Scoping meeting for the development of guidelines on screening for active TB

31 May – 1 June 2011
Geneva, Switzerland

Meeting report

Stop TB Department
World Health Organization
June 2011
CONTENT

1. EXECUTIVE SUMMARY AND ACTION POINTS

2. BACKGROUND
   2.1. Rationale for TB screening
   2.2. The need for guidance
   2.3. Definitions

3. MEETING OBJECTIVES

4. PROCESS OF IDENTIFYING SCOPE AND QUESTIONS FOR THE GUIDELINES
   4.1. Scoping of the evidence
   4.2. Identifying the scope and main questions to be addressed by the guidelines
   4.3. Formulating PICOT format questions

5. TENTATIVE SCOPE AND QUESTIONS FOR THE GUIDELINES
   5.1. Tentative outline of guidelines on TB screening
   5.2. Tentative assessment of generic screening criteria for TB
   5.3. Programmatic questions that the guidelines should answer
   5.4. Research questions and role division
   5.5. Questions in PICOT format

ANNEXES

I. GUIDELINE GROUP

II. MEETING AGENDA
1. EXECUTIVE SUMMARY AND ACTION POINTS

TB screening is a complement to “passive case finding” that can help improve early case detection and reduce TB transmission. Population-wide mass-screening has been widely discouraged due to high cost, low cost-effectiveness and poor sustainability. However, targeted risk group screening may be both feasible and cost-effectiveness. WHO already recommends universal screening in a few high-risk groups, namely people living with HIV and household contacts of infectious TB cases. However, there is no internationally agreed policy on when and how to pursue TB screening in other risk groups, how to prioritize risk groups, and what screening approaches to use. Many countries are currently exploring various modalities of TB screening. There is therefore a need to develop guidance and key screening principles. A national TB screening strategy need to be context specific, and based on the local epidemiological, demographic and health system situation. Guidance is therefore also needed on how to perform a situation assessment and prioritize screening accordingly.

A scoping meeting for the development of guidelines on TB screening was organized by WHO, 31 May and 1 June 2011. The meeting reviewed available evidence on TB screening; agreed on the scope for TB screening guidelines; identified key knowledge gaps; and formulated questions for additional systematic reviews and other analyses of secondary data that could be performed over the next 6-12 months to inform the guideline development. The key action points are summarised in the table below.

<table>
<thead>
<tr>
<th>Actions</th>
<th>Time-line</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Complete the guidelines;</td>
<td>Dec 2012</td>
<td>See annex I. All experts invited to the meeting, plus a representative from the NCD department of WHO (for harmonizing screening of infectious diseases and NCD), and a patient representative to be identified later.</td>
</tr>
<tr>
<td>a. Finalize guideline group composition</td>
<td>June 2011</td>
<td>All in the guideline group are invited to send written comments on the outline, programmatic questions and the PICOT questions listed in section 5, which have been revised after the plenary and group work sessions of the meeting. Thereafter this document will be posted on the STB website and distributed for external review</td>
</tr>
<tr>
<td>b. Get feedback on guideline scope and PICOT questions</td>
<td>June 2011</td>
<td>See section 5.5. This tentatively includes: Systematic reviews (2 ongoing, 2 to be outsourced) Modelling (4 groups already doing/planning, but detailed role division is needed) Analysis of secondary data (prevalence surveys and TB/HIV meta-analysis data, already planned but specific protocol and time line needed)</td>
</tr>
<tr>
<td>c. Feedback from TB-STAG</td>
<td>20 June 2011</td>
<td>Tentatively, this is the same as the list of questions unidentified in this meeting, see section 5. It should be harmonized with the questions listed in the document “Priorities in Operational Research to improve Tuberculosis Control”, which Stop TB Partnership is coordinating.</td>
</tr>
<tr>
<td>d. Additional research to complete guidelines</td>
<td>June 2012</td>
<td>This could build largely on the work initiated by WHO WPRO and HQ (see link in section 4.1.). The aim is to demonstrate the type of tool that could help countries make practical sense of the guidelines. It can include tentative values for parameters, which can be updated as better data becomes available.</td>
</tr>
</tbody>
</table>

2. Make a list of priorities for original research to build the long-term evidence base | June 2011 |

3. Develop test version of tool for prioritization of screening on national level | Dec 2011 |
2. BACKGROUND

2.1. Rationale for TB screening

"Passive" case finding is currently the main strategy to identify TB cases. This approach relies on four actions; (1) a person with active TB experiencing symptoms; (2) the person presenting to an appropriate health facility (3) a health worker correctly assessing if the person fulfils the criteria for suspected TB; and (4) successful application of a diagnostic algorithm with sufficient sensitivity and specificity. Barriers for early case detection can occur at each step.

Much effort has been made to improve passive case finding over the past two decades, including: improving diagnostic capacity; reducing access barriers; enforcing TB suspect identification in health facilities; information campaigns to make people seek care actively; and establishing links between all relevant public and private health providers. These efforts have resulted in increased TB notification rates globally. Still, in 2009 the global case notification rate corresponded to only about 60%. The global case notification trend has decelerated in recent years. Moreover, long delays from onset of disease to TB diagnosis and treatment have been documented in many settings, with average delay ranging from several weeks to several months, and with many people delaying treatment for years. Additional efforts are therefore needed to improve early case detection.

