CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

TAG Treatment Action Group

Partners In Health

Results from a Questionnaire Entitled:

Specifications for* Point-of-Care *TB Tests
Expert Opinion Check from TB Field Practitioners

Surveying TB practitioners in resource-limited settings on the current medical needs and diagnostic limitations

Survey Analysis Report

March 2009

Executive Summary

Sputum smear microscopy (SSM) and culture methods continue to be the main tuberculosis (TB) diagnostic tools available, despite significant shortcomings with both methods. Although the low sensitivity of the method fail to diagnose an important proportion of suspected TB cases, SSM continues to be the main TB diagnostic tool currently available at peripheral level. Therefore the need for a new, better adapted, higher performance and more accessible test is urgent.

With the objective to address and consider the crucial key medical questions prior to the development of a new test for TB, Médecins Sans Frontières (MSF), Treatment Action Group (TAG) and Partners In Health (PIH) designed a questionnaire (Expert Opinion Check) targeting TB field practitioners and focusing on the major gaps currently seen and what would be the intended use for a new TB Point-of-Care (POC) test.

A total of 30 survey respondents were reached including field practitioners and lab experts from 17 countries around the globe. The survey was conducted from January 30th to February 24th 2009 and data captured by phone interviews.

This document highlights the main trends emerging from the analysis of the Expert Opinion Check. The data analysis reported in this document has also been used to voice-out the medical needs as perceived by field practitioners during an expert meeting entitled "Defining Test Specifications for a TB POC Test" scheduled in Paris on March 17th-18th 2009.

The main survey outcomes concerning the use of a new TB POC test are:

- **The POC test must be able to diagnose active TB in HIV/TB co-infected patients and children, followed in importance by paucibacillary, drug resistant-TB (DR-TB) and extrapulmonary TB (EPTB)**
- **The POC test should allow direct treatment initiation and ideally also provide drug susceptibility testing (DST) information**
- **The POC test should be used at the place where patients are treated**
- **The POC test should enable to communicate the result to the patient on the day of collection (could be longer if also provides DST)**
- **The POC test should be designed in such a way that nurses and/or community health workers (CHWs) could use it**
- **The POC test should be adapted to non-invasive samples, either capillary blood, urine or breath**
- **The POC test should be qualitative and a YES/NO answer is sufficient**
- **The POC test should aim to be adapted to a broader population (HIV, children) rather than super high sensitivity in a restricted population**

In a nutshell, a new TB POC test should AT LEAST: have an increased sensitivity over SSM AND diagnose active pulmonary TB (pTB) in ALL patients, be used by nurses or CHWs where patients are treated, allow results from capillary blood, urine or breath samples in less than a day and preferably also give DST information.

These specifications should now be presented to a larger group of stakeholders involved in TB management for refined discussion and further endorsement. Confronted with the technical feasibility options and limitations promoted by tests developers, this study might be of some guidance in the identification of the most appropriate specifications, at least in regards to medical needs faced in resource-limited settings. Similarly, it might help in circulating the unrecognised or neglected medical needs and eventually result in accelerating the development of the desperately needed TB tests.

Background

An effective TB-control programme requires early diagnosis and immediate initiation of treatment. Accordingly, delays in diagnosing tuberculosis can significantly impair not only patient prognosis but also transmission of the disease among the community. Nevertheless, caregivers currently providing TB care in resource-limited, high burden countries are still facing enormous challenges in ensuring timely diagnosis with the currently available diagnostic tools.

Recent efforts in scaling up sputum smear microscopy (SSM) capacity at peripheral level were made and allowed for SSM to be considered as the only test closest to a "point-of-care" test. However, there are still many patients who will not have access to microscopy at their nearest health facility. It has been estimated that a small fraction of patients are seen at microscopy-centre level (25%), as compared to 60% seen at peripheral health clinics where none/trivial lab infrastructures are available[1]. In addition, it has been described that potential public health gains from a new TB diagnostic test would rise proportionally with increased access to testing[2].

Although the low sensitivity of the method fail to diagnose an important proportion of suspected TB cases, sputum smear microscopy continues to be the main TB diagnostic tool currently available at peripheral level. An additional drawback is that SSM is limited in the type of patient population it can detect TB in. Indeed, sputum specimens show a high degree of variability in quality. Moreover, infants and weak adult patients are unable to produce an adequate sputum sample.

Like any other test to be used in low-resource settings and high-burden countries, the characteristics of the tests to be developed are somehow easy to list: high sensitivity and specificity, robustness (shelf-life, stability at high temperature), user-friendly, quick turn-around time, sample easy to collect. Nevertheless, **the intended use** of the test, including the main medical objective of the test and the type of patients to whom the test is addressed are the essential conditions to take in consideration when defining further the TB-specific characteristics a new POC test should have. Some of these parameters are medical decisions triggered by the test result, implementation and test combination strategies, throughput, reading system, detection method etc.

With the objective to address these key questions, Médecins Sans Frontières (MSF), Treatment Action Group (TAG) and Partners In Health (PIH) designed a questionnaire targeting TB field practitioners. Indeed, this Expert Opinion Check aimed to identify the most important medical needs seen in current TB practice while focusing on the major gaps the current diagnostic tools fail to fulfil.

This document highlights the main trends emerging from the analysis of the Expert Opinion Check. The data analysis reported in this document has also been used to voice-out the medical needs as perceived by field practitioners during an expert meeting entitled "Defining Test Specifications for a TB POC Test" scheduled in Paris on March 17th-18th 2009. This meeting had for its purpose to gather experts from both the test development and field medical practice spheres. Indeed, while experts in test development updated the rest of the participants on the current scientific knowledge and innovations, the medical and community experts provided important information on the medical needs currently experienced in TB diagnostics in developing countries. Therefore, this meeting aimed to ensure the involvement of a broad variety of expert opinions while focusing on the priority medical needs that have to be thought of in the development of the new TB POC diagnostic test.

Methodology

The questionnaire used for the Expert Opinion Check was based on a total of 21 open, semi-open and ranking questions (Appendix 1). The survey was conducted from January 30th to February 24th 2009. Data were captured by phone interviews using the questionnaire template previously sent to the participants after verbal or email consent. The 30 respondents to the survey included field

[1] Diagnostics for tuberculosis – Global demand and market potential. WHO/TDR and FIND. 2006

[2] Keeler *et al.*Reducing the global burden of tuberculosis: the contribution of improved diagnostics. Nature. 2006. 444 Suppl 1:49-57

practitioners and lab experts from 17 countries in Asia, Africa, Eastern Europe and Latin America and from different types of institutions and organizations (national TB programmes, NGOs, academic institutions).

