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# Commercial Serodiagnostic Tests for Diagnosis of Tuberculosis

## Policy Statement



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## Executive summary

**Background:** An antibody detection-based diagnostic test in a user-friendly format could potentially replace microscopy and extend tuberculosis diagnosis to lower levels of health services. Dozens of commercial serological tests for tuberculosis are being marketed in many parts of the world, despite previous systematic reviews having reported variable sensitivity and specificity of these tests. Since the publication of these reviews, the evidence base has grown, methods for meta-analyses of diagnostic tests have evolved, and the WHO Stop TB Department (STB) has implemented a systematic approach to evidence synthesis for TB diagnostic policy development involving systematic reviews and meta-analyses, assessment of the evidence base by Expert Group review, and implementation of the GRADE process for evidence synthesis.

**Methods:** An updated systematic review was commissioned to synthesize the evidence on the diagnostic accuracy of commercial serological tests for pulmonary and extrapulmonary tuberculosis. Database searches for relevant studies in all languages were updated through May 2010 and a bivariate meta-analysis was performed that jointly models both test sensitivity and specificity. The findings were presented to an independent WHO Expert Group and the evidence assessed using the GRADE approach. As conflict of interest in diagnostic studies is a known concern the systematic review also evaluated the involvement of commercial test manufacturers in published studies.

**Results:** For pulmonary tuberculosis, 67 unique studies were identified, including 32 studies from low- and middle-income countries. None of these studies evaluated the tests in children. The results demonstrated that (1) for all commercial tests, sensitivity (0% to 100%) and specificity (31% to 100%) from individual studies were highly variable; (2) using bivariate meta-analysis for Anda-TB IgG (the most commonly evaluated test), the pooled sensitivity was 76% (95% CI 63% to 87%) in studies of smear-positive and 59% (95% CI 10% to 96%) in studies of smear-negative patients, respectively; the pooled specificity in these studies was similar: 92% (95% CI 74% to 98%) and 91% (95% CI 79% to 96%), respectively; (3) for Anda-TB IgG, sensitivity values in smear-positive (54% to 85%) and smear-negative (35% to 73%) patients from individual studies were highly variable; (4) for Anda-TB IgG, specificity values from individual studies were variable (68% to 100%); (5) a TDR evaluation of 19 rapid commercial tests, in comparison with culture plus clinical follow-up, showed similar variability with sensitivity values of 1% to 60% and specificity of 53% to 99%; (6) compared with ELISAs [60% (95% CI 6% to 65%), immuno-chromatographic assays had lower sensitivity [53%, 95% CI 42% to 64%]; and (7) in a single study involving HIV-infected TB patients, the sensitivity of the SDHO test was 16% (95% CI 5% to 34%).

For extrapulmonary tuberculosis, 25 unique studies were identified, including 10 studies from low- and middle-income countries. None of these studies evaluated the tests in children. The results demonstrated that (1) for all commercial tests, sensitivity (0% to 100%) and specificity (59% to 100%) values from individual studies were highly variable; (2) pooled sensitivity was 64% (95% CI 28% to 92%) for lymph node tuberculosis and 46% (95% CI 29% to 63%) for pleural tuberculosis; (3) for Anda-TB IgG, the pooled sensitivity and specificity were 81% (95% CI 49% to 97%) and 85% (95% CI 77% to 92%) respectively while sensitivity (26% to 100%) and specificity (59% to 100%) values from individual studies were highly variable; and (5) in one study involving HIV-infected TB patients, the sensitivity of the MycoDot test was 33% (95% CI 19% to 39%).

The vast majority of studies were either sponsored by industry, involved commercial test manufacturers, or failed to provide information on industry sponsorship.

**Conclusions:** Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes, and high proportions of false-positive and false-negative results adversely impact patient safety. Overall data quality was graded as very low and it is strongly recommended that these tests **not be used** for the diagnosis of pulmonary and extra-pulmonary TB.

## Acknowledgements

This document was prepared by Karin Weyer, Fuad Mirzayev, Wayne van Gemert and Christopher Gilpin (WHO Stop TB Department) on the basis of consensus at an international Expert Group Meeting convened by WHO in Geneva on 22 July 2010.

WHO gratefully acknowledges the contributions of the Chair of the Expert Group (Holger Schünemann) and the members of the Expert Group (Annex 1) who developed the recommendations.

The findings and recommendations from the Expert Group Meeting were presented to the WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB, Annex 2), in September 2010 ([http://www.who.int/tb/advisory\\_bodies/stag/en/](http://www.who.int/tb/advisory_bodies/stag/en/)). STAG-TB acknowledged a 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 using these tests for the diagnosis of active TB.

STAG TB endorsed the findings of the Expert Group and supported the strategic approach to develop 'negative' WHO policy recommendations to discourage and prevent the use of commercial TB serodiagnostics.

This document was finalized following consideration of all comments and suggestions from the participants of the Expert Group and STAG-TB.

USAID is acknowledged for funding the development of these guidelines through USAID-WHO Consolidated Grant No. GHA-G-00-09-00003. TDR is acknowledged for sponsoring the systematic review commissioned in advance of the Expert Group meeting.