This is further underscored by the estimation that TB incidence seems to be falling much slower than anticipated in most settings implementing the current recommended TB control strategy. The estimated global rate of decline is less than 1% per year and this trend is seen also in those regions that have experienced significant improvements in TB case detection. While improved access to quality treatment has substantially reduce TB prevalence and TB case fatality, the combination of incomplete case detection and long diagnostic delays translates into sustained TB transmission in the community.

There are some limitations to how much the current passive case detection approach can help further improve early case detection, including:

1. A large proportion of people with bacteriologically confirmed TB do not to report symptoms that they clearly associate with illness requiring prompt medical attention. Recent prevalence surveys have shown that about 15-25% of bacteriologically confirmed cases do not report any symptoms (at least not early in the disease course).

2. Among those who experience symptoms, a large proportion do not fulfil the "TB suspect" definition (usually 2-3 weeks of cough). The recent prevalence surveys reconfirmed that 50-60% of bacteriologically confirmed cases did not fulfil criteria for being a suspected TB case.

3. Despite efforts to improve knowledge and change attitudes many people with TB symptoms do not seek care rapidly enough to allow for early treatment and effective interruption of TB transmission.

4. Some of the barriers to access quality TB care are so severe that it will be difficult to completely overcome them in a foreseeable future for all relevant sub-populations.

One potential strategy to improve early care detection is to actively screen for TB in the general populations or in specific risk groups. Mass population screening was a key component of TB control in many developed countries until the second half of the 20th century and helped accelerate TB burden decline in some places. However, it has been
widely discouraged in resource-constrained settings due to high cost per identified TB case, as compared to passive case finding, especially for the detection of the most infectious, smear positive, TB cases. Already in the early 1960s, the WHO’s Expert Committee on Tuberculosis emphasized that passive case finding is much more feasible and cost-effective than mass screening and that mass screening should never preceded the development of good diagnostic and treatment services in the general health services. The Committee concluded in its eights report that “mass screening is expensive but may be indicated if there is adequate basic diagnostic and treatment programme and if financial resources permit” (WHO 1964, p9). Ten years later, in 1974, the ninths report of the Committee refined and strengthened this conclusion and recommended that “the policy of indiscriminate tuberculosis case finding by mobile mass radiography should now be abandoned” (WHO 1974, p 16). However, the word “indiscriminate” is very important in this recommendation, since the Committee at the same time recommended screening of selected risk groups, such as contacts, and “immigrants and foreign workers coming from high prevalence areas” (WHO 1974, p 16).

Targeted screening in selected high risk groups can be feasible and effective, though data on cost-effectiveness are very scarce. A systematic review has recently been performed which highlights successes and challenges with TB screening, while showing potential for improving early TB case detection through screening in selected risk groups. Moreover, mathematical modelling suggest that TB screening, under some conditions, can be effective, cost effective and even cost saving from a long-term health systems perspective by averting future TB cases.

In summary, while mass screening is likely to be an inefficient strategy in most settings, TB screening in selected risk groups has a potentially important role to play in all settings. However, the evidence base is still limited and few systematic reviews on the issue have been performed.

2.2. The need for guidance

There is currently no internationally agreed policy on if, when, where and how to pursue TB screening, how to prioritize risk groups, and what screening methods and approaches to use. Many countries, especially those with stagnated TB case detection trend and no or slow decline in estimated TB incidence, are currently exploring various modalities of active TB case finding, including screening in risk groups. There is therefore a need to develop guidance and key screening principles.

Risk group screening is already recommended by WHO, and guidelines are available, for a few specific risk groups, namely people living with HIV, and household contacts of infectious TB cases. There are guidelines for TB control in prisons and refugee camps, including some specific recommendations on how to screen for TB. A collaborative framework for care and control of TB and diabetes is soon to be published. It includes general recommendation on screening for TB among people with diabetes, but does not provide details on how. TB screening in immigrants, homeless people, drug addicts and other selected groups are done in several countries and national or regional guidelines do exist. Screening in other risk groups have been increasingly discussed over the past few years, but scientific evidence and documented experiences in high burden countries are limited. Guidelines on TB screening should review, build on, and refer to those existing guidelines, as appropriate.
A national TB screening strategy need to be context specific and based on local epidemiological, demographic and health systems data. Guidance is therefore also needed on how to collect and analyse such data, as well as for monitoring and evaluation of screening initiatives.

Screening and treatment of latent TB infection (LTBI) is a related topic, which will not be covered by the first iteration of these guidelines. However, future iterations of TB screening guidelines may cover LTBI as well. From here on, TB screening refers to screening for active TB disease only.

2.3. Definitions

2.3.1. Screening
The WHO has defined screening as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."20

A briefer definition has been suggested by McKeown: "Any medical investigation which does not arise from a patient's request for advice for specific complaints"21. Reviewing these and other definition of screening, Holland and Stewart suggested that screening implies "Actively seeking to identify a disease or pre-disease condition in people who are presumed and who presume themselves to be healthy."22

There are generally agreed criteria for when screening is appropriate, which are summarized in table 1.

Table 1. Summary of criteria for screening21

<table>
<thead>
<tr>
<th>Wilson and Jungner criteria for screening (WHO 1968)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Condition is an important health problem for individual and community.</td>
</tr>
<tr>
<td>2. There is accepted treatment for patients with the disease.</td>
</tr>
<tr>
<td>3. The natural history of the disease should be adequately understood.</td>
</tr>
<tr>
<td>4. There should be a latent or early symptomatic stage.</td>
</tr>
<tr>
<td>5. There should be a suitable and acceptable screening test.</td>
</tr>
<tr>
<td>6. Facilities for diagnosis and treatment should be available.</td>
</tr>
<tr>
<td>7. There should be an agreed policy on whom to treat as patients.</td>
</tr>
<tr>
<td>8. Early treatments has more benefit than treatment started later.</td>
</tr>
<tr>
<td>9. The cost should be economically balanced.</td>
</tr>
</tbody>
</table>
In brief, the disease should be important, screening and diagnostic tests should be able to correctly and efficiently identify people with disease, effective treatment should be available, there should be benefits from early treatment (for the individual and/or society), and the cost of case finding and treatment should be reasonable.

