cost is actually ~$10 per antibody (e.g. IgG). Testing for all 3 antibodies (IgG, IgA, IgM) is often done at cost of ~$30 per patient; for simplicity, we have used $10 per patient, a conservative estimate (RNTCP annual budget ~ $65 million)

Pai et al. Unpublished

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Case report 1: A 25-year-old man from Chhattisgarh presenting with cough, fever, and weight loss for several months received a TB serology test at a community clinic. Based on a false negative test result, the patient was sent home with a Rx for vitamins and cough syrup. Within a few weeks, his condition rapidly deteriorated. Sputum smear microscopy was 3+ positive for acid-fast bacilli and the patient eventually died of his disease.
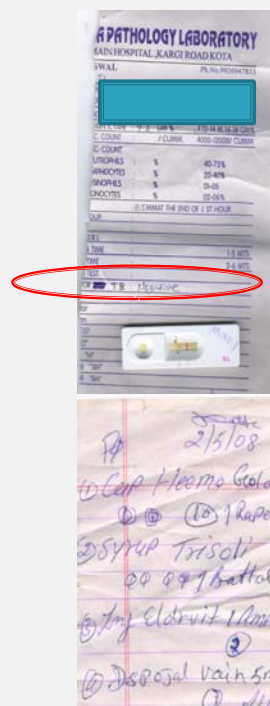
Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: An updated systematic review and meta-analysis

Steingart KR, Flores LL, Dendukuri N , Schiller I, Laal S, Ramsay A, Hopewell PC, Pai M

Commercial serological tests, framing the question

Population - adults and children with and without HIV infection suspected of active TB, all countries

Intervention - commercial serological test

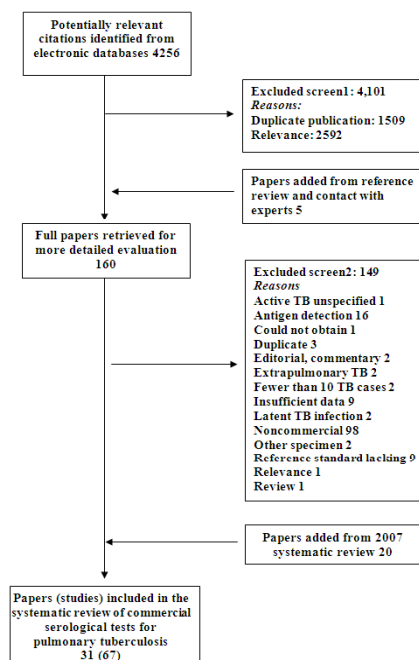Comparison - no test/smear microscopy

Outcomes - sensitivity and specificity

Reference standard - culture (either solid or liquid)

Excluded studies published before 1990 and studies with < 10 TB cases

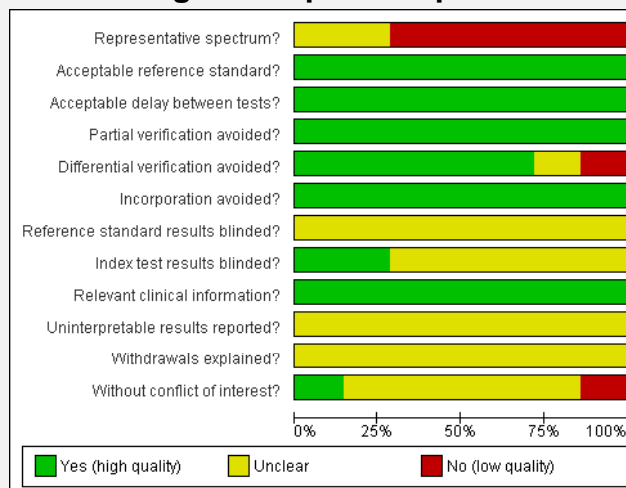## Results - Pulmonary TB

Flow of studies


```
Potentially relevant
citations identified from
electronic databases 4256

            →  Excluded screen1: 4,101
               Reasons:
               Duplicate publication: 1509
               Relevance: 2592

            ←  Papers added from reference
               review and contact with
               experts 5

Full papers retrieved for
more detailed evaluation
160

            →  Excluded screen2: 149
               Reasons
               Active TB unspecified 1
               Antigen detection 16
               Could not obtain 1
               Duplicate 3
               Editorial, commentary 2
               Extrapulmonary TB 2
               Fewer than 10 TB cases 2
               Insufficient data 9
               Latent TB infection 2
               Noncommercial 98
               Other specimen 2
               Reference standard lacking 9
               Relevance 1
               Review 1

            ←  Papers added from 2007
               systematic review 20

Papers (studies) included in the
systematic review of commercial
serological tests for
pulmonary tuberculosis
31 (67)
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Study characteristics

▸ 67 studies used 18 different serological tests (anda-TB IgG most common, 19% of studies)

▸ 32 (48%) studies in low/middle-income countries

▸ Zero studies involved children; 1 study involved HIV-infected individuals

▸ Median TB patients 41 (IQR 33, 54)

▸ Studies were considered low quality (only 28% included a representative patient spectrum; only 51% reported blinding of the serological test result)

▸ No studies reported on patient-important outcomes
- increased number of TB patients detected
- decreased number false-positive TB patients treated
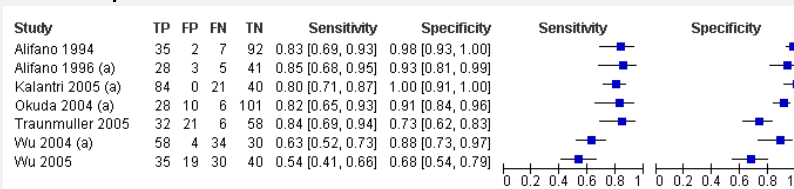- decreased number of patients lost due to fewer visits

Plot of sensitivity versus specificity for all 67 studies in the review

Sensitivity range: 0 to 100%
Specificity range: 31 to 100%

anda-TB IgG (Anda Biologicals, Strasbourg, France) studies involving smear-positive patients

Steingart et al. submitted manuscript

anda-TB IgG

A. Smear positive

Study	TP	FP	FN	TN	Sensitivity	Specificity
Alifano 1994	35	2	7	92	0.83 [0.69, 0.93]	0.98 [0.93, 1.00]