## Declarations of Interest

Individuals were selected to be members of the Expert Group to represent and balance important perspectives for the process of formulating recommendations. The Expert Group therefore included technical experts, end-users, patient representatives and evidence synthesis methodologists.

Interchange by Expert Group meeting participants was restricted to those who attended the Expert Group meeting in person, both for the discussion and follow-up dialogue.

Expert Group members were asked to submit completed Declaration of Interest (DOI) forms. These were reviewed by the WHO legal department prior to the Expert Group meeting. DOI statements were summarised by the co-chair (Karin Weyer, WHO-STB) of the Expert Group meeting at the start of the meeting.

Selected individuals with intellectual and/or research involvement in serodiagnostic methods were invited as observers to provide technical input and answer technical questions. These individuals did not participate in the GRADE evaluation process and were excluded from the Expert Group discussions when recommendations were developed. They were also not involved in the development of the final Expert Group meeting reports, nor in preparation of the STAG-TB documentation or preparation of the final WHO policy statements.

Two Expert Group members (Catharina Boehme, Rick O'Brien) declared FIND (Foundation for Innovative New Diagnostics) support to academia to develop POC serodiagnostic test via the FIND biomarker discovery project. These declarations were deemed to be insignificant.

Three Expert Group members (David Dowdy, Madhukar Pai, Sumaan Laal) declared involvement in relevant research and participation in the systematic review. Karen Steingart declared her role as principal systematic reviewer. These declarations were deemed to be significant and members were observers to the meeting, providing technical clarifications on the findings of the systematic review. They did not participate in the GRADE evaluation process, contributed to the meeting discussions where recommendations were developed, or provided comments on the final document.

# COMMERCIAL SERODIAGNOSTIC TESTS FOR DIAGNOSIS OF TUBERCULOSIS

## 1. Background

Tuberculosis (TB) serological tests almost exclusively rely on antibody recognition of antigens of *Mycobacterium tuberculosis* by the humoral immune response, as opposed to antigen recognition by the cellular immune response (e.g. interferon-gamma release assays). An accurate serological test that could provide rapid diagnosis of TB and in a suitable format (e.g. point-of-care) would be particularly useful both as a replacement for laboratory-based tests and for extending TB diagnosis to lower levels of health services, especially those without on-site laboratories. Although no serological TB test is recommended by international guidelines for clinical use nor approved by the US Food and Drug Administration, dozens of distinct commercial serological tests (also referred to as 'commercial serodiagnostics' in this document) are marketed in many parts of the world, especially in developing countries with weak regulatory systems.

Several systematic reviews and one laboratory-based evaluation on this topic have been published. Two reviews evaluating commercial tests for pulmonary TB (68 studies) and extrapulmonary TB (21 studies) found sensitivity and specificity of these tests to be highly variable.<sup>1-3</sup> A meta-analysis of non-commercial tests for pulmonary TB (254 datasets including 51 distinct single antigens and 30 distinct multiple-antigen combinations) identified potential candidate antigens for inclusion in an antibody detection based TB test in HIV-uninfected and -infected individuals; however, no antigen or antigen combination achieved sufficient sensitivity to replace smear microscopy.<sup>2</sup> Previous systematic reviews of rapid TB serodiagnostic tests (literature search through 2003, seven datasets) reported pooled sensitivity and specificity values of 34% and 91% respectively, in studies meeting at least two design-related criteria.<sup>4</sup>

In 2005, the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) performed an evaluation of 19 commercially available rapid diagnostic TB tests ('rapid' defined as having a test result available in less than 15 minutes).<sup>5</sup> The evaluation reported that, in comparison with culture plus clinical follow-up, commercial tests provided sensitivity and specificity values of 1% to 60% and 53% to 99%, respectively.

Since the publication of previous reviews, the evidence base has grown and approaches to meta-analyses of diagnostic tests have evolved. WHO-STB and TDR therefore commissioned an updated systematic review to synthesize new evidence since 2006 on the diagnostic accuracy of commercial tests for pulmonary and extrapulmonary TB. In addition, the findings from the previous TDR evaluation are summarised below.

The systematic review and this document are limited to commercial serological tests only. In-house tests are likely to be less standardised, have less quality assurance during manufacture, and are prone to be more operator dependent. As a result, the quality issues of limitations, precision, consistency, directness and probable publication bias are expected to be more severe.

## 2. Methods

### 2.1 Evidence synthesis

The systematic evidence-based process for TB diagnostic policy generation developed by WHO-STB was followed: The first step constituted a systematic review and meta-analysis of available data (published and unpublished) using standard methods appropriate for diagnostic accuracy studies. The second step involved the convening of an Expert Group to a) evaluate the strength of the evidence base; b) evaluate the risks and benefits of using commercial serodiagnostic tests in national TB control programmes; and c) identify gaps to be addressed in future research. Based on the Expert Group findings, the third and final step involved WHO policy guidance on the use of these tests, presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) for consideration.