Screening was first applied for communicable diseases. Initially, screening programmes were developed for malaria, worm infestation, leprosy and trachoma, followed by TB and venereal diseases. The basic screening concepts and criteria were further refined when screened also started to encompass non-communicable diseases (NCDs) in the 1950s and 1960s, such as screening for early stages of diabetes, cardio-vascular diseases and cancer for secondary and tertiary prevention, and later for NCD risk factors (e.g. dyslipidaemia) for primary NCD prevention. The number needed to screen (NNS) is a measure that conventionally expresses the number of individuals that need to be screened for a given duration to prevent one death or other adverse event. It can also be used to express NNS to detect one additional case, or avert an additional transmission (in the case of infectious diseases).

### 2.3.2. TB screening

TB has been used as a classical example of screening rationale: for secondary prevention through early detection of latent infection; tertiary prevention through early treatment of active TB; and primary prevention of secondary cases by stopping transmission. The applicability of the generic screening criteria listed above to TB is further discussed in section 5 below.

For the purpose of these guidelines, TB screening implies systematic investigation for active TB diseases among people who do not seek care because of symptoms/signs compatible with TB. This includes both people who do not seek care because they do not perceive that they have a health problem that warrants medical attention, as well as people who perceive that they have a health problem that warrants medical attention, but who do not seek care due to access barriers, or due to other reasons. TB screening can also be done among people attending health facilities for other reasons than symptoms/signs compatible with TB, for example: people treated for other conditions that are risk factors for TB (e.g. HIV, diabetes, substance abuse, chronic obstructive lung disease); people attending preventive/health promotion services (e.g. antenatal care); general hospital outpatient or inpatient attendees regardless of symptoms and reason for seeking care. TB screening may target the whole population, or specific TB risk groups (see definition of TB risk group below).

### 2.3.3. Screening tool vs. diagnostic tool

A screening tool should efficiently distinguish “persons who probably have a disease from those who probably do not”. Among those who probably have the disease, the diagnosis needs to be established through application of diagnostic test with very high specificity, as well as high sensitivity. A screening tool must have high sensitivity. High specificity is not necessary. However, if specificity is too low, a large proportion will have a false positive screening result and require the confirmatory diagnostic test.

### 2.3.4. TB risk group

A TB risk group is any group of people within which prevalence of TB is significantly higher than in the general population. A risk group may be a group of people sharing a specific individual-level risk profile (e.g. close contact with a case of active TB; living with HIV;
having diabetes). A risk group can also be defined as all people living in a specific geographical location (e.g. all people living in an urban slum) or a specific type of institution (e.g. all prisoners in a country) associated with high burden of TB. It is not necessary that the characterizing factor is a causal risk factor for TB. The association of a risk marker with TB may be confounded by other factors, but still valid as an identifier for higher TB risk.

3. MEETING OBJECTIVES

The objectives of the meeting were:

1. To review available evidence on screening for active TB disease, including:
   - Results of a systematic literature review on active case finding
   - Recent/ongoing original research
   - Country and regional case studies
   - Results of mathematical modelling studies assessing potential effectiveness, cost-effectiveness and epidemiological impact of active case finding

2. To agree on the type, scope, and set timeline for development of global guidelines on screening for active TB disease

3. To identify key knowledge gaps and suggested additional analysis of secondary data, which could be completed during 2011, and inform the guideline development, e.g.:
   - Additional systematic literature reviews
   - Re-analysis / primary meta analysis of existing data, such as prevalence survey data
   - Mathematical modelling

The expected outcomes were:

4. A plan for development of guidelines on TB screening, for submission to the WHO Guideline Review Committee

5. An agreed list of priority research to inform the completion of such guidance
4. PROCESS OF IDENTIFYING SCOPE AND QUESTIONS FOR THE GUIDELINES

4.1. Scoping of the evidence

A systematic review on TB screening / active TB case finding was commissioned by WHO to Johns Hopkins University in 2010. This review was finalised in May 2011, though some sub-group analyses are yet to be completed. This was the main scoping of the evidence prepared prior to the scoping meeting and a draft report of the systematic review was presented to the meeting. The following presentations were reviewed and discussed by the meeting, under the chairmanship of Dr Peter Godfrey-Faussett (see agenda in annex II):

Session I: The rationale for TB screening
- A historical perspective on TB screening and lessons for the future (Dr Hans Rieder)
- History of active case finding for leprosy elimination and potential lessons for TB control (Dr Denis Daumerie)
- Lessons from TB prevalence surveys and the role of chest X-ray in TB screening (Dr Ikushi Onozaki)
- New diagnostics and their potential role in TB screening/diagnostic algorithms (Dr Fuad Mirzayev)

Session II: Systematic review findings
- Systematic review of number needed to screen in selected risk groups with different screening approaches (Dr Jonathan Golub)
- Plans for a systematic review of how to identify risk groups and how to ensure participation in screening and treatment (Dr Ellen Mitchell)
- Screening for TB in people with HIV – implication for policy of meta analysis and modelling results (Dr Heileyesus Getahun)