Alifano 1996 (a)	28	3	5	41	0.85 [0.68, 0.95]	0.93 [0.81, 0.99]
Kalantri 2005 (a)	84	0	21	40	0.80 [0.71, 0.87]	1.00 [0.91, 1.00]
Okuda 2004 (a)	28	10	6	101	0.82 [0.65, 0.93]	0.91 [0.84, 0.96]
Traunmuller 2005	32	21	6	58	0.84 [0.69, 0.94]	0.73 [0.62, 0.83]
Wu 2004 (a)	58	4	34	30	0.63 [0.52, 0.73]	0.88 [0.73, 0.97]
Wu 2005	35	19	30	40	0.54 [0.41, 0.66]	0.68 [0.54, 0.79]

B. Smear negative

Study	TP	FP	FN	TN	Sensitivity	Specificity
Alifano 1996 (c)	23	3	13	41	0.64 [0.46, 0.79]	0.93 [0.81, 0.99]
Luh 1996 (b)	50	33	20	260	0.71 [0.59, 0.82]	0.89 [0.85, 0.92]
Okuda 2004 (b)	19	10	7	101	0.73 [0.52, 0.88]	0.91 [0.84, 0.96]
Wu 2004 (b)	30	4	56	30	0.35 [0.25, 0.46]	0.88 [0.73, 0.97]

Bivariate meta-analysis, random effects, pooled estimates
Smear+ Sensitivity = 76% (63,87); Specificity = 92% (74, 98)
Smear-   Sensitivity = 59% (10,96); Specificity = 91% (79, 96)

Steingart et al. submitted manuscript

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Summary ROC plots for anda-TB IgG showing better performance in studies of smear-positive patients (A) than smear-negative patients (B).The red squares are summary sensitivity and specificity
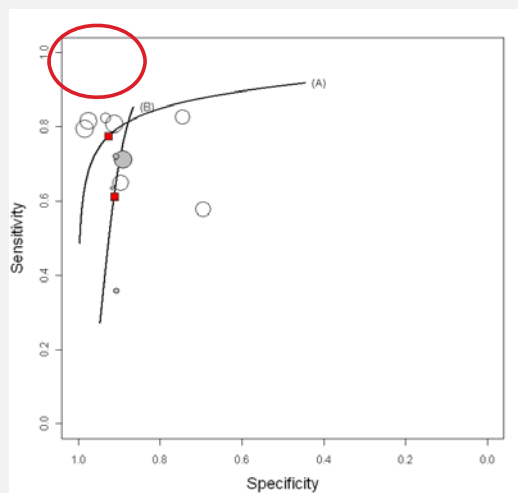
Steingart et al. submitted manuscript

Head-to-head comparison SDHO and smear microscopy, HIV-infected individuals

Test	Sensitivity % (95% CI)	Specificity (95% CI)
SDHO (Saint-Sauveur des Monts, Canada)	16 (5, 34)	90 (74, 98)
Smear microscopy	68 (49, 83)	100 (89,100)

- 55 HIV-infected pulmonary TB suspects, hospitalized and outpatient
- 31 culture-confirmed TB cases
- Median age 31
- Central African Republic

Kassa-Kelembho et al. Clin Vaccine Immunol. 2006 June; 13(6): 702–3

Discussion

The sensitivity and specificity estimates in the meta-analysis are likely to be overly optimistic for at least two reasons:

1. study quality generally suffered from lack of a representative patient spectrum and could have resulted in inflated estimates of test accuracy
2. publication bias was possible because studies with poor performance were unlikely to be unpublished

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NOVEMBER 8, 2010
THE POLITICAL SCENE
Hendrik Hertzberg and Ryan Lizza discuss the midterm results.

LETTER FROM INDIA

A DEADLY MISDIAGNOSIS
Is it possible to save the millions of people who die from TB?
by Michael Specter

SUBSCRIBE and save up to 88%
• SUBSCRIBE
• RENEW
• GIVE A GIFT
• INTERNATIONAL ORDERS
• DIGITAL EDITION

WELCOME   LOG IN | HEL

POPULAR   MOST E-MAILED   THIS ISSUE

Case report 2: A middle-aged woman from India complaining of cough received a serological TB test at a private medical clinic. Based on a false positive test result, the patient was misdiagnosed as having active TB disease and received a six month course of multidrug antituberculous therapy. After treatment completion, the patient's cough recurred, her condition worsened, and she was eventually diagnosed with active TB

Serological Testing for Active Tuberculosis in India is More Costly and Less Effective than Sputum Smear Microscopy

Dowdy DW, Steingart KR; Pai M

Hypothetical "Study Population"

▶ 1.5 million TB suspects
  ◦ Conservative estimate of annual number of serologic tests in India
▶ 1 in 7 actually have TB
  ◦ Estimate from FIND, comparable to other studies
▶ Among TB patients, 53% are "highly infectious"
  ◦ Would be diagnosed with 2 sputum smears in ideal lab
▶ 5% HIV prevalence
  ◦ 10% with access to ART (UNAIDS 2009); does not affect model results
▶ Accuracy estimates obtained from the systematic review

Dowdy et al., 2010 submitted manuscript

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What is the cost for 1.5 million TB suspects who undergo serologic testing in India?