The Expert Group (Annex 1) consisted of researchers, clinicians, epidemiologists, end-users (programme and laboratory representatives), community representatives and evidence synthesis experts. The Expert Group meeting followed a structured agenda (Annex 1) and was co-chaired by WHO-STB and a clinical epidemiologist with expertise and extensive experience in evidence synthesis and guideline development.

To comply with current standards for evidence assessment in formulation of policy recommendations, the GRADE system ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)), adopted by WHO for all policy and guidelines development, was used.

Recognising that test results may be surrogates for patient-important outcomes, the Expert Group evaluated diagnostic accuracy while also drawing inferences on the likely impact of these approaches on patient outcomes, as reflected by false-negatives (ie. cases missed) or false-positives. In addition, the Expert Group was presented with an epidemiological and economic model on the cost-effectiveness and cost-benefit of commercial serodiagnostics using a case study from India, where an estimated 1.5 million TB commercial (ELISA) tests are performed every year.<sup>7,8</sup> These tests are used mostly by the private sector (the primary source for TB care) in India, predominantly using imported TB ELISA kits at expenditure conservatively estimated at 15 million US dollars per year.

#### 2.1.1 Systematic review and meta-analyses

An updated systematic review was done following standard protocols and using predetermined eligibility criteria for primary analyses of diagnostic accuracy of commercial serological tests, for both pulmonary and extra-pulmonary TB. Detailed methodology and the lists of included and excluded studies are provided in the Expert Group Meeting report available at [http://www.who.int/tb/laboratory/policy\\_statements/en/index.html](http://www.who.int/tb/laboratory/policy_statements/en/index.html). In summary, database searches for relevant studies from 1990 through May 2010 in all languages were updated and summarised, and a bivariate meta-analysis was performed which jointly models sensitivity and specificity. Hierarchical receiver operating characteristic (HSROC) curves from relevant meta-analyses were done to assess the overall performance of tests across different thresholds.

Studies were heterogeneous in many respects, particularly concerning the commercial test evaluated, antibody (ies) detected, sputum smear status (pulmonary TB), site of extrapulmonary TB, and assay technique. Therefore, in order to address heterogeneity and combine study results, subgroups of comparable tests and extrapulmonary sites were pre-specified. When possible, studies were stratified by smear and HIV status.

Studies using culture of *M. tuberculosis* from patient specimens as the reference standard were included for pulmonary tuberculosis. For extra-pulmonary TB, studies using microscopy, culture or histopathology as reference standard were included. The following studies were excluded: (1) studies published before 1990; (2) animal studies; (3) conference abstracts and proceedings; (4)

studies on the detection of latent TB infection; (5) studies on nontuberculous mycobacterial infection; (6) studies that used non-immunological methods for detection antibodies; and (7) basic science literature that focused on detection/cloning of new antigens or their immunological properties (ie. early pre-clinical studies).

### **2.1.2 WHO/TDR laboratory-based evaluation of 19 commercially available rapid diagnostic tests for tuberculosis**

The TDR test data were synthesised separately since this evaluation was a head-to-head comparison of serodiagnostic tests of which performance was assessed with the same archived frozen specimens. Because of this unique design, it was preferable not to pool data from the TDR evaluation with data from the systematic review. The objective of the evaluation was two-fold: (1) to compare the performance and reproducibility of rapid *M. tuberculosis*-specific antibody detection tests using well-characterized serum samples from the WHO/TDR TB Specimen Bank and (2) to assess the operational characteristics of rapid *M. tuberculosis* tests, including ease of use, technical complexity, and inter-reader variability.

Details regarding the analyses can be found in the Expert Group meeting report available at [http://www.who.int/tb/laboratory/policy\\_statements/en/index.html](http://www.who.int/tb/laboratory/policy_statements/en/index.html). The TDR report is available at <http://apps.who.int/tdr/svc/publications/tdr-research-publications/diagnostics-evaluation-2>.

### **2.1.3 Case study of economic and epidemiological impact of serologic testing for active tuberculosis in India**

As no data were available on the cost implications of commercial serodiagnostics, a case study of serologic testing versus other strategies for diagnosis of active TB in India was performed, including construction of a decision-analytic model to estimate the impact of such testing.

## **2.2 Decision-making during the Expert Group meeting and external review**

The systematic review report and the TDR report were made available to the Expert Group for scrutiny before the meeting.

The Expert Group meeting was co-chaired by the WHO-STB secretariat and an evidence synthesis expert. Decisions were based on consensus. Concerns and opinions by Expert Group members were noted and included in the final meeting report. The detailed meeting report was prepared by the WHO-STB secretariat and underwent several iterations (managed by the secretariat) before being finally signed off by all Expert Group members.

Recommendations from the Expert Group meeting were presented to WHO STAG-TB. STAG-TB endorsed the recommendations and requested WHO to proceed with the development of final policy guidance. This was circulated to the Expert Group and STAG-TB members and comments incorporated as relevant.