Session III: Country experiences and research projects on TB screening
- Tuberculosis active case finding strategies in the United States (Dr Mary Reichler)
- TB active case finding in western Kenya (Dr Jane Carter)
- Tuberculosis screening in South Africa (Dr Gavin Churchyard)
- Impact of periodic case-finding for symptomatic smear-positive disease on community control of prevalent infectious tuberculosis: A cluster randomised trial of two delivery strategies in Harare, Zimbabwe (Dr Elizabeth Corbett)
- Community case finding for TB: Approaches and Outcomes (The ZAMSTAR project in Zambia, with the CREATE consortium) (Dr Helen Ayles)

Session IV: Regional perspectives
- Experiences and policy development on TB screening in Europe (Dr Masoud Dara and Dr Davide Manisero)
- Experiences and policy development on TB screening in the Western Pacific Region (Dr Nobu Nishikiori)

Session V: Modelling and other analyses
Factors influencing the performance of active case-finding for TB: results from mathematical modelling (Dr Pete Dodd)

Knowledge gaps for TB screening (Dr Philippe Glaziou)

The draft systematic review report and all the presentation are available on the website: www.who.int/tb.

4.2. Identifying the scope and main questions to be addressed by the guidelines

The WHO principles for guideline development were presented by Dr Laragh Gollogly from the Guideline Review Committee (GRC) secretariat.

A discussion paper outlining potential scope and general questions for the guidelines had been prepared and circulated to all participants prior to the meeting. In the second day of the meeting this was discussed in plenary with the specific objectives to agree on:

1. Applicability of the generic screening criteria to TB screening, and related knowledge gaps
2. Main programmatic questions to be addressed by the guidelines, and related knowledge gaps
3. Possible content of the guidelines

4.3. Formulating PICOT format questions

A group work session was organised to formulate questions using the PICOT format (Population, Indicator / Intervention, Comparator, Outcome, Time).

The groups were presented with sets of tentative questions related to the knowledge gaps concerning the applicability of the generic screening criteria to TB screening, and the main programmatic questions to be addressed by guidelines. The aim was to develop questions and outcomes that could be addressed primarily through systematic reviews, other secondary data analysis or modelling.

The groups reviewed and changed/deleted the listed questions, and suggested additional questions, as required. They formulated questions using the PICOT format and specific outcomes and sub-group analyses. The group outputs were then discussed in plenary.

The results of the plenary discussion and group work are presented in sections 5.
5. TENTATIVE SCOPE AND QUESTIONS FOR THE GUIDELINES

5.1. Tentative outline of guidelines on TB screening

Main target audience
NTP managers, partner organizations, clinicians, public health practitioners.

Separate products are probably needed for other target groups such as general population and specific groups eligible for screening

Scope
Screening for active TB disease (excluding screening for latent TB, excluding other interventions to intensify/enhance case finding)

Tentative content
1. Rationale, potential benefits and risk of TB screening
2. Scope of guidelines, target audience, guideline development process
3. Definitions of active case finding / screening, screening test, TB risk groups, etc
4. Generic criteria for screening and establish if they are fulfilled for active TB disease screening: (a) in general; (b) in specific risk groups.
5. Ethical, human rights and legal basis for screening
6. Recommended screening tools and screening approach in general, and for each risk group as required.
7. Recommendations on which risk groups should be screened for TB in all settings, regardless of epidemiological situation (e.g. HIV, contacts,…).
8. Situation(s) when mass TB screening in the whole population is relevant (or establish that this is never recommended). Recommended approach for mass screening.
9. Essential criteria and the appropriate decision making algorithm to prioritize and sequence TB screening in other groups in a given setting. Tentatively the criteria can be categorized under:
   a. Feasibility (how to identify, reach, and ensure uptake of screening in a given risk groups);
   b. Cost-effectiveness (indicated by number needed to screen: to detect a case; prevent one future case, prevent one death, increase one DALY, etc)
   c. Total impact on transmission, disease burden and cost of illness for patient, health system and society (influenced by the prevalence of undetected disease and size of risk group)
   d. Affordability, health systems requirements, and risk of doing harm
10. Data requirements and data collection approaches for situation assessment.
11. Practical steps and programmatic considerations
12. Monitoring and evaluation of screening to adjust prioritization and approaches.

Annexes with findings from systematic reviews and other support material.
### 5.2. Tentative assessment of generic screening criteria for TB

<table>
<thead>
<tr>
<th>Wilson’s and Jungner’s criteria for screening (WHO 1968)</th>
<th>Tentative assessment for TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria fulfilled?</strong></td>
<td><strong>Comment</strong></td>
</tr>
<tr>
<td>1. Condition is an important health problem for individual and community.</td>
<td>Yes</td>
</tr>
<tr>
<td>2. There is accepted treatment for patients with the disease.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| 3. The natural history of the disease should be adequately understood. | Not fully | More research needed:  
- Speed of disease progress, also in relation to risk factors for progression  
- Transmission in early stages of disease  
- Progression from smear negative to smear positive TB  
- Likelihood of recovery among people with no or vague symptoms |
| 4. There should be a latent or early symptomatic stage. | Yes | Details captured under question 3 (NOTE: for these guideline, early symptomatic or non-symptomatic stage of disease is relevant, not latent TB infection) |
| 5. There should be a suitable and acceptable screening test. | Yes | More research needed:  
- Sensitivity, specificity, cost, feasibility and acceptability of different tests, for different risk groups and settings. |
| 6. Facilities for diagnosis and treatment should be available. | Depends on local situation | National/local situation assessment needed:  
- Capacity of national TB programme  
- Diagnostic and treatment services  
- Health system |
| 7. There should be an agreed policy on whom to treat as patients. | Yes (for active TB) though some uncertainty for certain TB types. | TB case definitions and treatment guidelines need not be addressed in these guidelines |
| 8. Early treatment has more benefit than treatment started later. | Yes, but how much? Different benefit for individual and community | More research needed:  
- How much benefit for individual and society? Research under (3) above plus screening trials needed  
- The answer may vary risk group |
| 9. The cost should be economically balanced | Depends on: (1) answers to all above questions; (2) screening approach*; and (3) local situation | Research needed:  
- Cost in relation benefits under question 8  
National/local situation assessment needed:  
- Risk groups / potential targets groups for screening  
- Local TB epidemiology  
- Health system and health seeking pattern  
- Competing needs in TB control, health care, and generally in society |