The qualitative methodology applied to the Expert Opinion Check hampered any exact statistical analysis to be born from the data, nevertheless, descriptive statistics were used to illustrate the measures taken from the survey. Score gained, relative importance, or summary statistics (single numbers) were graphically displayed. From participant answers to open questions, a number of recurrent themes were identified. The analysis of these answers was performed in respect to those themes and the data is presented through tailored categories and included in the narrative sections of the report.

Data Analysis

1. Challenges and gaps in current medical practice: *the objective of this section was to map out the main barriers field practitioners are encountering in the diagnosis of tuberculosis and the identification of TB resistant strains in a variety of geographical and epidemiological contexts.*

1.1 Diagnosing tuberculosis in a variety of contexts

The study population can be described as a heterogeneous group composed of TB practitioners involved at all levels of care, from regional and district hospitals, health centres, urban clinics, and rural health posts, together with professionals in charge of TB programmes at national level or working in a research institution as illustrated in Figure1. The aim of selecting participants working in a variety of healthcare structures was to capture a broad range of opinions regarding the main medical needs faced by TB practitioners, especially the ones encountered at the periphery which are often overlooked.

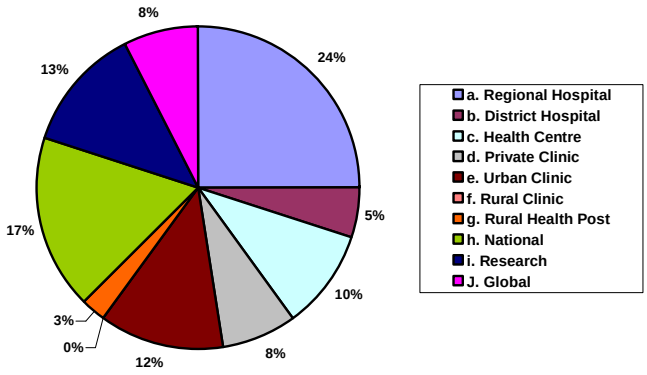

Figure 1: Overall distribution of participant experiences in various healthcare structure levels

Similarly, the epidemiological contexts in which the study population was involved were diverse as shown in Figure 2. Children under the age of 15 were treated in the majority of the settings. Over a third of the participants able to estimate the proportion of suspected patients <15 years mentioned that this group represented >20% of all suspected cases in their setting, whereas another third described this group as counting for less than 10% of suspected cases. The residual group of participants (around 30%) observed the proportion of under 15 years as representing more than 20% of the suspected cases. Three quarters of all participant settings were working with a population presenting a rate of HIV/TB co-infection above 25% (Figure 2B), while over 80% of the participants mentioned an observed rate of extrapulmonary TB (EPTB) above 20% among their patient population (Figure 2C). It is to note that less than a third of the respondents were able to provide data on drug resistance, primarily due to the lack of technical means available in the country. Among the locations well documented, half of the settings had a DR-TB rate above 3% as illustrated by Figure 2D.

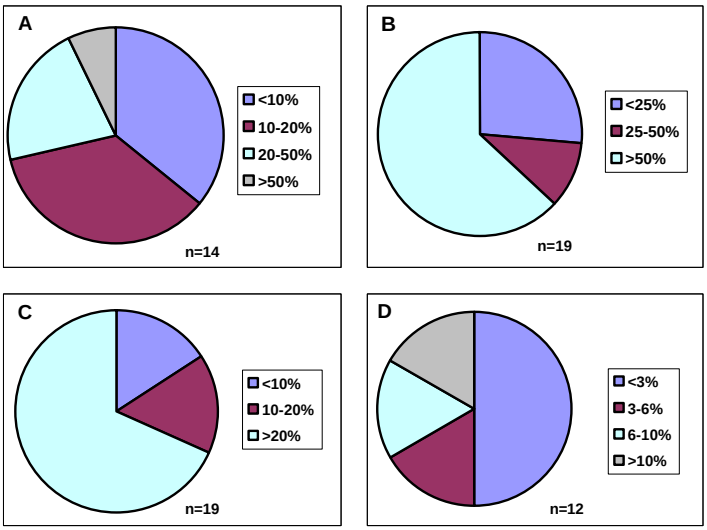

Figure 2: Overall distribution of the proportions of suspected populations being: A) below 15 years old, B) HIV co-infected, C) EPTB cases and D) DR-TB cases

In the practicing contexts showing a high rate of HIV/TB co-infection, half of the respondents declared that HIV and TB care were fully integrated and another 25% estimated the integration process not yet fully completed (Figure 3A). Consistently with this, 75% of participants declared that in their settings most TB patients had access to HIV infection testing (Figure 3B), although only 56% of them revealed that HIV positive patients were offered TB testing (Figure 3C).

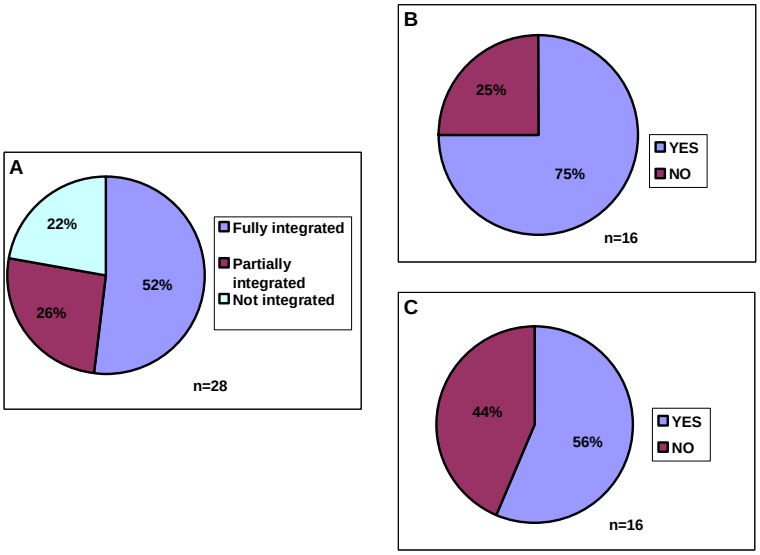

Figure 3: Graphical representation of the participant's programmes distribution regarding A) the overall HIV/TB care integration, B) the programmes where TB patients are tested for HIV and C) the programmes where HIV patients are tested for TB

1.2 Availability of laboratory support

In terms of laboratory support, the vast majority of the participants' settings did have access to internal facilities to diagnose their patients as described in Figure 4. However, the level of laboratory infrastructure referred to was variable among the settings. The lab tests available in the different settings included a wide range of technical tools (optical and fluorescent microscopy, liquid and solid cultures, molecular tests). However, in the majority of places access to TB diagnosis was limited to sputum smear microscopy analysis. About 80% of the respondents had access to DST services through the referral of samples to a central laboratory centre within the

country or to an external supranational laboratory. The majority of the participants estimated the sample transportation system to be efficient when available, as in a number of cases the system was organised and funded by the NGO or the research institution running the programme. The main complaints recorded through the interviews were high delays for results, loss of samples in the referral process and high cost to the programmes. However, optical microscopy, the cheapest and simplest method, was not available in all settings at the most remote levels of health care.