The final policy guidance document was approved by the WHO Guidelines Review Committee (GRC), having satisfied the GRC requirements for guideline development.<sup>i</sup>

## **2.3 Scope of the policy guidance**

This document provides a pragmatic summary of the evidence and recommendations related to commercial serodiagnostic tests and should be read in conjunction with the detailed findings from the Expert Group Meeting Report available at:

[http://www.who.int/tb/laboratory/policy\\_statements/en/index.html](http://www.who.int/tb/laboratory/policy_statements/en/index.html).

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<sup>i</sup>GRC statement: This guideline was developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (current version).

This policy guidance should be used to prevent and discourage the use of commercial serodiagnostic tests for diagnosis of TB. It is intended for National TB Managers and Laboratory Directors, external laboratory consultants, donor agencies, technical advisors, laboratory technicians, laboratory equipment procurement officers, and private sector service providers. Individuals responsible for programme planning, budgeting, resource mobilization, and training activities for TB diagnostic services may also benefit from using this document.

Date of review: 2015

### 3. Evidence base for policy formulation

#### 3.1 Pulmonary TB

The updated systematic review of the diagnostic accuracy of commercial tests for pulmonary TB identified 67 unique studies, including 32 studies from low- and middle-income countries.<sup>6</sup> None of these studies evaluated the tests in children. The results demonstrate that:

(1) for all commercial tests, sensitivity (0% to 100%) and specificity (31 to 100%) from individual studies are highly variable;

(2) using bivariate meta-analysis, for Anda-TB IgG (the most commonly evaluated test), the pooled sensitivity is 76% (95% CI 63 to 87%) in studies of smear-positive and 59% (95% CI 10 to 96%) in studies of smear-negative patients, respectively; the pooled specificity in these studies was similar: 92% (95% CI 74 to 98%) and 91% (95% CI 79 to 96%), respectively;

(3) for Anda-TB IgG, sensitivity values in smear-positive (54% to 85%) and smear-negative (35% to 73%) patients from individual studies are highly variable;

(4) for Anda-TB IgG, specificity values from individual studies are variable (68% to 100%);

(5) in the TDR evaluation of 19 rapid commercial tests, in comparison with culture plus clinical follow-up, sensitivity (1% to 60%) and specificity (53% to 99%) values are highly variable;

(6) compared with ELISAs [60% (95% CI 6% to 65%)], immuno-chromatographic assays have similar sensitivity [53%, 95% CI 42% to 64%]; and

(7) in the single study involving HIV-infected TB patients, the sensitivity of the SDHO test is 16% (95% CI 5% to 34%).

The only commercial test (Anda-TB) that could be included in sub-analyses provided poor performance and the other commercial tests did not have enough data to analyse. None of the tests reviewed could replace smear microscopy, a finding consistent with those reported in a previous systematic review.

The sensitivity and specificity estimates in this 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 which could result in exaggerated estimates of test accuracy and (2) potential publication bias, where studies with poor performance were likely to be unpublished.

#### 3.2 Extra-pulmonary TB

The updated systematic review of the diagnostic accuracy of commercial tests for extrapulmonary TB identified 25 unique studies, including 10 studies from low- and middle-income countries.<sup>6</sup> None of these studies evaluated the tests predominantly in children. The results demonstrate that:

(1) for all commercial tests, sensitivity (0% to 100%) and specificity (59% to 100%) values from individual studies are highly variable;

(2) pooled sensitivity is 64% (95% CI 28% to 92%) for lymph node tuberculosis and 46% (95% CI 29% to 63%) for pleural tuberculosis;

(3) for Anda-TB IgG, although the pooled sensitivity and specificity are 81% (95% CI 49% to 97%) and 85% (95% CI 77 to 92%) respectively, sensitivity (26% to 100%) and specificity (59% to 100%) values from individual studies are highly variable;

(4) in the single study involving HIV-infected individuals, the sensitivity of MycoDot is 33% (95% CI 19% to 39%).

As for pulmonary TB, the only commercial test (Anda-TB) that could be included in subgroup-analyses for extrapulmonary TB provided poor performance and the other commercial tests did not have enough data to analyze. These findings are consistent with those reported in a previous systematic review.

The sensitivity and specificity estimates in this meta-analysis are likely to be overly optimistic for at least two reasons: (1) as described earlier, study quality generally suffered from lack of a representative patient spectrum which could result in exaggerated estimates of test accuracy and (2) potential publication bias, where studies with poor performance were likely to be unpublished.