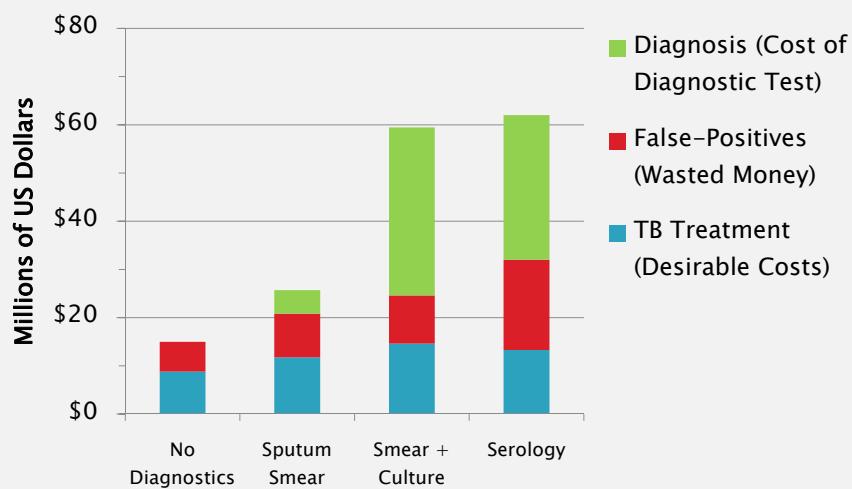
Dowdy et al., unpublished

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Table 3. Cost-Effectiveness of Diagnostic Strategies for 1.5 Million TB Suspects in India, Relative

Diagnostic Test	Cost (US$)	Additional TB Cases Treated	Additional False-Positive Cases Treated	Secondary Cases Averted
Sputum smear microscopy	$11.9 million	44,000	36,000	443,000
Sputum smear + TB culture	$45.0 million	71,000	48,000	555,000
Serological testing	$47.5 million	58,000	157,000	411,000
Rapid molecular testing	$52.8 million	86,000	12,000	629,000

Dowdy et al., 2010 submitted manuscript

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In conclusion

- **Published data on commercial serological tests for the diagnosis of active TB inconsistent and imprecise estimates of sensitivity and specificity**

- **Modeling study in a hypothetical cohort of 1.5 million adult Indian TB suspects suggests that serological testing for active TB is both more costly and less effective than sputum smear microscopy**

Acknowledgements
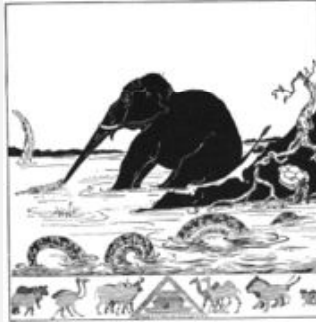
Questions?

"Satiable curiosity…
and that means he asked ever so many questions."

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STRATEGIC AND TECHNICAL ADVISORY GROUP
FOR TUBERCULOSIS
(STAG-TB)

REPORT OF THE TENTH MEETING

27–29 September 2010
WHO headquarters

Geneva, Switzerland

WHO/HTM/TB/2010.18

Report of the Tenth Meeting

**WHO STRATEGIC AND TECHNICAL ADVISORY GROUP
FOR TUBERCULOSIS
(STAG-TB)
27 - 29 September 2010**

Background

The World Health Organization (WHO) recognizes its critical role in supporting urgent national efforts to enable universal access to treatment and care in order to meet the Millennium Development Goal 6 of reversing TB incidence and the Stop TB targets of halving TB prevalence and mortality rates by 2015. The WHO Secretariat requires ongoing scientific, technical and strategic advice in TB care and control from its Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) to help guide implementation of the Stop TB Strategy and the Stop TB Partnership's Global Plan to Stop TB, 2006–2015.

The tenth meeting of STAG-TB took place at WHO headquarters in Geneva, Switzerland, on 27–29 September 2010. The meeting was organized by the WHO Stop TB Department (HTM/STB), which provides the Secretariat for the STAG-TB.

Overall objectives of STAG-TB

1. To provide to the Director-General independent evaluation of the strategic, scientific and technical aspects of WHO's Tuberculosis Area of Work;

2. To review progress and challenges in WHO's pursuit of its TB-related core functions:
   - Policies, strategies and standards;
   - Collaboration and support of countries' efforts;
   - Epidemiological surveillance, monitoring, evaluation and operational research;
   - Support to partnerships, advocacy and communications;

3. To review and make recommendations on committees, working groups, etc.;

4. To advise on priorities between possible areas of WHO activities.

Objectives of the tenth meeting

WHO requested STAG-TB to review and advise on the following areas of policy, strategy, technical assistance and analytical work for global TB control:

1. Revised roles in support of scaling up treatment of multidrug-resistant TB (MDR-TB), including in supporting technical review of Global Fund grant proposals, technical assistance to overcome bottlenecks, and monitoring and evaluation of implementation.

2. Plans for preparing guidance on evidence needed on the programmatic use of new anti-TB drugs, which are expected to become available in the next few years.

3. Draft WHO policy guidance for the use of new TB molecular diagnostics and draft recommendations on current serodiagnostics and IGRAs (interferon gamma release assays).

4. Development of evidence-based policies on active TB case-finding for earlier detection of cases.

5. Process for finalizing the WHO policy guidance on TB/HIV interventions.

6. Approaches to defining and measuring universal access and related TB prevention, care and control targets for 2015 and beyond.

7. Provision of effective support at regional and country levels for implementation of TB control measures.

8. Guidance on framing interventions to address the co-morbidity of TB and diabetes.

9. Priority-setting for addressing TB within maternal, women's and child health agendas.

The meeting agenda as adopted is attached as Annex 1, and Annex 2 provides the list of participants.

