Recommendations from the WHO Task Force on TB Impact Measurement on key methodological issues concerning TB disease prevalence surveys, with particular attention to issues that were not fully covered in the book Assessing TB prevalence through population-based surveys (http://www.wpro.who.int/publications/PUB_978+92+9061+314+5.htm)

Whether or not TB surveys should be carried out
Survey in intermediate or low burden countries:

- Countries expecting a prevalence of smear positive TB of less than 100 per 100,000 in target population are not recommended to carry out a survey unless they have had a previous survey. Alternative studies based on an in depth analysis of surveillance data and operational research such studies of diagnostic delay and detection of TB through active case finding are recommended.

Security:

- Security is an essential condition to carry out a TB prevalence survey. TB disease prevalence survey must not be conducted in the areas where UN security Level 3 or more is imposed. Countries in which a significant proportion of the population is living in Security Level 3 areas should not carry out a National survey. Technical assistance activities in those areas cannot be endorsed. Only essential health care activities are authorized in this areas, and a TB prevalence survey cannot be categorized as an essential activity.

- The NTP should carefully assess the security situation before deciding on the implementation of a TB prevalence survey. Staff and participants' safety is a top priority. TA activities are not recommended in the areas where UN Security Level 2 is imposed. TA for countries where a significant proportion of the population is living in Level 2 areas should be carefully planed in consultation with related offices and departments.

Screening strategy
The minimum screening strategy that should be used in surveys of the prevalence of TB disease is Strategy 3 in the WHO guidelines. In this strategy, the sampled population is screened using X-rays and a questionnaire about symptoms. All TB suspects are then asked to provide at least two sputum samples for smear microscopy and culture examination. While screening all of the sampled population with an X-ray considerably increases the cost of a survey, it reduces the workload of microscopy and culture laboratories and is thought to provide the best possible estimates.

Survey design
The Task Force recommends that countries should design TB prevalence surveys and calculate the sample sizes based on the idea that only one survey with a good precision will be performed, and not based on the idea that two consecutive surveys will be performed. This decision is based on the fact that in some of the previous surveys conducted in the Asian countries, the observed prevalence was often far from the initial estimated prevalence. In order to detect changes in TB prevalence in 10
years or less, the Task Force recommends that any subsequent survey should only be
designed after the results of 1st survey become available.

Excluded areas
Areas where survey operations are considered not to be feasible (insecurity, military
zones, etc.) should be excluded from the sampling frame from the beginning.

Age
TB disease prevalence survey should exclude children aged under 15 years old, unless
there is a certain evidence that children under 15 occupy a significant proportion of
the bacteriological positive cases in a country and the survey is expected to detect
those cases. Adding children aged between 10 and 15 to the samples may not increase
a number of detected cases by the survey. Usually, most of these children will be
smear negative. They will not have any benefit from the survey, on the contrary, they
be exposed to unnecessary examinations and they will be absent from school.

Stratification
Stratification is highly recommended for the purpose of improving sampling
efficiency and the precision of the national point-estimate of TB prevalence.
Stratification will help us to obtain more precise estimates if there are good reasons to
believe that prevalence will be different between strata. Therefore, stratification
should be done on a geographical or other basis, when evidence such as notification
rates suggests different levels of prevalence. The purpose of stratification here is not
to compare prevalence rates between strata, but only to increase the precision of
national point-estimates of prevalence. The Task Force does not recommend countries
should not attempt to estimate TB prevalence at sub-national as well as national level
To obtain precise estimates at sub-national levels, the required overall sample size,
needs to be greatly increased.

Minimum expected participation rate
It should be estimated taking into consideration only people to be examined (usually
for those 15 years old or more), not the entire population of all ages.

For issues related to sample size determination, precision and design effect, please
refer to a separate document.

Test methods
- Informed consent for CXR: Risks and safety of CXR should be explained to
guarantee the right of every participant to refuse the procedure.

- Pregnant women in first trimester should not be submitted to a CXR
examination. The Task Force recommends that protective measures such as
the regular practice of strict focus of radiation and a led shield to cover the
abdomen should be taken for every woman.