### **3.3 Case study of economic and epidemiological impact of serologic testing for active tuberculosis in India**

India is the country with the greatest burden of TB, nearly 2 million incident cases per year. Conservatively, over 10 million TB suspects need diagnostic testing for TB each year. Findings from a country survey done for the Bill & Melinda Gates Foundation showed that the market for TB serology in India exceeds that for sputum smear and TB culture; six major private lab networks (out of hundreds) perform >500,000 TB ELISA tests each year, at a cost of approximately \$10 per test or \$30 per patient (for three simultaneous tests).<sup>7</sup> Overall an estimated 1.5 million TB ELISA tests are performed every year in the country, mostly in the private sector.<sup>8</sup>

The impact of serological testing was compared against that of other TB testing modalities (sputum smear and culture) with sensitivity analysis performed around the accuracy of the test and the annual number of tests performed. Results showed that replacing sputum microscopy with serological testing in a country like India would result in an estimated 14,000 additional cases of TB diagnosed but also result in 121,000 additional false-positive diagnoses relative to microscopy. In addition, the results indicated that for each additional smear-negative TB case diagnosed by serology, more than six additional false-positive would be inappropriately diagnosed.<sup>7</sup>

Most serological tests on the market in developing countries have no published evidence to support their claims of sensitivity and specificity (usually in excess of 95%, according to package inserts). These tests are often performed in an environment with no external quality assurance, and tests from different labs on specimens from the same patient often yield widely varying results. A recent survey in the 22 high TB burden countries showed that regulation of TB diagnostics is weak in most countries, allowing for poorly performing tests to enter the market. Once on the market, incentives and financial gains by stakeholders (doctors, laboratories, diagnostic companies) keep these products profitable.<sup>8</sup>

### **3.4 Strengths and limitations of the evidence base**

Strengths of the systematic review include the use of a standard protocol and comprehensive search strategy, independent reviewers, a bivariate model for meta-analysis, and pre-specified subgroups to account for heterogeneity.

Limitations related to the evidence base include the fact that the majority of studies was not considered to have a representative patient spectrum and was not performed in a blinded manner or blinding was not explicitly stated. Also, subgroup analyses were limited by the small number of studies for a particular commercial test or type of extrapulmonary disease. Differing criteria for patient selection and greater duration and severity of illness of the study populations may have introduced variability in findings among studies. Finally, although statistical tests and graphical methods are available to detect potential publication bias in meta-analyses of randomized controlled trials, such techniques have not been adequately evaluated for diagnostic data.

Nevertheless, it was considered prudent to assume some degree of publication bias as studies showing poor performance of commercial tests may be less likely to be published. This in turn may have introduced 'optimism bias' in the pooled estimates of sensitivity and specificity.

Concerning the TDR evaluation,<sup>5</sup> a few additional limitations were discussed:

- Testing was done retrospectively using stored frozen sera that passed through two freeze-thaw cycles. It is possible that the use of fresh serum may increase sensitivity;
- There was limited geographic diversity amongst TB and HIV-positive patients whose specimens were used for evaluating the commercial tests. It is possible that there may be variations in the anti-mycobacterial antibody responses both due to patient genetic diversity and differential antigen expression by different mycobacterial isolates that could have led to reduced sensitivity with these specimens;
- The duration of illness in patients was unknown. Greater duration or severity of illness may be correlated with the likelihood of a positive diagnostic test;
- It is possible that infections with nontuberculous mycobacteria or exposure to environmental mycobacteria led to cross reactivity and decreased specificity;

The systematic review focused on test accuracy (ie. sensitivity and specificity). None of the papers reviewed provided information on patient-important outcomes, ie. showing that commercial tests used in a given situation resulted in a clinically relevant improvement in patient care and/or outcomes. In addition, no information was available on the values and preferences of patients.

No studies were identified that directly assessed the value of serology over and above conventional tests such as sputum smear microscopy. The TDR study did evaluate added value of smear plus serology and reported a gain equivalent to the detection of 57% of the smear-negative, culture-positive TB cases. However, there was a corresponding unacceptable decrease in specificity (58%).

## 4. GRADE evidence profiles and final policy recommendations

The GRADE evidence assessment (Tables 1 to 4) confirmed that the quality of evidence for commercial serodiagnostic tests was **very low**, with harms/risks far outweighing any potential benefits (strong recommendation). It is therefore recommended that **these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status**.

- This recommendation also applies to paediatric TB based on the generalisation of data 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.

## 5. Implications for further research

Targeted further research to identify new/alternative point-of-care tests for TB diagnosis and/or serological tests with improved accuracy is strongly encouraged. Such research should be based on adequate study design including quality principles such as representative suspect populations, prospective follow-up and adequate, explicit blinding. It is also strongly recommended 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.

## 6. GRADE Tables

*Table 1. Should commercial serological tests be used as a replacement test for conventional tests such as smear microscopy in patients suspected of having pulmonary tuberculosis?*

*Table 2. Should commercial serological tests be used as an add-on to conventional tests such as smear microscopy in patients suspected of having pulmonary tuberculosis?*

*Table 3. Diagnostic accuracy of Anda-TB IgG*

*Table 4. Diagnostic accuracy of Anda-TB IgG in studies of smear-negative patients (i.e. as an 'add on' test to smear microscopy)*

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**Table 1. Should commercial serological tests be used as a replacement test for conventional tests such as smear microscopy in patients suspected of having pulmonary tuberculosis?**