Dr Jeremiah Chakaya served as Chair of the Meeting. Dr Paula Fujiwara served as Vice-Chair.

STAG-TB members were joined at the meeting by the Chairs of some of the Stop TB Partnership's working groups and subgroups, invited technical experts, technical and development cooperation agencies and civil society partners, as well as WHO staff from headquarters and all regions.

Each STAG-TB session began with an introductory presentation by WHO staff or other experts, followed by comments from STAG-TB members serving as discussants. Open discussion was followed for each session by recommendations from STAG-TB members. WHO staff and STAG-TB discussants served jointly as session rapporteurs. Draft written recommendations from all sessions were reviewed and revised by STAG-TB members at the conclusion of meeting, and again via review of this report in draft form.

Following the meeting, STAG-TB conclusions and recommendations were presented by Dr Jeremiah Chakaya to Dr Margaret Chan, WHO Director-General. The meeting report will be posted on the WHO Stop TB Department web site at http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf It will also be circulated to all WHO senior management and offices of the Organization for their active use and further dissemination. The Chair of STAG-TB is a member of the Stop TB Partnership Coordinating Board, and all Board members will receive the report.

Conclusions and recommendations

The introductory session included a welcome and overview of STAG-TB objectives by Dr H. Nakatani, WHO Assistant Director-General for HIV, TB, Malaria and Neglected Tropical Diseases. Dr J. Chakaya, STAG-TB Chair, opened the meeting and led the introduction of all participants. Ms D. Weil, Coordinator, Policy & Strategy (HTM/STB) introduced the objectives of the meeting and the agenda, and noted the documentation of WHO actions taken on the recommendations made by STAG-TB at its 2009 meeting

Session 1. Global priorities in TB prevention, care and control

Dr M. Raviglione, Director, HTM/STB, provided an introductory presentation on the global TB situation, priorities and challenges in TB prevention, care and control in 2010 and priorities for WHO action according to its core functions. Based on this presentation and deliberations during the two days, STAG-TB members made the following statement:

STAG-TB notes that this is a time of tremendous innovation and opportunity in TB prevention, care and control, building on success in moving towards global Stop TB targets for 2015 and beyond. To date, TB mortality has declined 35% compared to 1990 l and incidence and prevalence rates are falling. This success has depended on TB care, research, health systems responses, and overall social and economic development. Comprehensive action, very strong advocacy for implementation of effective policies, and civil society engagement will be crucial to achieve universal access and drive down TB deaths and incidence faster.

WHO plays a crucial role in guiding Member States and their partners and in enabling universal access to life-saving interventions for all persons with TB and for those communities at highest risk. We acknowledge that all of WHO's core functions are needed to support country-level adoption, adaptation and implementation of policies, as well as innovation. National TB programmes need help to build their capacity to prioritize, manage and steward their partners within primary health care and the community.

We endorse and applaud WHO's expanded efforts in:
* guiding rapid uptake of effective new diagnostics that are essential for universal access;
* building the evidence base to expand early case detection, scale-up of TB, MDR-TB, and TB-HIV interventions along with increased prevention efforts, including addressing the social determinants of TB and co-morbidities;
* engaging governments, the private sector and affected communities;

- ensuring proper research and planning for the safe and effective use of new tools;
- promoting research, and developing updated policies to reduce suffering and mortality from TB and in moving faster towards the elimination of TB as a scourge of humanity.

Session 2. Scaling up MDR-TB treatment: revising strategies and roles in supporting countries

STAG-TB

- Acknowledges the accomplishments of the Green Light Committee (GLC), but endorses the need for a new approach that meets global demand in scaling up high-quality management of drug resistant-TB (DR-TB) in line with World Health Assembly resolution 62.15;

- Stresses that increased human resources capacity is a critical prerequisite for success of the planned scale-up;

- Endorses the need for a comprehensive, working monitoring and evaluation system for DR-TB management;

- Recognizes that drug supply, procurement and technical support provision have been bottlenecks in the scale-up of DR-TB treatment via existing mechanisms, and notes with concern the increased demands that GDF (Global Drug Facility), TBTEAM and other mechanisms involved will likely face under the proposed architecture and expansion.

STAG-TB recommends that WHO, in cooperation with partners:

1. Pursue a revised and rebranded approach to care and control of DR-TB that mainstreams DR-TB into TB control and:
   a. prioritizes the building of national and regional capacity and strengthens the roles of WHO and partners in the coordination and provision of technical assistance;
   b. strengthens country ownership, leadership and accountability of programmes;
   c. ensures strengthening of human resources capacity;
   d. promotes inclusion of all partners including civil society and the private sector;
   e. establishes a comprehensive monitoring and evaluation system;
   f. ensures expanded capacity for laboratory diagnosis, including provision of new tools, and the tight linkage of case management to it;
   g. promotes operational research and advocacy as tools for scaling up the response to DR-TB;

2. Mobilizes resources and develops capacity to ensure TBTEAM and other mechanisms, at national, regional and Headquarters (HQ) levels are able to absorb the increased responsibilities they are expected to hold in coordination of technical assistance under the revised approach;

3. Ensures acceleration of a quality-assured supply of second-line drugs;

4. Encourages WHO to reinforce its monitoring and evaluation of DR-TB scale up in countries;

5. Ensures that the mechanisms developed align with the strategies, policies and needs of countries and donors;

6. Identifies effective country-specific mechanisms of DR-TB care and control, including successful models for provision of care and involvement of private-sector providers, and promotes their adoption in similar settings.