- CXR reading: All images should be re-read by a second reader. The purpose
of the second reading is to identify abnormalities missed by the first reader.
The second reading may be done in the field if the second physician is
available. Joint screening reading by two or more screening readers is an
alternative strategy.
• Sample images: Sample images of normal and abnormal CXR should be provided for training purposes in order to standardize the screening reading methods. The sub-task force will develop a sample image set.

• Results of CXR: Individuals who are sick and/or have CXR abnormalities that require an immediate medical investigation or intervention should be referred to an appropriate medical facility with their CXR result.

• Selection of CXR equipment and radiation safety arrangement should be done in close consultation with national radiation regulation authorities and experts.

• Digital CXR are solving many technical and logistic constraints: supply of films and water is not necessary; image can be handled easily; distant reading is possible after transmitting image files by internet. In order to adopt digital technology, it is essential to guarantee that in-country maintenance system/services are fully available, and that the survey has budgeted for the maintenance of the CXR equipment.

• For a funding proposal, a plan of usage for the use of CXR equipment after the survey should be documented to justify procurement especially when CXR van or digital technology is requested. CXR equipment occupies a significant proportion of the survey budget in some proposals.

• A CXR equipment manual should be available from the manufacturer. Initial training by an engineer from the manufacturer should be included in the procurement contract.
Case definition

• Smear positive case
Since culture and identification of *Mycobacterium tuberculosis* are always available in a survey, the survey definition for smear positive case may be different from the NTP's clinical definition. Isolation of mycobacteria other than tuberculosis is not rare in survey specimens. The sub-Task Force will elaborate a decision tree diagnostic algorithm to be used by all the upcoming surveys. The decision tree will consider the recommendations from the new guidelines of mycobacteriosis other than tuberculosis.

• Smear negative / culture positive case
When culture is positive with only one test tube showing less than five colonies, a cross contamination from another sample should be ruled out. If the survey team cannot rule out a cross contamination, the patient should not be categorized as a culture positive TB case, unless he/she has a CXR image which is compatible with TB or other evidence has been obtained though follow up examinations. Example: An individual with a normal CXR, a negative smear, and a culture positive with just 3 colonies should not be categorized as culture positive TB.

HIV Testing
All TB cases identified in a survey should be offered HIV testing according to national policies and standard practice. In general, however, HIV testing should not be undertaken for all of the sampled or suspect population. Reasons include: (i) providing HIV screening for all of the sampled population is logistically difficult; (ii) requiring informed consent for HIV testing from all participants may result in less people willing to participate in the survey; and (iii) it may be difficult to ensure that results are provided to all those who are tested.

Data management (please also refer to the attached document)

- A data manager should participate in the survey planning from an earlier stage.

- Participant's names in survey documents. Survey records and forms will hold individual's names as correct identification is required for case management purposes. However, measures to protect confidentiality should be documented in the protocol and in SOPs.

- Data entry should be done during cluster operations.

- A case (with individuals having positive results) list should be maintained to facilitate case management and timely feedback of results to participants.

- The Task Force will develop standard data entry forms.

Other studies

• Health-seeking behavior: questions about health-seeking behaviour and the extent to which identified cases had already had contact with health services are strongly recommended. Results can be used to assess how many cases have not had contact with health services, the number that had not been diagnosed despite visiting health services, and the number of cases that had not been notified due to health-care providers not being linked to the NTP.
Such findings will help to identify the fraction of cases likely to be included in TB notification data, reasons for lack of access to TB care and the absence of notification, and to develop interventions that will accelerate progress in TB control.

- Socio-economic evaluation: The collection of data on socio-economic status and risk factors for TB should be carefully considered. It is essential that the time and effort required to collect such data do not compromise the quality of the basic survey data. It is often not necessary to collect socio-economic data from all the survey subjects. In general, nested case-control studies of socio-economic factors are more appropriate and cost-effective.

**Technical Assistance**
A plan for the provision of technical assistance should be included in the survey protocol, and budgeted.