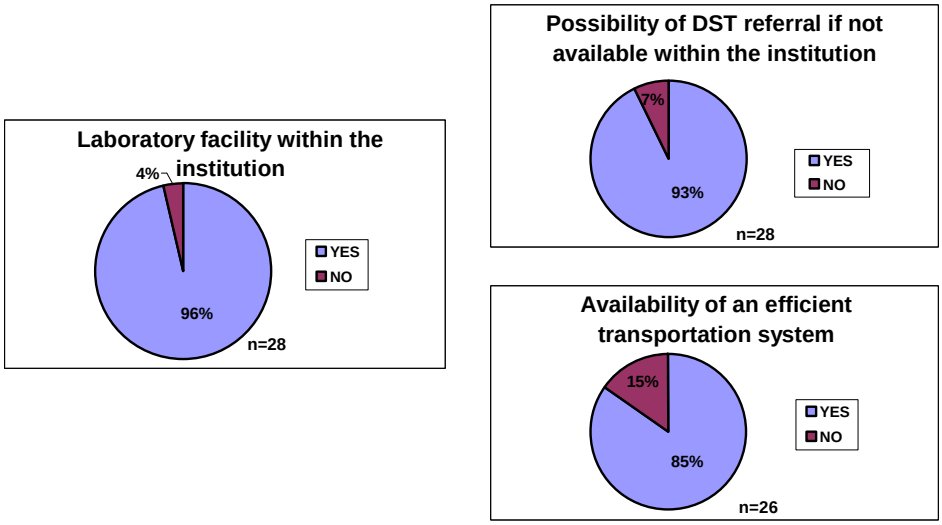

Figure 4: Representation of the overall laboratory infrastructures available to practitioners either at practice site or at referral level

The performance of laboratories is a key asset for the support of TB programmes and despite the implementation of quality assurance initiatives, clinicians are often confronted with suspicions of false test results. The type of action taken when those specific suspicions arise was surveyed. Results show that when suspecting a false negative test result, only about 60% of all participants would ask for retesting while over 25% of the participants would initiate treatment anyway without waiting for any laboratory confirmation. However, interestingly enough over 70% of the clinicians would use further clinical evaluation and follow-up of the patient, some wait for a second test result while others do not, prior to a treatment decision. When the respondents suspected false positive lab results, half of them would retest while 40% of the participants would follow the clinical algorithm without retesting. Interestingly, 10% of the participants would initiate treatment even when suspecting a false positive test result. Moreover, 20% of the respondents commented on this question by mentioning that the estimated risk of false positive results being irrelevant for their routine practice due to the high proportion of strongly symptomatic patients presenting at their facility.

1.3 The main gaps to be addressed

Despite disparities in terms of geographical locations and epidemiological context of practice, a large consensus was reached concerning the gaps to be addressed with high priority. The participants were asked to identify the 5 most important gaps from a list of 12 well-documented barriers to high detection rate. The participants were also asked to rank these 5 gaps in terms of relative importance. Figure 5 illustrates the main gaps identified and represented by relative importance of each of the gaps compared to the highest ranked gap. Data were compiled considering at the same time, both the number of time each gap was identified as being part of the 5 most important gaps, and the ranking value attributed to each gap. **The highest gap to be addressed with great priority was the inadequacy of sputum specimen sample in diagnosing paediatric, HIV/TB co-infected and EPTB patients, followed closely by the low sensitivity of SSM.** Other emerging gaps identified were the lack of drug susceptibility evidence without further referral, the low overall diagnostic performance of SSM due to variability of analysis, and the lengthy turn-around-time to results of current methods.

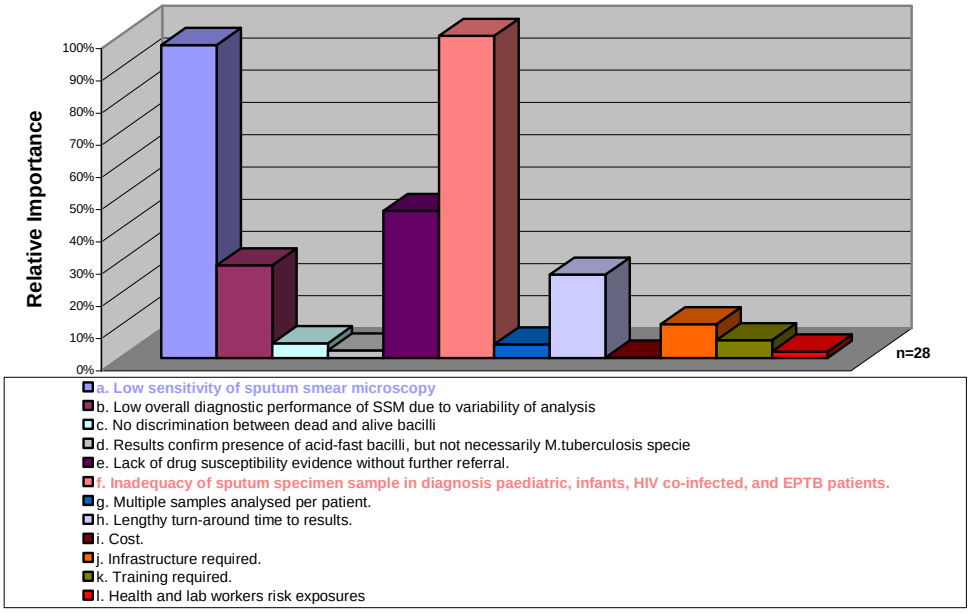

Figure 5: Main gaps in TB diagnostics. Each participant selected and ranked what they considered to be the five most important gaps. Relative importances as compared to the highest score are shown

2. What ideal characteristics should a TB diagnostic test have in order to ensure better performance of TB programme at the most remote health care facilities? *This second section was meant to drive the discussion outside the current practice and propose technical options. The respondents' suggestions, comments and opinions on these technical solutions are critical for the new tests to answer the unmet needs considered as a priority.*

2. 1 **New TB POC test to address the most important medical needs**

It was unanimously acknowledged by the survey respondents that there is an absolute need to increase the adequacy of TB diagnostics to diagnose other populations of TB suspects than the current most-targeted non-HIV adult population. In order to better identify which additional population(s) is a clear priority to adapt a new test for, the respondents were asked to rank in importance various patient categories. Figure 6 illustrates ranking importance for each category relative to the highest ranked option. Two main populations were clearly identified as the highest priorities to be addressed. Indeed, **HIV/TB co-infected patients were ranked as the first priority followed closely by paediatric suspected cases**. Smear negative, drug-resistant and EPTB specific cases have also been identified as three other important categories to prioritise. Interestingly, discordant opinions were recorded in settings where prevalence of co-infection and DR-TB was low or not properly documented. Latent TB cases and patients at risk of dying quickly were not perceived to be of high priority to be addressed by a new TB diagnostic tool.