Outcome	No. studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	Final Quality <sup>1</sup>	Effect per 1000	Importance
<b>True Positives</b>	67 (8318) <sup>A1</sup>	Cross-sectional and case-control	Very Serious <sup>A2</sup> (-2)	No Serious Indirectness <sup>A3</sup>	Very Serious <sup>A4</sup> (-2)	Serious <sup>A5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 64 Prev 30%: 192	Critical
<b>True Negatives</b>	67 (8318) <sup>A1</sup>	Cross-sectional and case-control	Very Serious <sup>A2</sup> (-2)	No Serious Indirectness <sup>A3</sup>	Very Serious <sup>A4</sup> (-2)	Serious <sup>A5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 819 Prev 30%: 637	Critical
<b>False Positives</b>	67 (8318) <sup>A1</sup>	Cross-sectional and case-control	Very Serious <sup>A2</sup> (-2)	No Serious Indirectness <sup>A3</sup>	Very Serious <sup>A4</sup> (-2)	Serious <sup>A5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 81 Prev 30%: 63	Critical
<b>False Negatives</b>	67 (8318) <sup>A1</sup>	Cross-sectional and case-control	Very Serious <sup>A2</sup> (-2)	No Serious Indirectness <sup>A3</sup>	Very Serious <sup>A4</sup> (-2)	Serious <sup>A5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 36 Prev 30%: 108	Critical

Accuracy estimates were not pooled because of the considerable heterogeneity among studies. Based on sensitivity median = 64%, specificity median = 91%

<sup>1</sup>Quality of evidence rated as high (no points subtracted), moderate (1 point subtracted), low (2 points subtracted), or very low (>2 points subtracted) based on five factors: study limitations, indirectness of evidence, inconsistency in results across studies, imprecision in summary estimates, and likelihood of publication bias. For each outcome, the quality of evidence started at high when there were randomized controlled trials or high quality observational studies (cross-sectional or cohort studies enrolling patients with diagnostic uncertainty) and at moderate when these types of studies were absent. One point was then subtracted when there was a serious issue identified or two points when there was a very serious issue identified in any of the criteria used to judge the quality of evidence.

<sup>A1</sup>67 studies evaluated 18 commercial tests. 37/67 (55%) studies used a cross-sectional design and 30/67 (45%) studies used a case-control design.

<sup>A2</sup>Study limitations were assessed using the QUADAS tool. Overall, study quality suffered from lack of a representative patient spectrum as only 19/67 (28%) studies were considered to include a representative sample (scored as yes when ambulatory patients suspected of having active TB were consecutively selected). 27/67 (40%) of studies recruited patients in a consecutive manner. 29/67 (43%) studies were conducted in an outpatient setting. Blinding of commercial test results was reported in 34/67 (51%) studies.

<sup>A3</sup>Diagnostic accuracy was considered a surrogate for patient-important outcomes; therefore this factor was not downgraded. Uncertainty about directness for false-negatives relates to possible detrimental effects from delayed diagnosis and uncertain but likely deterioration of health status. Uncertainty about directness for false-positives relates to the following concerns: diagnosing other respiratory diseases (such as pneumonia) as pulmonary TB may lead to delayed diagnosis or death from the other disease; false-positives unnecessarily consume health care and patient resources through DOT administration and patient misclassification (resulting in potentially inappropriate treatment regimens); adverse drug reactions may increase. Only 32 (48%) studies were conducted in low/middle-income countries limiting generalisability to these settings.

<sup>A4</sup>Heterogeneity was assessed visually and statistically. There was significant heterogeneity in accuracy estimates: sensitivity range 0% to 100%, I-square = 89.6%; p = 0.0000; specificity range 31% to 100%, I-square = 93.8%; p = 0.0000. In further analyses, subgroups were pre-specified by identity of commercial test, antibody detected, and smear status to decrease heterogeneity. Differing criteria for patient selection and greater duration and severity of illness of the study populations may have introduced variability in findings among studies. The heterogeneity between studies could also be explained by use of different cut-offs for positivity, a factor that could not be addressed.

<sup>A5</sup>Accuracy estimates were not pooled. The 95% confidence intervals were wide for many individual studies; however, this factor was not downgraded as there were a large number of studies and 2 points had already been subtracted for inconsistency.

<sup>A6</sup>Data included in the systematic review did not allow for formal assessment of publication bias using methods such as funnel plots or regression tests. Therefore, publication bias cannot be ruled out and it was considered prudent to assume a degree of publication bias as studies showing poor performance of commercial tests were probably less likely to be published. Industry involvement was recorded in 40/67 studies(32/40 involved donation of test kits)

**Table 2. Should commercial serological tests be used as an add-on to conventional tests such as smear microscopy in patients suspected of having pulmonary tuberculosis?**