* A given screening approach for a specific risk group is characterised by:  
1. The screening tool, diagnostic tool and algorithm for screening and diagnosis  
2. The screening interval  
3. The method to identify eligible individuals, reach them with screening, refer them to diagnosis and TB treatment or other clinical management  
4. Possible linkage with other public health/screening programmes for other diseases/risk factors.
### 5.3. Programmatic questions that the guidelines should answer

<table>
<thead>
<tr>
<th>Question</th>
<th>Tentative answer</th>
<th>Comment</th>
<th>Further evidence needed</th>
</tr>
</thead>
</table>
| 1. Is TB screening ever appropriate, at least in some risk groups? | Yes | • Easy to construct scenario where all screening criteria are fulfilled  
• Empirical evidence available for several risk groups and approaches  
• Already WHO policy for HIV and contacts | No |
| 2. Which risk group(s) should always be screened, regardless of epidemiological and health system context | People with HIV and TB contacts. | • Existing guidelines on universal ICF in HIV and contact investigation  
• Need to review evidence on other risk groups | Yes:  
• The ongoing systematic review  
• Original research |
| 3. Which screening test(s) should be used? | Symptom screening and/or CXR (any abnormality) | • Depends on sensitivity, specificity, cost, feasibility, time required, health systems requirement and acceptability.  
• May vary between risk groups | Yes:  
• New systematic review required on screening tests. |
| 4. In a given setting, should risk group X be screened? What are the minimal programmatic and epidemiological requirements? With what approach? How should risk groups be prioritized and sequenced? | Depends on setting. Basic programmatic and epidemiological conditions for screening need to be established | • A careful situation analysis is required.  
• The guidelines should set out the required analysis and criteria* for prioritization and choice of approach. | Yes:  
• The ongoing systematic review  
• Additional reviews on specific risk groups and screening approaches in different settings  
• Original research |
| 5. Is mass TB screening in the whole population ever appropriate? If yes, what conditions apply? What approach? | Yes, but conditions are probably met in few settings | • Possible to construct hypothetical scenario where all criteria are fulfilled (e.g. abundant resources)  
• Evidence is mixed, several positive and negative experiences reported: what determines? | Yes:  
• The ongoing systematic review  
• Unpublished country data  
• Original research |

*Criteria for the prioritization of risk groups may include:

1. Feasibility to identify, reach, and screen a given risk group
2. Likelihood of completion of diagnostic algorithm, uptake of treatment and completion of treatment in a given risk group.
3. Number needed to screen (NNS) to detect one case of TB in a given risk group (which is the inverse of prevalence and thus indirectly reflects the risk of TB and risk of delayed TB diagnosis and treatment in a given risk group)
4. Cost of detecting one additional case of TB in a given risk group (NNS is an indirect cost effectiveness indicator, but it also depends on which screening approach is used)
5. Estimated health, social and economic impact for the screened individual
6. Estimated impact on TB epidemiology, health care cost and societal cost of TB (which depends on improvement of early case detection in the risk group, as well as on the size of the risk group and the likelihood of transmission within and beyond the risk group)
5.4. Research questions and role division

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>STUDY</th>
<th>RESPONSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL BENEFITS OF TB SCREENING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does TB screening increase case detection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does TB screening reduce delay from onset of disease to initiation of TB treatment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does TB screening improve TB treatment outcomes for those diagnosed with TB?</td>
<td>Systematic review 1</td>
<td>To be outsourced</td>
</tr>
<tr>
<td>Does TB screening have economic and social consequences for the person with disease and his/her family?</td>
<td>Modelling</td>
<td>LSHTM WHO ECDC/Erasmus Harvard SPH</td>
</tr>
<tr>
<td>Does TB screening affect TB epidemiology in the community</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does TB screening reduce the economic impact of TB to the community</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHOICE OF SCREENING AND DIAGNOSTIC TOOLS AND ALGORITHMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the sensitivity and specificity of screening test X?</td>
<td>Systematic review 2</td>
<td>To be outsourced</td>
</tr>
<tr>
<td>What is the required time from application of screening test X to availability of test results?</td>
<td>Re-analysis of prevalence survey data</td>
<td>WHO/STB (TME and TBS)</td>
</tr>
<tr>
<td>What is the cost of screening test X?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What are the health systems requirements for screening test X?</td>
<td>Re-analysis of data set used for metal analysis of TB screening among PLHIV</td>
<td>CDC and WHO/STB (TBS and TME)</td>
</tr>
<tr>
<td>What is the acceptability of screening test X for persons screened and health care providers?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRIORITIZING RISK GROUPS AND SCREENING APPROACHES</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the number needed to screen to detect a case of TB in risk group X?</td>
<td>Systematic review 3</td>
<td>JHU</td>
</tr>
<tr>
<td>How effective is a given screening approach in risk group X to identify, reach, screen, diagnose and ensure treatment uptake?</td>
<td>Systematic review 4</td>
<td>KNCV</td>
</tr>
<tr>
<td>What factors determine feasibility and acceptability of screening in risk group X, and how can feasibility and acceptability be improved?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A given screening approach for a specific risk group is characterised by:
  1. The screening tool, diagnostic tool and algorithm for screening and diagnosis
  2. The screening interval
  3. The method to identify eligible individuals, reach them with screening, refer them to diagnosis and TB treatment or other clinical management
  4. Possible linkage with other public health/screening programmes for other diseases/risk factors.
5.5. **Questions in PICOT format**