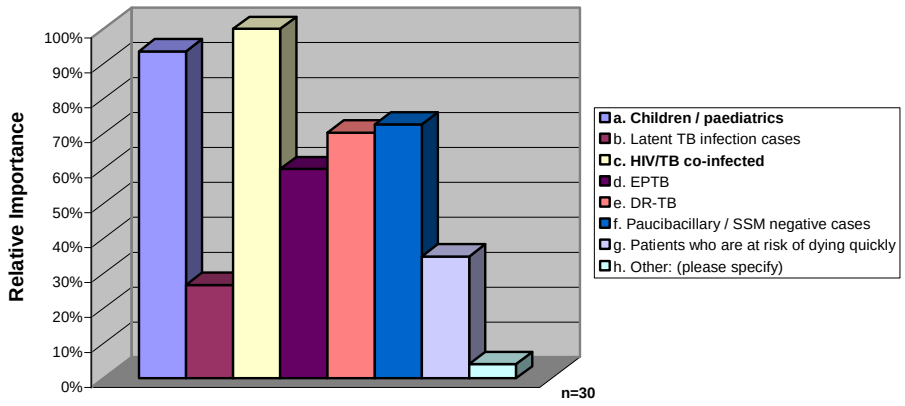

Figure 6: Priority populations to diagnose in addition to non-HIV adult patients

The intended use of a new POC test was also surveyed through questioning which of the following information should be provided by the new test: treatment initiation, DST, treatment monitoring and differentiation between active and latent TB. Participants almost unanimously expressed their desire for a POC test to support treatment initiation decision as shown in Figure 7. When we surveyed the type of combination of sample analysis that would be ideal (if technologically feasible) to allow such use, over ¾ of the participants mentioned their desire to combine the capacity for diagnostic and drug susceptibility testing (Figure 8). Nevertheless, 17% of the respondents had a preference for a test combining diagnostic and treatment monitoring, where treatment monitoring was considered a tool to inform about cure and showing that the patient was free of TB bacilli. Only 2 respondents preferred a test allowing diagnosis alone.

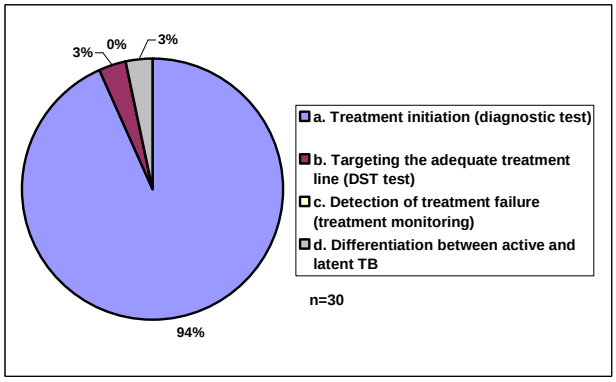

Figure 7: Medical decision to be influenced by POC TB test results

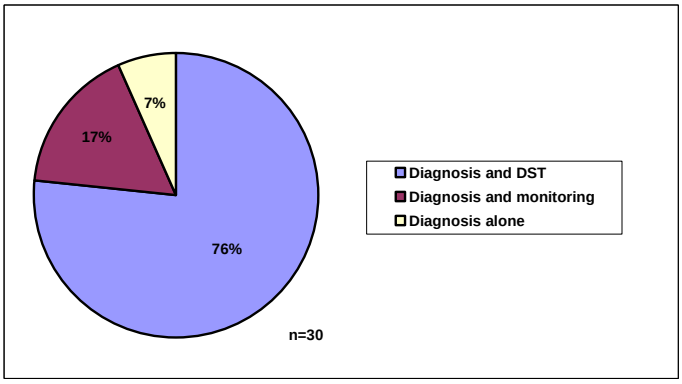

Figure 8: Preferred combination of test analyses among diagnosis, DST and treatment monitoring

2.2 **New TB POC test to overcome health system barriers**

A test aiming to address the main medical needs should also present suitable characteristics for an easy deployment up to the most isolated settings where the priority categories of patients are presenting to the health staff. In the recent past, tests showing high performance were left on the shelf because of poor suitability in field conditions.

Although decentralization is strongly supported as a strategy to increase case finding, the definition of "Point-of-Care" varies for each specific disease. For study participants involved in TB management, the present opinion check revealed that for 60% of the participants, POC level of healthcare was considered as the place where the patients would receive treatment as illustrated by Figure 9. Another 30% defined POC level as an outreach location where community health workers would see the patients. Nevertheless, three participants defined POC level as being any point of contact a suspected case can have with any health worker.

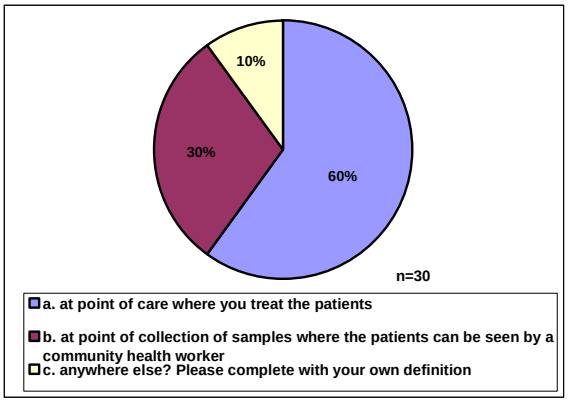

Figure 9: Interpretation of the definition of Point-of-Care

The timely delivery of results to the prescriber is known to improve TB programme performance. The TB practitioners were herein surveyed about the acceptable turn-around time-to-result defined as the time period between sample collection time and the time the result is communicated back to the patient for a POC TB test. Figure 10 illustrates that almost ¾ of the participants would find the delivery of results under 24 hours following the sample collection as acceptable. **The priority was obviously to give a result to the patient on the same day of sample collection** and before he leaves the health care facility. Various participants mentioned that practically, this means a turn-around time being <4 hours as it is expected that some patients might be tested in the afternoon for example. Interestingly, some participants mentioned that they would accept longer delays (>24 hours) if the POC test allows additional testing such as DST information. This emphasis towards a test with rapid detection of drug resistance was mainly mentioned by participants working in settings already confronted with DR-TB.