Session 3. Preparing for rapid policy review of new drugs

STAG-TB:

• Recognizes that substantial progress has been made over the past year in preparing for the development of WHO policy guidance on the use of new anti-TB drugs.

• Endorses the HTM/STB plan to organize an expert meeting in Geneva in early Quarter 2, 2011, that will assemble a large variety of partners, including regulators, scientists, drug developers, managers of national TB control programmes, Stop TB partnership groups and subgroups, WHO/Guidelines Review Committee and prequalification programmes, with the following objectives:

   a. to develop a document describing the evidence and information needed to develop WHO policy recommendations related to new drugs and regimens for treatment of drug-susceptible TB (DS-TB) and drug-resistant-TB (DR-TB), and describe the process to be undertaken in the review;

   b. to develop a WHO plan for policy development to guide countries on the use of new drugs and regimens for drug-susceptible and drug-resistant TB.

• Recognizes that although the availability of new drugs may revolutionize treatment of DS-TB and DR-TB, issues of their compassionate use and expanded access need to be addressed urgently.

STAG-TB recommends that WHO:

1. Continues dialogue with regulatory authorities, ensuring the contribution of experienced regulators from countries with both low and high burdens of TB. This dialogue should explore possibilities for:
   • harmonizing the registration of anti-TB drugs,
   • including regulators from high-burden countries in the review carried out by stringent national regulatory authorities,
   • deploying strategies to ensure rapid registration of new medicines and promoting their rational use;

2. Expands the aims of the planned expert meeting to include establishing criteria to guide the drug development process towards the use of new drugs for treatment of

DS-TB and DR-TB, including addressing critical issues related to the drug development pathway, clinical trial design and the need for combination therapy;

3. Develops a set of criteria to recommend for optimal use of anti-TB drugs in various programmatic settings, with clearly established timelines and priorities for public health, ensuring proper, equitable and cost-effective access;

4. Assists countries to develop mechanisms for compassionate use and expanded access to new drugs in the context of legislation and national regulatory structures;

5. Pending the results of clinical trials, organizes a meeting with partners to consider the risks and benefits of using fluoroquinolones as first-line drugs within shortened treatment regimens.

Session 4. Diagnostics policies (A): commercial serodiagnostics

STAG-TB:
- Acknowledges the compelling evidence base and large body of work demonstrating the poor performance of commercial serodiagnostics and the adverse impact of misdiagnosis and wasted resources on patients and health services when using these tests for the diagnosis of active TB;

- Endorses the findings of the Expert Group[1] and supports the strategic approach to develop "negative" WHO policy recommendations to discourage the use of commercial TB serodiagnostics;

STAG-TB recommends that:

1. WHO pursues a policy that current commercial TB serodiagnostics tests should not be used in individuals with suspected active pulmonary or extrapulmonary TB, irrespective of their HIV status;

This recommendation also applies to childhood TB, based on the generalization of data derived from adults (while acknowledging the limitations of microbiological diagnosis in children);

This recommendation also applies to the use of commercial serodiagnostic tests as add-on tests in smear-negative individuals given the high risk of false-positives and the consequent adverse effects;

2. WHO provides a strong message to the TB scientific community and research funding agencies that further targeted research is needed to develop an accurate, simple serodiagnostic test for TB and strongly recommends that proof-of-principle studies be followed by evidence produced from prospectively implemented and well designed evaluation and demonstration studies, including assessment of patient impact.

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[1] Report on WHO Expert Group on Commercial serodiagnostic tests for diagnosis of tuberculosis, 22 July, 2010.

Session 4. Diagnostics policies (B): use of commercial IGRAs in low-income and middle-income countries

STAG-TB:

- Acknowledges the large body of work and compelling evidence base demonstrating the poor performance of current commercial IGRAs in low-income and middle-income countries (typically high-TB[1] settings and/or high HIV-burden settings) and the adverse impact of misdiagnosis and wasted resources on patients and health services when using these tests for the diagnosis of <u>active TB disease</u>;

- Acknowledges the large body of work and compelling evidence base to discourage the use of IGRAs for the detection of <u>latent TB infection</u> (LTBI) in adults, children, health-care workers, contacts and those involved in outbreak investigations in low-income and middle-income countries (typically high-TB[1] settings and/or high-HIV burden settings), acknowledging the difficulty in obtaining high-quality data on the diagnosis of LTBI in the absence of a reference standard;

- Endorses the findings of the WHO Expert Group[2] land supports the strategic approach to develop "negative" WHO policy recommendations to discourage the use of commercial IGRAs in low-income and middle-income countries (typically high-TB[3] settings and/or high-HIV burden settings).

Session 4. Diagnostics policies (C): Xpert MTB/RIF system

STAG-TB:

- Acknowledges the transforming potential of this new technology and the solid evidence base to support its widespread use for detection of TB and rifampicin resistance. STAG-TB also acknowledges the need for access to this innovation in individuals at risk of TB and MDR-TB in resource-constrained settings.

STAG-TB therefore supports the Expert Group[4] findings that:

1. Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB[5] or HIV-associated TB;

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[2] Report of the WHO Expert Group on use of interferon-γ release assays (IGRAs) in tuberculosis control in low- and middle-income settings, 20-21 July, 2010

[3] No globally agreed definition for high TB incidence/burden is available; selected systematic reviews used arbitrary cut-offs of 100 per 100 000 population for stratified analyses. All used World Bank income stratification as proxy.

[4] Report of WHO Expert Group on Automated nucleic acid amplification technology for simultaneous and rapid detection of tuberculosis and rifampicin resistance: Xpert MTB/Rif system, 1 September, 2010.