**A. General benefits of TB screening**

1. *Does TB screening increase case detection?*

   **PICOT format:** Does TB screening, compared to passive case finding, initially increase the number of TB cases detected?

   **Outcomes:**
   - Total number of TB cases, and by type of TB: sputum smear positive vs. negative; confirmed vs. non-confirmed; pulmonary vs. EP; adults vs. children
   - Case notification rate by 100,000 pop (disaggregated by above types, and sex)

   **Timing of outcome:**
   - Directly after each completed screening round
   - By calendar year

   **NOTE:** A beneficial initial outcome is an increase in the number of cases detected, while long term positive effective is a decline in number of cases, assuming continued case finding intensity and effectiveness

2. *Does TB screening reduce delay from onset of disease to initiation of TB treatment?*

   **PICOT format:** Among people with active TB, does TB screening, compared to passive case finding, identify cases at an earlier stage of disease?

   **Outcomes:**
   - Average / median delay from onset of disease to start of treatment
   - Average / median delay from onset of symptoms to start of treatment
   - Proportion of sputum smear positive (1+, 2+, 3+ respectively) cases among all detected cases
   - BMI at time of diagnosis
   - Proportion of diagnosed cases with cavitations
   - Extent of radiographic abnormalities at time of diagnosis

   **Timing of outcome:**
   - Directly after each completed screening round
   - By calendar year

   **Sub-groups, for targeted population and intervention:**
   - By risk group(s) screened (*NOTE: this question will be discussed by group 3 as well*)
   - By estimated background prevalence/incidence in the general population
   - By baseline case detection and delay
   - By screening approach
3. **Does TB screening improve TB treatment outcomes for those diagnosed with TB?**

**PICOT format:** Is there a difference in TB treatment outcomes between TB cases who have been found by screening and those who have been found through routine passive case detection systems?

**Outcomes:**
- Cure (6 months)
- Completion (6 months)
- Failure (6 months)
- Interruption (6 months)
- Death (6 months)
- Relapse (24 months)
- Acquired drug resistance (6 months)
- Long-term disability (10 years)
- DALY (10 years)

**Subgroup analysis**
- Smear positive TB vs. smear negative TB
- Pulmonary vs. Extrapulmonary TB
- MDR-TB vs. no MDR-TB
- Children vs. adults
- HIV infected vs. non-HIV infected
- Urban/rural
- Men vs. women

4. **Does TB screening have economic and social consequences for the person with disease and his/her family?**

**PICOT format:** For people with active TB and their families, does starting treatment after case detection through screening, compared to starting treatment after detection through passive case finding, have a different cost of illness and risk of adverse social consequences?

**Outcomes:**
- Direct and indirect costs of illness for the patient and family (6 months)
- Social consequences for the patient and the family, including stigma, social exclusion, etc (6 months)

**Subgroups:**
- By socio-economic status
- By sex
- By health systems and social welfare characteristics of the country

5. **Does TB screening affect TB epidemiology in the community**
PICOT format:

a. Among people in TB affected communities, does TB screening in addition to passive case-finding, compared to passive case finding alone, affect TB epidemiology?

Outcomes:
- Prevalance of undiagnosed TB (yearly, up to 10 years from screening initiation)
- TB transmission
- Death rate (yearly, up to 10 years from screening initiation)
- Notification rate (yearly, up to 10 years from screening initiation)
- DALY (yearly, up to 10 years from screening initiation)
- MDR-TB prevalence

Subgroups:
- By risk group targeted
- By screening approach (including periodicity)
- By baseline TB prevalence
- Congregate settings vs. not congregate settings
- By background HIV prevalence

6. Does TB screening reduce the economic impact of TB to the community

PICOT format: In the community, what is the impact of TB screening in addition to passive case finding, compared to passive case finding alone, on health system cost and societal productivity?

Outcomes:
- Cost of TB screening, diagnosis, treatment and care (1 year, 5 years, 10 years)
- Loss of productivity (1 year, 5 years, 10 years)

Subgroups:
- By risk group targeted
- By screening approach
- By baseline TB prevalence
- By baseline cost of illness
- Congregate settings vs. not congregate settings
- By background HIV epidemiology
B. Choice of screening tool

1. What is the sensitivity and specificity of the screening test/algorithim?
   PICOT format: Among people eligible for TB screening, what is the sensitivity and specificity of screening test/algorithim X, compared to screening with the gold standard (i.e. culture)?
   Outcomes:
   - Sensitivity and specificity for all types of TB combined, and disaggregated by:
     - Smear positive TB vs. smear negative TB
     - Pulmonary vs. extrapulmonary TB
     - MDR-TB
   Subgroups
   - Children vs. adults
   - HIV infected vs. non-HIV infected
   - Other risk groups