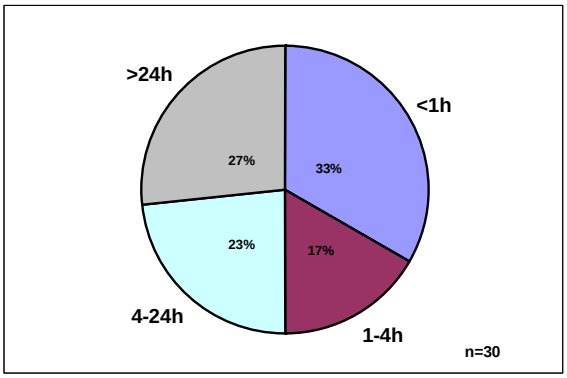

Figure 10: Acceptable turn-around time for a POC TB test

The introduction of new technology might allow non-laboratory health staff to perform the tests and so strengthening diagnostic capacities where the patients are presenting. Indeed, Figure 11 illustrates that more than half of the participants are expecting a new POC test to be performed by staff other than lab personnel. Nevertheless, more than a third of the study respondents were expecting lab staff to remain the end-users of a TB POC test if the test was to be deployed within the classical health care system. Interestingly, some of those participants were attributing this to the fact that in some settings where lab staffs are the traditional and unique players in the field of diagnostics, vested interests could prevent new end-user strategies to be easily implemented. Other categories of staff to be expected to use the test are divided between nurses and community health workers. In addition, when the participants were questioned whether it would be feasible to have nurses and/or community health workers performing the POC test, more than two thirds of the participants said that this would be a reasonably realistic solution to implement (Figure 12). Moreover, 7% of those respondents in favour of the concept of nurses and/or community health workers performing the test, consider the involvement of these categories of health staff as being the only way possible for an adequate deployment of a POC test to reach patients in need. The type of sample to work with was considered as being a key parameter for the acceptance of the new policy by the staff in charge of TB testing. The main concerns for the rest of the study population were the risk to overload a category of staff that is already under high pressure.

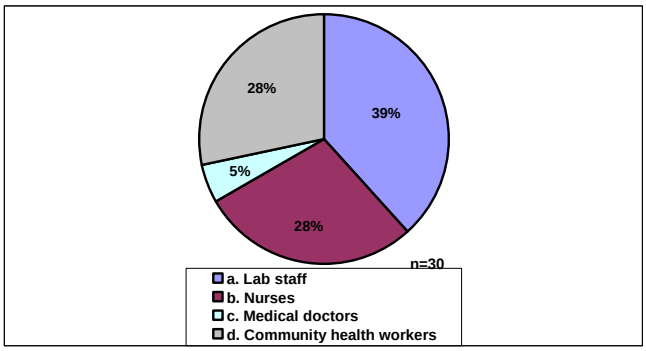

Figure 11: Categories of health staff expected to perform the POC TB test

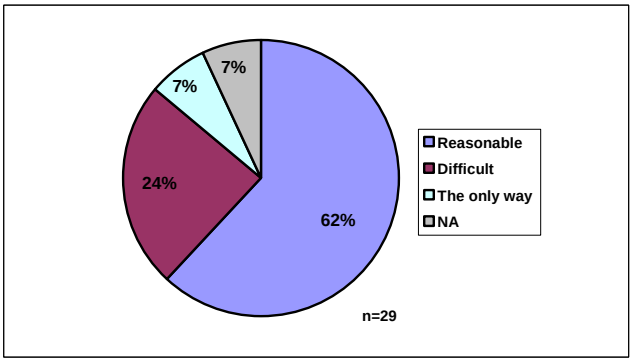

Figure 12: Feasibility of nurses and/or CHWs to perform the POC test

The handling of sputum specimen is considered a barrier to TB diagnosis. Therefore, in the hypothesis of a POC test to be specifically developed to reach the patients currently misdiagnosed, microscopy, capillary blood, urine and breath were the preferred samples for the majority of the respondents, as illustrated by Figure 13. Coherently with results described above and illustrated by Figure 6, those three categories of non-sputum based sample types were identified also as best suited to allow TB diagnosis in paediatrics and HIV/TB co-infected populations. Another priority was to select non-invasive and easy procedures to collect samples for the staff in charge of the sample collection. Safety for the staff was often mentioned as an important issue to address. Constraints in the use of capillary blood were raised: notably for the extra material needed for venous blood collection, difficulty in obtaining this sample in paediatrics and the potential need for legal authorization for health staff in charge of TB testing and therefore limiting its use for community health workers in a number of countries.

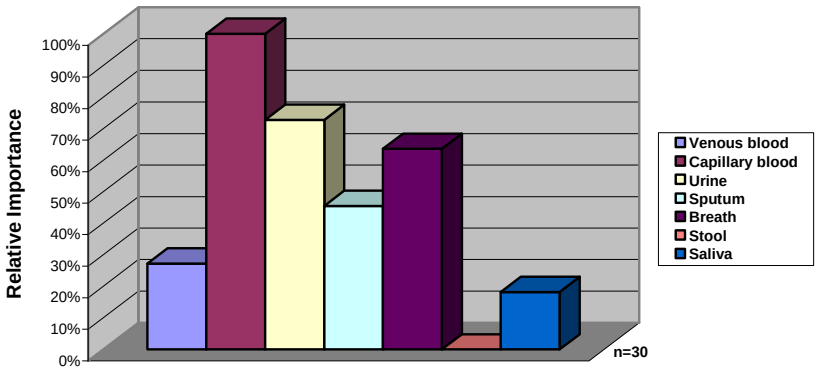

Figure 13: Preferred types of samples

Considering constraints in test development, it might be difficult to aim for a perfect test. Therefore there is a possibility that the first generation of POC test may need a combination of different samples. When participants were asked, the vast majority of them considered it acceptable to have a test that would require a combination of different samples, although simplification was often mentioned as an important element of TB management. Interestingly, some of the participants considered the option of combining different samples rather innovative.