**Analysis (please also refer to the attached document)**
A survey analysis plan should be included in the survey protocol. How absentees and missing data will be handled in the analysis should be carefully discussed. Expert consultations are essential.

**Dissemination plan**
A dissemination plan of the survey results with a time line should be included in the survey protocol.

**Ethical issues**
In most of the protocols reviewed by the Task Force there was no mention of ethical considerations, or the need to submit the protocol for approval by a national ethical review committee. Apart from , the protocols also should be reviewed and approved by international donors and technical assistance agencies that support the survey. Though WHO Global Task Force on impact measurement provides technical review, it is not an ethical review committee. Please consult WHO country office if country or regional ethical review mechanism is available when WHO NPO or MO is involved in the study.
Laboratory

Recommendations of the Task Force about transportation and processing of sputum samples, smear microscopy and culture procedures

1. How many samples should be collected from each suspect?

2. What is the best way to collect the samples in terms of guarantying a good participation and the best positivity rate (early morning collection at home x site collection)?

3. What bio-safety requirements should be available in the field site in order to avoid transmission of TB to the staff survey team?

4. What should be done if a suspect cannot produce a sputum sample? Should we accept a sample of saliva? Should we try to stimulate the production of sputum? If so, how can this be done?

5. Should we chase defaulted suspects and suspects that cannot produce a sputum sample at the site in their homes/work places?

6. What type of container should be used?

7. Should all samples be put in a special transport specimen box with ice packs or in a refrigerator (cold chain) immediately after collection? Or this is valid only for the samples that will be separated for culture? What is the maximum interval of time that a sample can be left out of the transport specimen box? If a sample is collected at home at 6 am and the patient can only hand it in at 6 pm, is it still valid, even if it was not kept in any transport specimen box?

8. What is the preferable smear microscopy technique: Ziehl-Neelsen staining (ZN) or fluorescence microscopy (FM)? What are the minimum requirements for a lab to perform smear microscopy using each technique?

9. Is it OK if in a survey a country uses ZN in some labs and FM in others? Or should the same technique be used for every sample (even if some samples are submitted to both techniques so as to compare their yield)? Should FM results be confirmed by ZN?

10. Should we try to optimize the sputum smear microscopy by processing the sputum samples with bleach or sodium hydroxide, or sedimentation (there is extensive literature is support of these procedures)? Does this depend on the capacity of the labs performing the smear examinations?

11. What culture method should be used (liquid x solid, with and without decontamination procedures)? Should the choice of method be guided by the length of the interval from sputum collection to processing? Please explain the
choice of method in terms of culture yield, availability of trained staff and bio-
safety facilities, distance/time from the field sites to the laboratories.

12. Is it preferable to process all cultures in a central lab? If cultures are to be
processed in a peripheral lab, what would be the minimum requirements of
such lab?

13. If two samples are collected from every patient, which sample should be sent
for culture (the one collected early in the morning or the one collected at field
site)? Please explain.

14. Is it true that sputum specimen containers for culture examinations should not
be opened for smear examination at the site lab? Is it OK to use the same
specimen for field smear examinations and culture if direct inoculation is done
in the same lab?

15. Should a concentration method be adopted for all cultures? Or does this
depend on the volume of sputum that was collected?

16. Is it OK to use different methods for different clusters in an attempt to
maximize the yield as much as possible? For example, should CPC be added
only to the samples coming from clusters that are far away from the central lab?
What are the consequences of doing this in terms of the results of the survey?

17. What is the danger of introducing newer culture techniques just because of the
survey?

18. How can the country guarantee that the laboratories adapt to the increased
workload during the survey, without losing quality?

19. What methods should be used for species identification? Can the Capillia TB
assay be used instead of more conventional methods?

20. Should we do drug sensitivity testing (DST) for all culture positive samples?

21. How can the quality of smear microscopy, culture and DST be assured?
Should laboratories without quality assurance be excluded from the survey?

22. Is it true that the survey definition of a smear positive case may be different
from the NTP's clinical definition? Please explain.