2. What is the required time from application of screening test/algorithim to availability of results?
   PICOT format:
   a. Among people screened with screening test/algorithim X, compared to screening test/algorithim Y, what is the time from application of the test to availability to the screening result?
   Outcomes:
   - Time from screening to screening result is known to health worker
   - Time from screening to screening result is known to screened individual

3. What is the cost of the screening test/algorithim?
   PICOT: What is the cost of screening test/algorithim X, compared to screening test/algorithim Y?
   Outcomes:
   - Cost per screened individual (for patient and health system respectively)
   - Cost per new case detected (for patient and health system respectively)

4. What are the health systems requirements for the screening test/algorithim?
   Non-PICOT question
   Variables:
   - # persons by job type (laboratory technician, radiographer, interviewer, nurse, etc.)
   - # and type of laboratory / imaging equipment
   - Infrastructure requirements (clinics, laboratories, imaging equipment, etc.)

5. What is the acceptability of the test/algorithim for persons screened and health care providers?
   Non-PICOT question
   Variables:
   - Interpretable result without ambiguity
   - Convenient / painless
   - Stigma
   - Other benefits (e.g. screening/diagnosis of other conditions)
C. Prioritizing risk groups and screening approaches

1. **What is the number needed to screen to detect a case of TB in risk group X?**
   **PICOT format:** Among people in risk group X, how many individuals need to be screened to detect one case of active TB?
   **Outcomes:**
   - NNS (Number needed to screen) = Number of screened individual / number of active TB cases detected (timing: in each screening round)
   - Separate outcomes for different types of TB (sputum smear positive vs. negative; confirmed vs. non-confirmed; pulmonary vs. EP; adults vs. children)
   **Sub-groups (within each risk group):**
   - By estimated background prevalence/incidence in the general population
   - By screening test and diagnostic algorithm used
   - By screening approach

2. **How effective is a given screening approach¹ in risk group X to identify, reach, screen, diagnose and ensure treatment uptake?**
   **PICOT format:** Among people in risk group X, does screening approach Y, compared to approach Z, improve the likelihood to identify, reach, screen, diagnose and ensure treatment uptake?
   **Outcomes:**
   - Proportion of risk group reached (1 month from identification)
   - Proportion of reached accepting screening (1 week from reaching)
   - Proportion screened completing diagnostic procedures (2 weeks from screening)
   - Proportion of diagnosed started on treatment (1 week from diagnosis)
   - Proportion of treated with successful treatment (6 months from treatment start)

3. **What factors determine feasibility and acceptability of screening in risk group X, and how can feasibility and acceptability be improved?**
   **Non-PICOT questions:**
   - What are the particular barriers to identify and reach a specific risk group, and ensure treatment success? How can the barriers be overcome?
   - Does the national TB programme have the capacity to manage a screening programme and provide high quality treatment to the additional cases detected? How can the capacity be improved, and how can screening become feasible by collaborating with other disease/screening programmes, social sector, NGOs, etc?
   - How important are there negative implications of screening for the eligible screening subjects, such as stigma, costs, or risk of unnecessary worry, and how can they be mitigated?
   - How important are potential negative implications for the health system, such as overburdening of health care workers and distortion of health care priorities, and how can they be mitigated?

¹ A given screening approach for a specific risk group should be further broken down by:
   1. The screening tool, diagnostic tool and algorithm for screening and diagnosis
   2. The screening interval
   3. The method to identify eligible individuals, reach them with screening, refer them to diagnosis and TB treatment or other clinical management
   4. Possible linkage with other public health/screening programmes for other diseases/risk factors.
ANNEX I. GUIDELINE GROUP

COUNTRY REPRESENTATIVES

GHANA
Dr Frank Adae Bonsu
Disease Control Unit, P.O. Box KB 493, Korle Bu, Accra

PHILIPPINES
Dr Rosalind Vianzon
TB Unit, Infectious Diseases Office, National Centre for Disease Prevention and Control Department of Health, Bldg 13, San Lazaro Compound, Rizal Avenue, Sta Cruz, Manila

RESEARCHERS

Dr Helen Ayles
ZAMBART project, PO Box 50697, Ridgeway Campus UNZA, Lusaka, Zambia

Dr Jane Carter
USAID – AMPATH Partnership, Eldoret, Kenya

Prof Gavin Churchyard
AURUM Institute, The Ridge, 29 Queens Road, Parktown, Johannesburg, South Africa

Dr Liz Corbett
Clinical Research Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Dr Pete Dodd
London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Dr P. Godfrey-Faussett
London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Dr Jonathan Golub
Johns Hopkins University, School of Medicine, Baltimore 733 N. Broadway, MD21218, United States

Dr Megan Murray
Harvard School of Public Health, Division of Global Health Equity 641 Huntington Avenue, 4th Floor, Room 4A07, Boston, Massachusetts 02215, United States
TECHNICAL PARTNERS

US Centers for Disease Control and Prevention (CDC)
Dr Mary Reichler
1600 Clifton Rd., Atlanta, GA 30333, USA

The Union
Dr Hans Rieder
Jetzkofenstrasse 12, 3038 Kirchlindach, Switzerland

KNCV Tuberculosis Foundation
Dr Ellen Mitchell
P.O. Box 146, 2501 CC The Hague, The Netherlands

European Centre for Disease Prevention and Control (ECDC)
Dr Davide Manissero
SE-171 83 Stockholm, Sweden