The various proposed detection methods were considered equally acceptable except for organic compounds and indirect markers as shown in Figure 14. Participants regretted a lack of information about organic compounds and referred to recent publications showing evidence of poor specificity for indirect markers. Some participants, especially clinicians, expressed their disinterest for that question mentioning that their only interest is to have a test that performs well and which is reliable, not matter what form it takes. However, a strong agreement was observed regarding **the preference in having a test purely qualitative** as shown by Figure 15. Consistently, the vast majority of participants did not see any treatment impact in having a test providing a semi-quantitative or a purely quantitative result (Figure 15B).

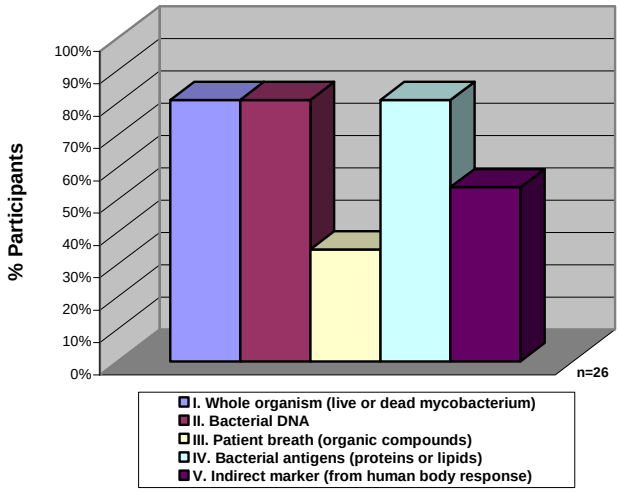

Figure 14: Willingness to rely on various detection methods

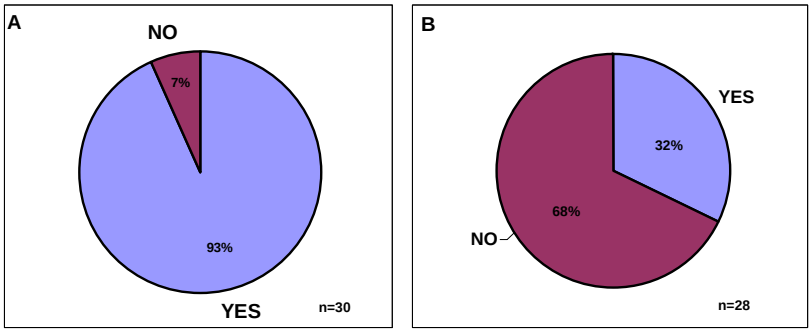

Figure 15: Acceptability and impact of qualitative test on treatment decision. A) acceptability of a qualitative "Yes or No" type of result. B) potential impact of a quantitative or semi-quantitative TB POC test on patient treatment

Other elements concerning the implementation of a new POC TB test were also surveyed, notably on the place a new test would have in relation to the existing SSM method. Indeed, when asked about their preferences as to whether a new test should replace SSM, or complement SSM by fulfilling its major gaps, both options seemed equally attractive. Similarly, the deployment of a new strategy based on a 2- or 3-test algorithm at point-of-care level was accepted by the broad majority the study respondents, provided that the tests were user-friendly, performed in parallel and would not require the patients to come back for multiple sample collections. Nevertheless, in very high burden settings, the idea of implementing a multiple test strategy is encountering strong questioning. The main concerns being the increased risk of confusion, increased bureaucracy, high risk of clerical error and misdiagnosis. For some participants, the new approach was described as potentially more time consuming and in conflict with the current dearth of health staff faced by most settings. Five participants insisted on the fact that such new testing algorithm would be easier to introduce in a well functioning system but nevertheless to resolve the problem of discordant results could result in a complicated process. To be fully endorsed the new approach would need to be carefully documented by evaluation studies and supported by WHO and the international scientific community. The implementation of the 2- or 3-test strategy was thought to be easier to launch by NGOs than by national TB programmes. Three participants insisted on the need to promote a phased introduction of the new tools and testing strategies through well supported pilot projects followed by deployment at regional level. Critical operational questions were mentioned as being often neglected, such as an alternative approach for quality assurance, a reporting system and case definition, together with a strategy to progressively phase out microscopy. It was strongly suggested by half of the participants that lessons learned from HIV testing should be used in terms of deployment, implementation of 2-3 tests strategy at peripheral levels of care and training of dedicated health staff.

The Opinion Check exercise was meant to identify the major gaps in current TB diagnostics as seen by field TB practitioners. Similarly, it is crucial that any new test addresses the medical needs currently faced by end-users. However, it might not be realistic to think that all current gaps and medical needs could be fulfilled all at once by a new test considering potential technical limitations in test development. Even the most recent technical innovations may be confronted with some capacity limitations in achieving the ideal specifications listed by the study participants. In which case, it becomes important to identify what categories of specifications could be traded-off first or last. Therefore, the last question of the interviews proposed some non-ideal test scenarios and respondents were asked to participate in a ranking exercise. From the five test options proposed, the trade-offs were designed to focus on sensitivity over targeted population and type of analyses performed by a new test. It is to note that some reluctance was expressed by many participants in answering this question, with the argument that none of the proposed scenarios were found optimal, as expected considering the purpose of the exercise. Interestingly, panel A in Figure 16 shows that the majority of participants ranked the option of trading-off some sensitivity performance for a broader population-adapted option as their first choice as defined by test option c) a test with "75% sensitivity, 95% specificity, diagnosing active pulmonary TB, irrespective of the HIV status and age". This is highly coherent with previous results shown in Figures 5 and 6, which clearly

identify the need to have a TB test adequate for HIV-positive and paediatric suspected cases. In contrast to panel A), that represents on number 1-rank occurrence frequency of each option, panel B) in Figure 16 illustrates the complete ranking data as expressed in gained scores representing ranking values from all respondents. Indeed, the sum of the scoring values of each option and their occurrence frequencies were taken into account in calculating the gained scores. Therefore, a gained score value of 100% represents a test option ranked as the best choice by all respondents whereas a gained score value of 0% represents a test option ranked last choice by all respondents. Results shown in panel B) and similarly in panel A), illustrate that the test option c) accumulated the highest score as the overall preferred option. The 4 other test options showed similar scores compared to each other. However, it is to note that test option b), highlighting a high sensitivity but limited use to HIV-negative adult cases, is the option with lowest score which again is coherent with previous results. Interestingly, the participants would be ready to trade-off sensitivity but only to a certain extent, as evident by the fact that test option c) was preferred over test options d) and e). Both of these options proposed the test characteristics found in option c) and furthermore included the ability to offer information on DST and/or diagnose EPTB but with a lower sensitivity than c). Participants would therefore trade the sensitivity of the test for the benefit of hugely enlarging the population to be diagnosed. However, they would not that easily trade the sensitivity criteria if that meant achieving sensitivity performance as poor as the one currently seen with SSM, even if the new test would be adapted to more lab analyses and to broader populations.