Outcome	No. studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	Final Quality	Effect per 1000	Importance
True Positives	28 (3433) <sup>B1</sup>	Mainly cross-sectional	Serious <sup>B2</sup> (-1)	Serious <sup>B3</sup> (-1)	Very Serious <sup>B4</sup> (-2)	Serious Imprecision <sup>B5</sup> (-1)	Likely <sup>B6</sup>	Very Low ⊕○○○	Prev 10%: 61	Critical
True Negatives	28 (3433)	Mainly cross-sectional	Serious <sup>B2</sup> (-1)	Serious <sup>B3</sup> (-1)	Very Serious <sup>B4</sup> (-2)	Serious Imprecision <sup>B5</sup> (-1)	Likely <sup>B6</sup>	Very Low ⊕○○○	Prev 10%: 828	Critical
False Positives	28 (3433)	Mainly cross-sectional	Serious <sup>B2</sup> (-1)	Serious <sup>B3</sup> (-1)	Very Serious <sup>B4</sup> (-2)	Serious Imprecision <sup>B5</sup> (-1)	Likely <sup>B6</sup>	Very Low ⊕○○○	Prev 10%: 72	Critical
False Negatives	28 (3433)	Mainly cross-sectional	Serious <sup>B2</sup> (-1)	Serious <sup>B3</sup> (-1)	Very Serious <sup>B4</sup> (-2)	Serious Imprecision <sup>B5</sup> (-1)	Likely <sup>B6</sup>	Very Low ⊕○○○	Prev 10%: 39	Critical

Accuracy estimates were not pooled because of the considerable heterogeneity among studies. Based on sensitivity median = 61%, specificity median = 92%

<sup>B1</sup>28 studies involving smear-negative patients were included; 21/28 (75%) used a cross-sectional design and 7/28 (25%) used a case-control design.

<sup>B2</sup>Study limitations were assessed using the QUADAS tool. 17/28 (61%) studies recruited patients in a consecutive manner; 18/28 (64%) studies were conducted in an outpatient setting. Blinding of the commercial test result was reported in 18/28 (64%) studies.

<sup>B3</sup>Diagnostic accuracy was considered a surrogate for patient-important outcomes (see <sup>A3</sup>). Indirectness was regarded as a greater concern if a commercial serological test is used as an 'add on' test, therefore this was downgraded one point. 16 (57%) were conducted in low/middle-income countries limiting generalisability to these settings.

<sup>B4</sup> Heterogeneity was assessed visually and statistically. There was significant heterogeneity in accuracy estimates: sensitivity range 29 to 77%, I-square = 72.5%; p = 0.0000; specificity range 77 to 100%, I-square = 72.1%; p = 0.0000. Subgroups were pre-specified by identity of commercial test, antibody detected, and smear status to decrease heterogeneity. Differing criteria for patient selection and greater duration and severity of illness of the study populations may have introduced variability in findings among studies. The heterogeneity between studies could also be explained by use of different cut-offs for positivity, a factor that could not be addressed.

<sup>B5</sup> Accuracy estimates were not pooled. The 95% confidence intervals were very wide for many individual studies; however, this factor was not downgraded as there were a large number of studies and 2 points had already been subtracted for inconsistency.

<sup>B6</sup>Data included in the systematic review did not allow for formal assessment of publication bias using methods such as funnel plots or regression tests (see <sup>A6</sup>). Therefore, publication bias cannot be ruled out and it was considered prudent to assume a degree of publication bias as studies showing poor performance of commercial tests were probably less likely to be published.

**Table 3. Diagnostic accuracy of Anda-TB IgG**

Outcome	No. studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	Final Quality	Effect per 1000	Importance
<b>True Positives</b>	7 (870) <sup>C1</sup>	Mainly case-control	Very Serious <sup>C2</sup> (-2)	No Serious Indirectness <sup>C3</sup>	No Serious Inconsistency <sup>C4</sup>	Serious <sup>C5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 76 Prev 30%: 228	Critical
<b>True Negatives</b>	7 (870) <sup>C1</sup>	Mainly case-control	Very Serious <sup>C2</sup> (-2)	No Serious Indirectness <sup>C3</sup>	No Serious Inconsistency <sup>C4</sup>	Serious <sup>C5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 828 Prev 30%: 644	Critical
<b>False Positives</b>	7 (870) <sup>C1</sup>	Mainly case-control	Very Serious <sup>C2</sup> (-2)	No Serious Indirectness <sup>C3</sup>	No Serious Inconsistency <sup>C4</sup>	Serious <sup>C5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 72 Prev 30%: 56	Critical
<b>False Negatives</b>	7 (870) <sup>C1</sup>	Mainly case-control	Very Serious <sup>C2</sup> (-2)	No Serious Indirectness <sup>C3</sup>	No Serious Inconsistency <sup>C4</sup>	Serious <sup>C5</sup> (-1)	Likely <sup>A6</sup>	Very Low ⊕○○○	Prev 10%: 24 Prev 30%: 72	Critical

Based on pooled sensitivity = 76% (95% CI 63 to 87%), pooled specificity = 92% (95% CI 74 to 98%)

<sup>C1</sup>7 studies were included in smear-positive patients that evaluated Anda-TB IgG (Anda Biologicals, Strasbourg), an A60-based ELISA.

<sup>C2</sup>Study limitations were assessed using the QUADAS tool. None of the studies was considered to have a representative spectrum (only 2/7 studies were conducted in an outpatient setting; 1/7 studies used a cross-sectional study design; and 1/7 studies reported selecting subjects in a consecutive manner). In 2/7 studies the index test was blinded and in 5/7 studies differential verification was avoided.