USAID
Dr Ya Diul Mukadi
Office of Health Infectious Diseases and Nutrition
1300 Pennsylvania Avenue, Washington DC 20523, USA

WHO SECRETARIAT

EUROPEAN REGION
Dr Masoud Dara
WHO Regional Office for Europe, Conpenhagen, Denmark

WESTERN PACIFIC REGION
Dr Nobuyuki Nishikiori
WHO Regional Office for Western Pacific, Manila, Philippines

WHO HEADQUARTERS
Dr Knut Lönnroth, HTM/STB/TBS*
Dr Denis Daumerie, HTM/NTD
Dr Gojka Roglic, NMH/CHP/CPM
Dr Haileyesus Getahun, HTM/STB/TBS*
Dr Fuad Mirzayev, HTM/STB/TBL
Dr Philippe Glaziou, HTM/STB/TME
Dr Malgorzata Grzemska, HTM/STB/TBC
Dr Ikushi Onozaki, HTM/STB/TME*

*WHO steering group
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.30-9.00</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>9.00-9.10</td>
<td><strong>Session I: The rationale for TB screening</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Welcome</td>
<td>Léopold Blanc</td>
</tr>
<tr>
<td>9.10-9.40</td>
<td>Meeting background and objectives, introduction of participants, declaration of interest</td>
<td>Knut Lönnroth</td>
</tr>
<tr>
<td>9.40-10.00</td>
<td>Historical perspective on TB screening and lessons for the future</td>
<td>Hans Rieder</td>
</tr>
<tr>
<td>10.00-10.20</td>
<td>Active case finding for leprosy elimination: lessons for TB</td>
<td>Denis Daumerie</td>
</tr>
<tr>
<td>10.20-11.00</td>
<td>Lessons from TB prevalence surveys and the role of chest X-ray in TB screening</td>
<td>Ikushi Onozaki</td>
</tr>
<tr>
<td>11.00-11.20</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>11.20-11.40</td>
<td>New diagnostics and their potential role in TB screening/diagnostic algorithms</td>
<td>Fuad Mirzayev</td>
</tr>
<tr>
<td></td>
<td><strong>Session II: Systematic review findings</strong></td>
<td></td>
</tr>
<tr>
<td>11.40-12.20</td>
<td>Systematic review of number needed to screen in selected risk groups with different screening approaches</td>
<td>Jonathan Golub</td>
</tr>
<tr>
<td>12.20-12.40</td>
<td>Systematic review of how to identify risk groups and how to ensure participation in screening and treatment</td>
<td>Ellen Mitchell</td>
</tr>
<tr>
<td>12.40-13.40</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13.40-14.00</td>
<td>Screening for TB in people with HIV – implication for policy of meta analysis and modelling results</td>
<td>Haileyesus Getahun</td>
</tr>
<tr>
<td>14.00-14.30</td>
<td>Discussion on implications, and knowledge gaps</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td><strong>Session III: Country experiences of TB screening</strong></td>
<td></td>
</tr>
<tr>
<td>14.30-15.00</td>
<td>USA</td>
<td>Mary Reichler</td>
</tr>
<tr>
<td>15.00-15.30</td>
<td>Kenya</td>
<td>Jane Carter</td>
</tr>
<tr>
<td>15.30-16.00</td>
<td>South Africa</td>
<td>Gavin Churchyard</td>
</tr>
<tr>
<td>16.00-16.15</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>16.15-16.45</td>
<td>Zimbabwe</td>
<td>Elizabeth Corbett</td>
</tr>
<tr>
<td>16.45-17.15</td>
<td>Zambia</td>
<td>Helen Ayles</td>
</tr>
<tr>
<td>17.15-18.00</td>
<td>Discussion on country experiences</td>
<td>Discussants: Lynn Vianzon and Frank Bonsu</td>
</tr>
<tr>
<td>Time</td>
<td>Session IV: Regional perspectives</td>
<td>Session V: Modelling and other analyses</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>9.00-9.20</td>
<td>Experiences and policy development on TB screening in Europe</td>
<td>Session V: Modelling and other analyses</td>
</tr>
<tr>
<td>9.20-9.40</td>
<td>Experiences and policy development on TB screening in the Western Pacific Region</td>
<td>Modelling impact of TB screening I</td>
</tr>
<tr>
<td>9.40-10.00</td>
<td>Discussion</td>
<td>Modelling impact of TB screening II</td>
</tr>
<tr>
<td>10.00-10.15</td>
<td>Session V: Modelling and other analyses</td>
<td>Discussion on knowledge gaps that can be filled by modelling and other analyses</td>
</tr>
<tr>
<td>10.15-10.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.30-10.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.50-11.00</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>11.00-11.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.15-12.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.00-13.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.00-14.00</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>14.00-15.00</td>
<td>Report back from group work, agreed tentative list of questions and outcomes</td>
<td>Group work rapporteur</td>
</tr>
<tr>
<td>15.00-15.45</td>
<td>Establishment of formal guideline group, role division, identification of individuals/institutions who can pursue the research questions, plan for resource mobilization, timeline</td>
<td></td>
</tr>
<tr>
<td>15.45-16.00</td>
<td>Next steps and closing of the meeting</td>
<td></td>
</tr>
</tbody>
</table>
References


13. See reference 2,6,12. There is also unpublished information from NTP reviews, TB REACH, GF, etc


15. These guidelines are in the process of being finalized


18. Provisional Collaborative Framework for Care and Control of Tuberculosis and Diabetes. WHO and The Union, 2011