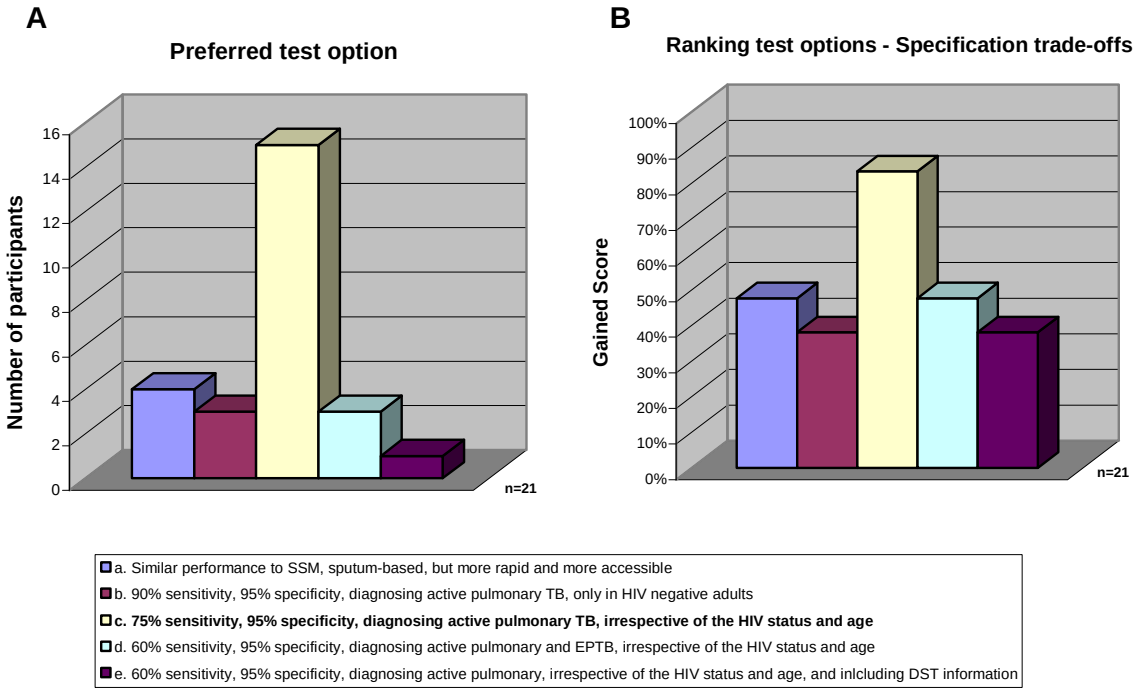

Figure 16: Ranking for tests performance options- specification trade-off. A) First choice option by category and represented by the number of participants. B) Gained scores obtained by each category accountable to the sum of ranking scores

Strengths and limitations of the survey

This Expert Opinion Check based on phone interviews allowed spontaneous contribution and refined answers to be collected which was sought for questions related with complex issues. The group of participants was representative of a wide range of settings in terms of geographical origin, involvement at health care levels, technical skills, and epidemiological context. 30 study respondents were interviewed including clinicians (n=21), (of which three were paediatricians) and laboratory specialists (n=11) (of which 2 were also clinicians). These professionals were affiliated with tuberculosis programmes run by national TB programmes (n= 13), non-governmental organizations (n=16) or supported by academic institutions (2). The field practitioners were working in a total of 17 different countries (10 African, 5 Asian, 1 Latin-American and 1 Eastern European). Data described a large consensus around the main technical specifications or the ranking of the priority questions to be addressed. Nevertheless, unexpected comments and suggestions were

recorded mainly from settings where prevalence of co-infection was low and/or not well documented. We are presenting data collected from a rather limited number of participants due to the lack of time devoted to the study, the difficulty to obtain collaboration to this kind of survey from overloaded health staff and the technical challenge to gain contact with programme managers working in remote and under-resourced settings.

Conclusion

The data gathered by our survey confirmed the interest of linking the design of a new test with the medical needs expressed by the field practitioners involved in TB management. The main gaps to be addressed are related with sputum smear low sensitivity, its technical limitations and inadequacy to diagnose tuberculosis in a many patients. In addition to the characteristics of any POC test to be deployed in areas presenting extreme climatic and logistic conditions, the new POC TB tests should therefore be able to address specific medical needs and overcome health system barriers.

Regarding specifications, the absolute priority is the need to dramatically increase the detection rate by diagnosing HIV/TB co-infected patients, children and to a lower extent patients with DRTB. The POC tests should trigger treatment initiation and would be used at the place where patients are treated. A quick turn around time (on the same day of sample collection for diagnostic and maximum of a few days for DST) is critical together with a significantly low level of technical sophistication that would allow nurses and community health workers to perform the tests in addition to traditional lab staff. Any detection method would be considered reliable providing the sensitivity and specificity are shown to be satisfactory in field conditions. Nevertheless, the preference is for a qualitative reading system. If the test would have the possibility of getting additional information beside TB diagnosis, a combination of diagnostic and drug susceptibility testing capacities was the preferred option. A non invasive, safe and easy to collect sample should be used (capillary blood, urine or breath). A strategy based on a combination of several tests using different types of samples was considered acceptable. Whether this test would replace or complement microscopy is still to be clarified. The way these POC tests should be implemented within the existing TB programmes remains to be carefully considered.

In a nutshell, a new TB POC test should AT LEAST: have an increased sensitivity over SSM AND diagnose active pTB in ALL patients, be used by nurses or CHWs where patients are treated, allow results from capillary blood, urine or breath samples in less than a day and preferably also give DST information.

These specifications should now be presented to a larger group of stakeholders involved in TB management for refined discussion and further endorsement. Confronted with the technical feasibility options and limitations promoted by tests developers, this study might be of some guidance in the identification of the most appropriate specifications at least in regards to medical needs faced in resource-limited settings. Similarly, it might help in circulating the unrecognised or neglected medical needs and eventually result in accelerating the development of the desperately needed TB tests.

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APPENDIX 1: Questionnaire for TB Field Practitioners

Specifications for POC TB Diagnostic 2009
QUESTIONNAIRE for TB Field Practitioners

Part ONE - IN YOUR MEDICAL PRACTICE:
This section is intended to gather information about the context of your current practice and/or past field experience. This will allow us to understand better the difficulties you are facing in TB diagnosis and to relate them adequately with the priorities you will define in Part TWO of this questionnaire.