[5] MDR-TB includes retreatment failures, chronic cases, non-converting cases (by month 3), relapses and return after default, contacts of confirmed MTB-TB cases, exposure in institutions with high rates of MDR-TB (prisons, areas where drug resistance is highly prevalent, etc.; see *Guidelines for the programmatic*

2. Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens.

STAG-TB acknowledges the major resource implications associated with this recommendation.

Remark: These recommendations also apply to children, based on the generalization of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;

Remark: Access to conventional microscopy, culture and drug-susceptibility testing (DST) is still needed for infection control, monitoring of therapy, for prevalence surveys and/or drug-resistance surveillance, and for recovering isolates for DST other than rifampicin (including second-line anti-TB drugs);

Remark: These recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens), as data on the utility of Xpert MTB/RIF in extrapulmonary specimens are still limited;

Remark: These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications for both health systems (cartridge costs) and patients (costs of visits to health services).

STAG-TB recommends that WHO:

1. Proceeds with detailed policy guidance on the use of Xpert MTB/RIF;

2. Develops 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;

3. Proceeds 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);

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

Furthermore, **STAG-TB:**

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management of drug-resistant tuberculosis: emergency update 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402)**]**.

1.   Encourages donors and funding agencies to support global uptake of Xpert MTB/RIF technology through public health services or other mechanisms that explicitly promote access by the poor;

2. Encourages further and continuing research for the development of a simple point of care test for the diagnosis of TB especially in low-bacillary samples, e.g. children and HIV-infected individuals;

3. Encourages further development of other equivalent or more sensitive test platforms for the diagnosis of TB and DR-TB.

Session 5. Early and increased case detection

STAG-TB:

• Recognizes the critical importance of early and complete case detection to achieve global TB control targets, and, for that purpose, the need to strengthen weak public-sector DOTS programmes, scale-up the engagement of all care providers through public–private mix (PPM) approaches and undertake active case-finding to identify cases that do not seek care from any care providers;

• Acknowledges the socioeconomic burden to individuals of accessing TB care in the context of weak health systems and a growing private sector deterring symptomatic individuals from seeking timely diagnosis;

• Notes that PPM projects in diverse settings have contributed to increasing case notification, maintaining high treatment success rates, enhancing access to care and saving costs of care for patients, and that some countries have successfully scaled up PPM;

• Recognizes that greater and more concerted efforts are required to engage all non-programme care providers in order to increase case detection including, for early detection, frontline care providers who are often the first point of contact for TB suspects;

• Recognizes that active case-finding may be required among high-risk communities such as close contacts of TB patients, people living with HIV/AIDS (PLHIV) or prison inmates, in order to detect all cases early enough and reduce TB transmission;

• Notes that a systematic review on active case-finding strategies and their impact is under way, and that a framework for action research will be required to enable development of new policies and guidance on active case-finding.

STAG-TB recommends that WHO, working with countries and partners:

1. Elevates advocacy for PPM to the ministerial level, to promote it as an essential intervention to strengthen broader health systems, improve access to TB diagnosis and ensure quality of TB care provision;

2. Mainstreams PPM also as part of MDR-TB response and TB/HIV collaborative activities; seek collaboration with other health programmes as an integrated approach to private sector engagement;
3. Pursues regulatory approaches such as certification and accreditation of care providers as a way to ensure rational use of anti-TB drugs and promote International Standards of TB Care;

4. Continues with ACF systematic review, with clarification of case-detection strategies and terminology, and prioritizing recommendations of high-risk persons, groups and communities where increased case detection will be beneficial;

5. Takes the following steps while awaiting the results of the current systematic review on ACF to:
    – compile a global inventory of ACF approaches being already implemented by countries, including prevalence surveys and related projects
    – plan to convene an Expert Group to examine available evidence, and develop a framework for designing ACF approaches and make recommendations on their implementation.

Session 6. WHO TB/HIV policy: from interim to definite

STAG-TB:

• Recognizes the important amount of emerging evidence on TB/HIV co-management since the publication of the interim policy in 2004 and endorses the need to move from an interim to a definite policy;

• Acknowledges the huge progress made to date in implementing collaborative TB activities in settings where the prevalence of HIV is both low and high;

STAG-TB recommends that WHO:

1. Includes, in the updated policy guidance, collaboration between TB and HIV programmes and other line ministries at national, regional and state levels, and integration of TB and HIV services, to provide patient-centred care at facility and community levels. In particular, WHO should recommend that TB and HIV laboratory and drug procurement services collaborate more closely at programme management levels;

2. Includes guidance on antiretroviral therapy (ART) for TB prevention; recognize the evidence for early initiation of ART for TB patients with HIV; and the need for definite TB screening for PLHIV at first care contact using the most sensitive available technologies; TB screening among PLHIV in the community; engagement of the civil society; and evidence-based models for the delivery of integrated TB and HIV services;

3. Provides guidance to countries on how to adapt global policy and targets to national and regional ones, and on how to implement collaborative TB/HIV activities at programme and service delivery levels;

4. Raises the need for global commitment to TB/HIV collaborative activities and recommends the inclusion of a TB/HIV session at the next meeting of the WHO HIV-STAC and the participation of selected STAG-TB members to this meeting;

5. Seeks endorsement from UNAIDS for the updated policy.

Session 7: Universal Access: definition and strategy

STAG-TB:

• Recognizes the first objective of the Stop TB Strategy – to ensure universal access to quality-assured care for all persons with TB – and notes the 2015 targets developed and promoted in the Global Plan to Stop TB, 2011–2015;

• Reinforces that the message that "all TB patients matter" is significant for the health and well-being of individuals and for the effective achievement of reductions in global incidence, prevalence and mortality, as well as TB elimination;

• Applauds WHO's promotion of new policies, tools and strategies that will help enable Member States and partners to pursue and measure their progress on universal access;

• Recognizes the resonance of the universal access in global health advocacy.