<sup>C3</sup>Diagnostic accuracy was considered a surrogate for patient-important outcomes (see <sup>A3</sup>); only 1/7 studies was conducted in low/middle-income countries limiting generalisability to these settings.

<sup>C4</sup>Heterogeneity was assessed by visual inspection of forest plots of sensitivity and specificity estimates. Sensitivity in the studies varied from 54% to 85% and specificity varied from 68% to 100%. However, except for two studies by the same author, the sensitivity estimates were consistent. Specificity estimates were more variable. Heterogeneity between studies could be explained by use of different cut-offs for positivity, a factor that could not be addressed.

<sup>C5</sup>Accuracy estimates were pooled by bivariate meta-analysis. Pooled sensitivity and specificity had relatively wide confidence intervals: sensitivity 76% (95% CI 63% to 87%); specificity 92% (95% CI 74 to 98%).

<sup>C6</sup>Data included in the systematic review did not allow for formal assessment of publication bias using methods such as funnel plots or regression tests. Therefore, publication bias cannot be ruled out and it was considered prudent to assume a degree of publication bias as studies showing poor performance of commercial tests were probably less likely to be published. This in turn may have introduced 'optimism bias' in the pooled estimates of sensitivity and specificity; nevertheless this factor was not downgraded.

**Table 4. Diagnostic accuracy of Anda-TB IgG in studies of smear-negative patients (i.e. as an ‘add on’ test to smear microscopy)**

Outcome	No. studies	Study Design	Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	Final Quality	Effect per 1000	Importance
<b>True Positives</b>	4 (700) <sup>D1</sup>	Mainly case-control	Very Serious <sup>D2</sup> (-2)	Serious <sup>D3</sup> (-1)	No Serious Inconsistency <sup>D4</sup>	Very Serious <sup>D5</sup> (-2)	Likely <sup>D6</sup>	Very Low ⊕○○○	Prev 10%: 59	Critical
<b>True Negatives</b>	4 (700) <sup>D1</sup>	Mainly case-control	Very Serious <sup>D2</sup> (-2)	Serious <sup>D3</sup> (-1)	No Serious Inconsistency <sup>D4</sup>	Very Serious <sup>D5</sup> (-2)	Likely <sup>D6</sup>	Very Low ⊕○○○	Prev 10%: 819	Critical
<b>False Positives</b>	4 (700) <sup>D1</sup>	Mainly case-control	Very Serious <sup>D2</sup> (-2)	Serious <sup>D3</sup> (-1)	No Serious Inconsistency <sup>D4</sup>	Very Serious <sup>D5</sup> (-2)	Likely <sup>D6</sup>	Very Low ⊕○○○	Prev 10%: 81	Critical
<b>False Negatives</b>	4 (700) <sup>D1</sup>	Mainly case-control	Very Serious <sup>D2</sup> (-2)	Serious <sup>D3</sup> (-1)	No Serious Inconsistency <sup>D4</sup>	Very Serious <sup>D5</sup> (-2)	Likely <sup>D6</sup>	Very Low ⊕○○○	Prev 10%: 41	Critical

Based on pooled sensitivity = 59% (95% CI 10 to 96%), pooled specificity = 91% (95% CI 79 to 96%)

<sup>D1</sup>Four studies were included of smear-negative patients that evaluated Anda-TB IgG (Anda Biologicals, Strasbourg), an A60-based ELISA.

<sup>D2</sup>Study limitations were assessed using the QUADAS tool. None of the studies was considered to have a representative spectrum (only one study was conducted in an outpatient setting; 2/4 studies used a cross-sectional study design; and 0/4 studies reported selecting subjects in a consecutive manner). In 1/4 studies the index test was blinded and in 1/4 studies differential verification was avoided.

<sup>D3</sup>Diagnostic accuracy was considered a surrogate for patient-important outcomes (see <sup>A3</sup>). Indirectness was regarded as a greater concern if Anda-TB were used as an add-on test; this factor was therefore downgraded by one point. No studies were conducted in low/middle-income countries limiting generalizability to these settings.

<sup>D4</sup>Heterogeneity was assessed by visual inspection of forest plots of accuracy estimates. The sensitivity varied from 35 to 73% and the specificity varied from 88 to 93%. However, except for one study, sensitivity was consistent and this factor was therefore not downgraded.

<sup>D5</sup>Accuracy estimates were pooled by bivariate meta-analysis. Pooled sensitivity had very wide confidence intervals: sensitivity 59% (95% CI 10 to 96%); specificity 91% (95% CI 79 to 96%).

<sup>D6</sup>Data included did not allow for formal assessment of publication bias using methods such as funnel plots or regression tests. Therefore, publication bias cannot be ruled out and it was considered prudent to assume a degree of publication bias as studies showing poor performance of commercial tests were probably less likely to be published. This in turn may have introduced ‘optimism bias’ in the pooled estimates of sensitivity and specificity; nevertheless, this factor was not downgraded.

## Annex 1: List of Expert Group Members

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## Annex 2: List of STAG-TB members

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27-29 September 2010, WHO Headquarters, Geneva, Switzerland

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