1. Which level of health care structure do you work in?
    a. Regional Hospital
    b. District Hospital
    c. Health Centre
    d. Private Clinic
    e. Urban Clinic
    f. Rural Clinic
    g. Rural Health Post

2. What is the distribution of the TB suspect population seen at your clinic:
    I. % of children 1-6 years old
    II. % of children 7-15 years old
    III. % of HIV/TB co-infected patients
    IV. % of Extra Pulmonary (EP)TB cases
    V. % of Drug-Resistant (DR)-TB cases

3. Is both TB and HIV care available in your institution? To what extent is TB/HIV care integrated?

4. Type of laboratory resources available to you:
    - Do you have a lab within your institution?
        ☐ Yes ☐ No

If Yes:
    a. What are the diagnostic tests used to detect TB patients in your setting?
    b. If you don't have access to Drug Susceptibility Testing (DST) in your lab, can you refer the analysis to an external lab? If yes, which DST test do they perform?

If No: If you have to send samples for microscopy, is the transport system available and efficient?

5. In order to strengthen your medical practice, which of the following gaps or problems should be addressed in priority (please rank the five gaps you think are the most important ones):
    a. Low sensitivity of sputum smear microscopy (SSM).
    b. Low overall diagnostic performance of SSM due to variability of analysis (due to lack of experienced microscopists, eye fatigue or work overload).
    c. No discrimination between dead and alive bacilli seen in SSM.
    d. Results confirm presence of acid-fast bacilli, mostly from *Mycobacterium sp.* but cannot say if part of the Mtb complex (could be *M.avium* for example).
    e. Lack of drug susceptibility evidence without further referral.
    f. Inadequacy of sputum specimen sample in diagnosis paediatric, infants, HIV coinfected, and EPTB patients.
    g. Multiple samples analysed per patient.
    h. Lengthy turn-around time to results.
    i. Cost.
    j. Infrastructure required.
    k. Training required.
    l. Health and lab workers risk exposure during handling, processing and decontamination of sputum specimen.

6. What would you define as an acceptable turn around time (time between sample collection and results back to the patient) for a POC TB test?

7. In a situation where you suspect a <u>false negative</u> test result, what steps do you take? (e.g.: re-test later, follow up, clinical algorithms or ignore lab results)

8. In a situation where you suspect a <u>false positive</u> test result, what steps do you take with the available tests at your site to rule out TB?

Part TWO - IN AN IDEAL SITUATION:

We now seek to gather information about your needs in daily practice and your vision of what an ideal test would be and how you would use it in daily practice. This will allow us to define the <u>intended use</u> of any new tests to be developed in the coming years.

9. What does “Point of Care (POC)” mean for you? Please complete this sentence:
   A POC test is a test used …
    a. at point of care where you treat the patients.
    b. at point of collection of samples where the patients can be seen by community health worker.
    c. anywhere else? Please complete with your own definition.

Please note that for the following questions, we refer to a POC test or POC level as being a test that can be performed at least (but not exclusively) at a most remote health care structure (e.g rural health post or mobile clinics).

10. Which of the following medical decisions would you most like to see being done at POC level? Choose one only.
    a. Treatment initiation (diagnostic test)
    b. Targeting the adequate treatment line (DST test)
    c. Detection of treatment failure (Treatment monitoring)
    d. Differentiation between active and latent TB

11. An ideal POC test for active TB would combine diagnosis, DST and treatment monitoring. If not all analyses could be integrated on a single device, which one would you accept to be part of a different test?

12. Which category of health workers is most likely to use a new TB POC test?
    a. Lab staff
    b. Nurses
    c. Medical doctors
    d. Community health workers

    Why?

13. How feasible would it be to introduce a new diagnostic test such as a TB POC test if nurses and/or community health workers were asked to perform the POC test (willingness, capacity, etc.)? How acceptable would it be to the patients?

14. Current TB diagnostic tools capacities are limited but best suitable for non-HIV adult patients. In your opinion, do we need a POC TB test that is able to diagnose a broader population?

    □ Yes □ No

    If Yes: Who are the additional patients you want to be able to diagnose with a new test? Please rank in order of priority.

    a. Children / paediatrics
    b. Latent TB infection cases
    c. HIV/TB co-infected
    d. EPTB
    e. DR-TB
    f. Paucibacillary / SSM negative cases
    g. Patients who are at risk of dying quickly
    h. Other: (please specify)

15. What would you consider to be the **best** sample(s) to use?
    (urine, sputum, venous blood, capillary blood, breath, stools, others)?
    Please explain why.

16. Would you accept a diagnostic made out of a combination of different samples?

    □ Yes □ No

17. Would you be happy to rely on a test with a detection based on:

I. Whole organism (live or dead mycobacterium)	□ Yes	□ No
II. Bacterial DNA	□ Yes	□ No
III. Patient breath (organic compounds)	□ Yes	□ No
IV. Bacterial antigens (proteins or lipids)	□ Yes	□ No
V. Indirect marker (from human body response)	□ Yes	□ No

18. Would a TB POC test giving a quantitative or semi-quantitative value affect patient treatment in any way (in comparison to a qualitative “yes/no” type of answer)?

    □ Yes □ No

    If yes, what incremental advantage in patient treatment or monitoring would have such answer with a quantitative test value?

    Would you accept a qualitative result through a yes/no answer?

    □ Yes □ No

19. Would you prefer to use a new test that totally replaces the sputum smear microscopy or a test that would complement microscopy by filling its performance gap?

20. In the overall TB management programme, do you think a 2 or 3 test-algorithm in order to allow treatment initiation would be reasonable? (Please consider the following: confusion versus simplified management; supply and pricing; reluctance from the staff or the patients).

21. Which of the following new POC tests would you prefer (please rank):
    a. A test with similar performance to SSM, sputum-based, but more rapid and more accessible.
    b. A test with 90% sensitivity, 95% specificity, diagnosing active pulmonary TB, only in HIV negative, and only in adults.
    c. A test with 75% sensitivity, 95% specificity, diagnosing active pulmonary TB, irrespective of the HIV status, and in all-ages patients.
    d. A test with 60% sensitivity, 95% specificity, diagnosing active pulmonary and EPTB, irrespective of the HIV status, and in all-ages patients.
    e. A test with 60% sensitivity, 95% specificity, diagnosing active pulmonary, irrespective of the HIV status, in all-ages patients and in the same test also drug susceptibility information.

GLOSSARY:

DNA Deoxyribonucleic Acid
DR Drug Resistant
DST Drug Susceptibility Testing
EPTB Extra Pulmonary Tuberculosis
HIV Human Immunodeficiency Virus
MTB *Mycobacterium tuberculosis*
POC Point of Care
SSM Sputum Smear Microscopy
TB Tuberculosis