STAG-TB recommends that WHO:

1. Establishes a Task Force, including Members of STAG-TB, the WHO TB Impact Measurement Task Force, and other experts on TB implementation, health equity, health system strengthening;

   The aims of the Task Force should include:
   a) proposing a definition of universal access applicable for TB prevention, care and control;
   b) reviewing TB indicators and targets on universal access, including those developed by Stop TB Partnership working groups to be released shortly in the revised Global Plan to Stop TB;
   c) proposing any new indicators and global target(s), as appropriate, and providing guidance on target-setting at the country level;
   d) recommending if and how universal access should be advocated for within global and national health agendas;

2. Reports back to STAG-TB at its 2011 meeting or earlier on the recommendations of the Task Force and on WHO's next steps based on these findings, including producing policy and operational guidance on any proposed revision of indicators and target-setting;

3. Informs the Stop TB Partnership's Coordinating Board of the results, which may have implications for the pursuit of the Global Plan to Stop TB, 2010–2015 and on global advocacy for TB and the health-related Millennium Development Goals.

Session 8. Report from the WHO regional offices on management of change

STAG-TB:

- Acknowledges that most countries require clear guidance on the introduction of new tools and that such introduction should be carefully matched with interdependent programme strategies (e.g. ensuring that all identified DR-TB patients have access to adequate care and high-quality drugs)

- Recognizes the crucial role of operational research in providing the evidence base for new interventions and rolling out new tools

- Acknowledges the crucial role of WHO regional offices and country offices in assisting countries to benefit from new tools and funding opportunities, and in building in-country capacity.

STAG-TB recommends that WHO, in collaboration with partners:

1. Assists countries with "change management" by:

   a) Providing effective communication strategies on innovations
   b) Offering differentiated support and addressing country specific needs and opportunities, ranging from countries that need special attention to countries that have the potential to set an example
   c) Facilitating joint programme reviews to guide and monitor progress on national and regional objectives
   d) Supporting the establishment of national strategic and technical advisory groups to assist national TB control programmes to introduce and evaluate new tools and strategies within a comprehensive programme framework

STAG-TB recommends that WHO:

1. Establishes and/or strengthens strategic and technical advisory groups in every region to regularly provide guidance on technical and strategic matters including internal (WHO) and external advocacy;

2. Ensures collaboration across all bodies and teams (e.g. Global Laboratory Initiative (GLI), Innovative New Approaches and Technologies (INAT)) to assist countries in introducing and scaling up use of new diagnostics and other tools;

3. Assists countries in:
   - developing a regulatory framework to protect existing and new drugs and to prevent the emergence of more drug resistance (rational use)

- building capacity to manufacture new drugs and tools in compliance with international standards (focus on large high-burden countries)
- building capacity to prioritize and implement operational research

Session 9. Framework for collaborative diabetes mellitus/TB (DM/TB) activities

STAG-TB:

- Recognizes the growing body of evidence on the link between diabetes and TB, but also important knowledge gaps

- Welcomes the draft Collaborative Framework for Care and Control of TB and DM, which is timely in light of the growing burden of non-communicable diseases in low-income and middle income countries, but proposes that the framework be field tested and carefully evaluated in selected sites before advocating for its broader implementation;

- Stresses that DM/TB be addressed as part of a TB co-morbidity package (along with HIV, tobacco, alcohol dependency, etc.) in the context of a health systems strengthening agenda and used at primary-care level rather than as a vertical initiative.

STAG-TB recommends that WHO:

1. On revision of the draft framework:
   a. Emphasizes that TB/DM collaboration should be developed within a framework of health systems strengthening and TB co-morbidities respectively, and be seen as a step towards generally improved collaboration between communicable and non-communicable disease programmes;
   b. Clearly delineates the responsibilities for TB and DM care by the respective control programmes and primary health services providers;
   c. Further guides countries on the relevance of pursuing TB/DM collaboration, according to TB and DM epidemiology and health systems infrastructure;
   d. Clearly states the need for monitoring and evaluation and operational research as a complement to clinical trials;
   e. Guides countries on where and how to mobilize resources;
   f. Ensures engagement of all relevant partners;

2. On implementation of the framework and associated operational research:
   a. Identifies and supports pilot implementation and operational research in selected sites, starting in countries with high burdens of TB and DM, a well-functioning TB control programme, and a sufficiently well-developed infrastructure for DM care;
   b. Advocates for resources from funding agencies to support TB/DM collaboration and research.

Session 10. Supporting access to, and quality of, TB care for women and children

STAG-TB:

- Recognizes the importance of prioritizing advocacy for increased access to TB prevention and care among women and children worldwide as part of a broader maternal and child health (MCH) agenda and to capitalize on the renewed global interest through engagement of "MCH champions";

- Applauds the renewed attention on women and children's health and calls for attention to the full spectrum of women's health issues, including, but not exclusively, reproductive health.

STAG-TB recommends that WHO:

1. Pursues collaborative activities within and beyond WHO towards mainstreaming TB control into existing maternal and child health initiatives (e.g. Safe Motherhood programmes and Prevention of Mother-to-Child Transmission of HIV (PMTCT) initiatives) to include key partners (e.g. UNICEF) and links with community initiatives and women's health support groups (e.g., White Ribbon Alliance);

2. Provides guidance and technical support for the introduction and evaluation of TB screening at PMTCT clinics;

3. Promotes and technically supports relevant operational research related to women's health, maternal and child health and TB prevention, care and control;

4. Promotes and technically supports relevant childhood research activities that will address:
   a. the needs for better diagnostics tools and treatment, including ensuring the inclusion of children in clinical trials and multicentre studies of new diagnostics and new drugs (including the development of new fixed-dose combination formulations;
   b. MDR-TB among children and the development of paediatric formulations.

