TPP LTBI SURVEY

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2ND EXPERT WORKSHOP ON THE DEVELOPMENT OF TESTS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION (LTBI) TO ACTIVE DISEASE

TPP LTBI progression

The TPP for LTBI was organized according:

- INTENDED USE
- PERFORMANCE CHARACTERISTICS
- OPERATIONAL CHARACTERISTICS
- PRICING

10/31 items have been selected according to their scientific and implementation relevance

TPP survey design

Stop TB Partnership
New Diagnostics Working Group

Target Product Profile: Test for Progression of Tuberculosis Infection

INTRODUCTION

About one third of the world's population is infected with *M. tuberculosis*. Infected individuals are at risk of endogenous reactivation of the same strain and progression to active tuberculosis (TB) with the highest risk in the first 2 years. The World Health Organization recommends systematic testing and treatment of latent tuberculosis infection (LTBI) in few, well identified, high risk populations.

Present tests (TST/IGRA) are very poor in predicting whether an individual belonging to a high risk population will progress to active TB in the future and they are not able to differentiate between recent and remote infection. An ideal test of progression should identify subjects that will progress to disease in the near future (conventionally 2 years). In other words, the test may identify very early stages of disease (incipient TB) before clinical symptoms and contagiousness arise. The test should have higher positive predictive value (PPV) for progression from infection to active TB than IGRAs. It should be easily accessible, available at primary and second level care and affordable.

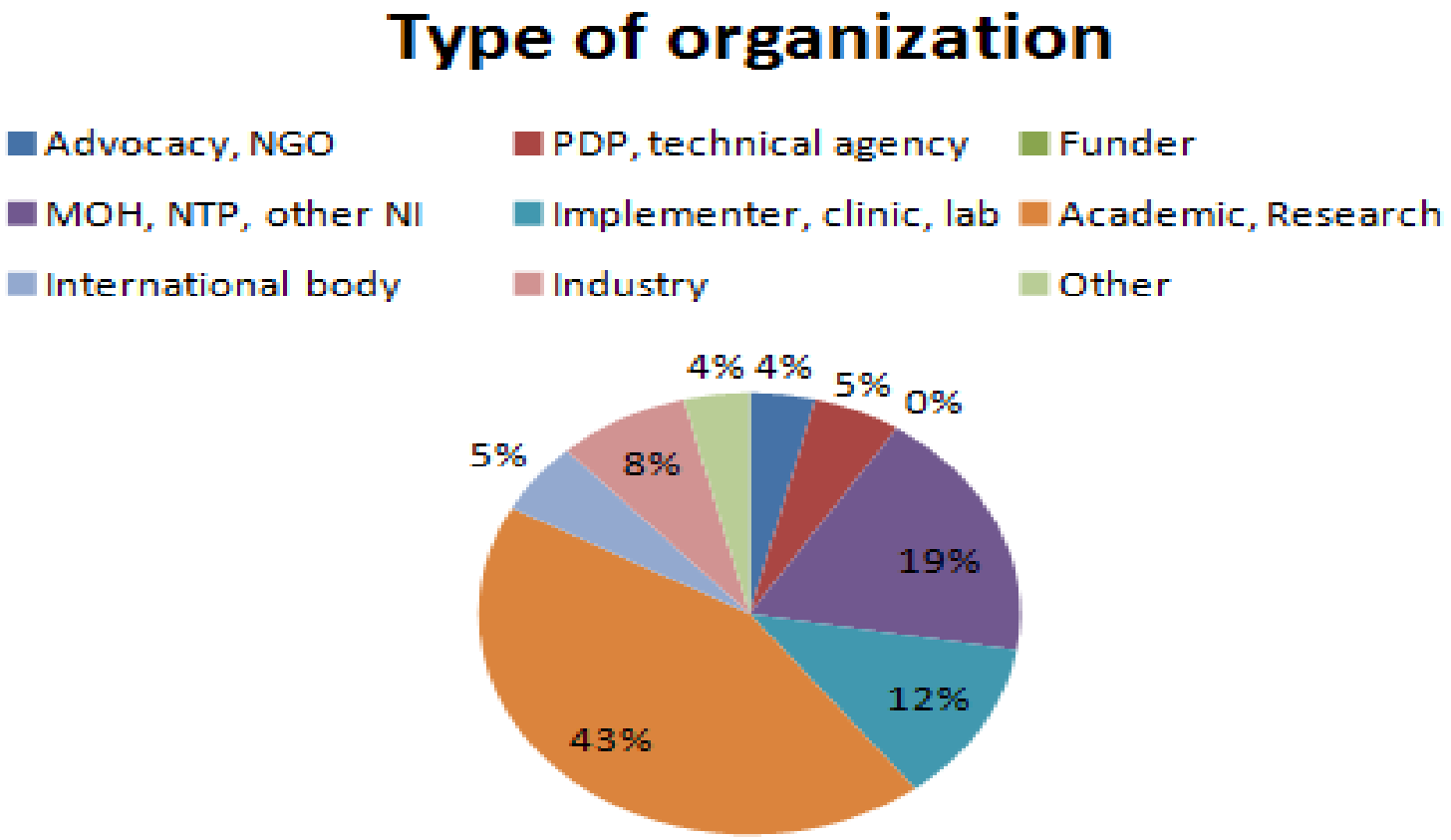
Below we describe optimal and minimal characteristics of such a test. We would like to invite you to express your level of agreement on each item. Please note that responses will be treated confidentially and answers will be anonymized and only identified by category.