NEXT MEETING DATE: The eleventh STAG-TB meeting is proposed for 20–22 June 2011.

Topics proposed for consideration by WHO in formulating the agenda for the eleventh meeting is included in Annex 3.   Note: it was recommended that a conference call be held with STAG-TB members in advance of the June meeting to review the agenda proposed by the WHO Secretariat, as a means to further help STAG-TB members prepare for the meeting.

Annex 1: AGENDA

Strategic and Technical Advisory Group for Tuberculosis STAG-TB

Tenth Meeting, 27-29 September 2010
Salle A, WHO Headquarters. Geneva, Switzerland
Monday, 27 September 2010

Time	Topic	Speaker	Discussants
9:00-9:30	Welcome Meeting Objectives Introduction of Participants Review of follow-up on 2009 Recommendations	H. Nakatani, ADG, HTM M. Raviglione, Dir, STB J. Chakaya, Chair D. Weil	
9:30-10:15	1. WHO Global Priorities in TB Prevention, Care and Control	M. Raviglione	R. Minghui K. Castro
10:15-10:35	Coffee		
10:35-11:45	2. MDR-TB Scale-up: Revising strategies and roles in supporting countries	P. Nunn L. Blanc	C. Daley G.B. Migliori
11:45-12:40	3. Progress in Preparing for the Development of Policy Guidance on Use of New Anti-TB Drugs	C. Lienhardt	S. Al-Awaidy T. von Schon-Angerer P. Das
12:40-13:40	Lunch		

Time	Topic	Speaker	Discussants
13:40-15:20	4. Diagnostic Policies A. Evidence synthesis process B. Policy recommendations on use of commercial serodiagnostic tests for TB diagnosis C. Policy recommendations on use of interferon gamma release assays (IGRAs) D. Policy recommendations on automated real-time PCR for rapid detection of TB and rifampicin resistance: Xpert MTB/RIF system	K Weyer A Ramsay C. Lienhardt K Weyer	R. Shukla F. Drobniewski V. Malakhov
15:20-15:40	Coffee		
15:40-16:45	5. Early and Increased Case Detection: A. PPM achievements to date and next steps B. Systematic review on active case finding	M. Uplekar J. Golub	M. van der Werf E. Corbett
16:45-17:00	Wrap-up		
17:00-18:00	Reception - WHO/UNAIDS Building Cafeteria		
18:15-19:00 STB Offices	Session Reviews (First Day Rapporteurs and Discussants)		

Strategic and Technical Advisory Group for TB
STAG-TB

Tuesday, 28 September 2010

Time	Topic	Speakers	Discussants
9:00-9:30	Day 1 Review of Recommendations	J. Chakaya	
9:30-10:30	6. WHO TB/HIV Policy: from interim to definite	H. Getahun	Y. Pillay Mao Tan Eang
10:30-10:50	Coffee		
10:50-12:00	7. Pursuing Universal Access - Definitions and strategy	D. Weil	J. Chakaya
12:00-13:30	Lunch	STAG-TB Members with STB Management Team - French Restaurant _____ Session 8-10: P. Fujiwara, Vice Chair	
13:30 - 14:30	8. WHO Regional Offices Report on "Management of Change"	C. van Weezenbeek, WPRO on behalf of all Regional TB Advisers	J. Broekmans P. Suarez
14:30 - 15:30	9.Framework for Collaborative Diabetes/Tuberculosis Activities	M. Murray	P. Fujiwara Y. Kasetjaroen
15:30-15:50	Coffee		

Time	Topic	Speaker	
15:50-16:45	10. *Discussion session:* Supporting access and quality TB care for women and children	M. Grzemska	L. Chesire L. Vianzon
16:45-17:00	Wrap-up	J. Chakaya, Chair	
17:00-18:00	Session Reviews (Rapporteurs and Discussants)		

Wednesday, 29 September 2010

Time	Topic	Speaker	
9:00-11:30	Full review of final recommendations	J. Chakaya	
11:30-11:45	Planning for next STAG-TB Meeting	D. Weil	
11:45-12:00	Conclusions	J. Chakaya H. Nakatani M. Raviglione	

Annex 2: List of Participants

10th Meeting Strategic and Technical Advisory Group for Tuberculosis (STAG-TB)
27-29 September 2010, WHO Headquarters, Geneva, Switzerland

STAG-TB Members 2010

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Annex 3: Topics proposed by STAG-TB Members for consideration for STAG-TB 2011 agenda (in order of noting by members, not prioritized)

1. Diabetes and TB: further review of evidence on interventions
2. Approaches to roll-out of new technologies, including policy review of new drugs and examination of feasibility/efficiency in implementation
3. WHO actions related to updated targets in Global Plan to Stop TB, 2001-2015
4. Engaging civil society, community care and participation
5. Shifting from performance to impact evaluation, including roll-out of new technologies, and associated equity analysis
6. MDR-TB management scale-up and how new diagnostics are contributing, and look at action against defined bottlenecks and quality assurance
7. WHO roles in addressing anti-TB drug stock-outs experienced in some countries
8. TB and Universal Health Coverage/insurance schemes
9. Presentation on prioritization of, and action on, 2010 STAG-TB recommendations
10. Impact of advocacy efforts
11. Examples of TB care and control within integrated PHC approaches and health system strengthening efforts
12. Overall review of implementation of Stop TB Strategy and gaps
13. Response to programme and financial management challenges, and building political commitment for sustainable financing and support
14. Review of rational use of existing anti-TB drugs
15. TB/HIV - next steps on the now "4 I's", and look at the safety of second-line ARVs and TB treatment