DEFINITIONS

TB infection: any person with a positive test for TB infection (TST ≥ 5 mm, positive IGRA according to manufacturer's instructions) without microbiological, radiological or clinical evidence of active TB.

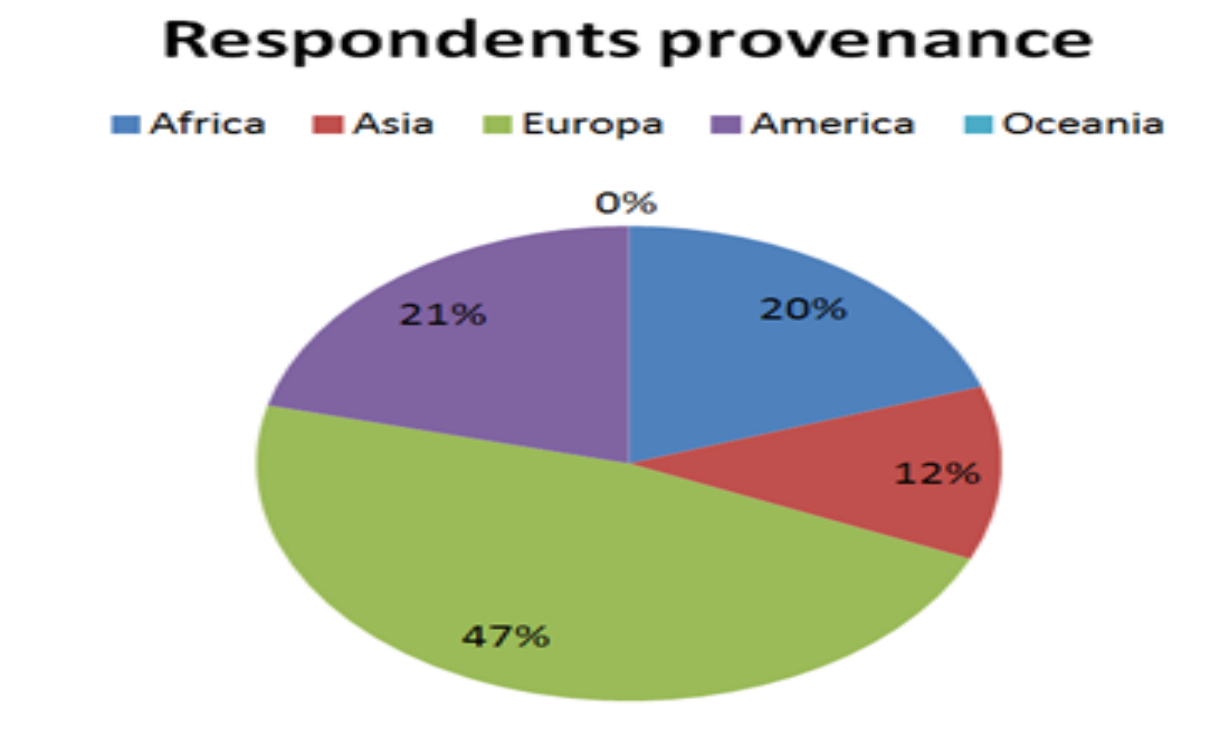
Active TB: symptomatic patients with compatible clinical and/or radiology and/or histology for TB and a positive microbiological test and started TB treatment (confirmed TB), or with compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB).

Who answered?



76/473 subjects took part to the survey

Where did they come from?

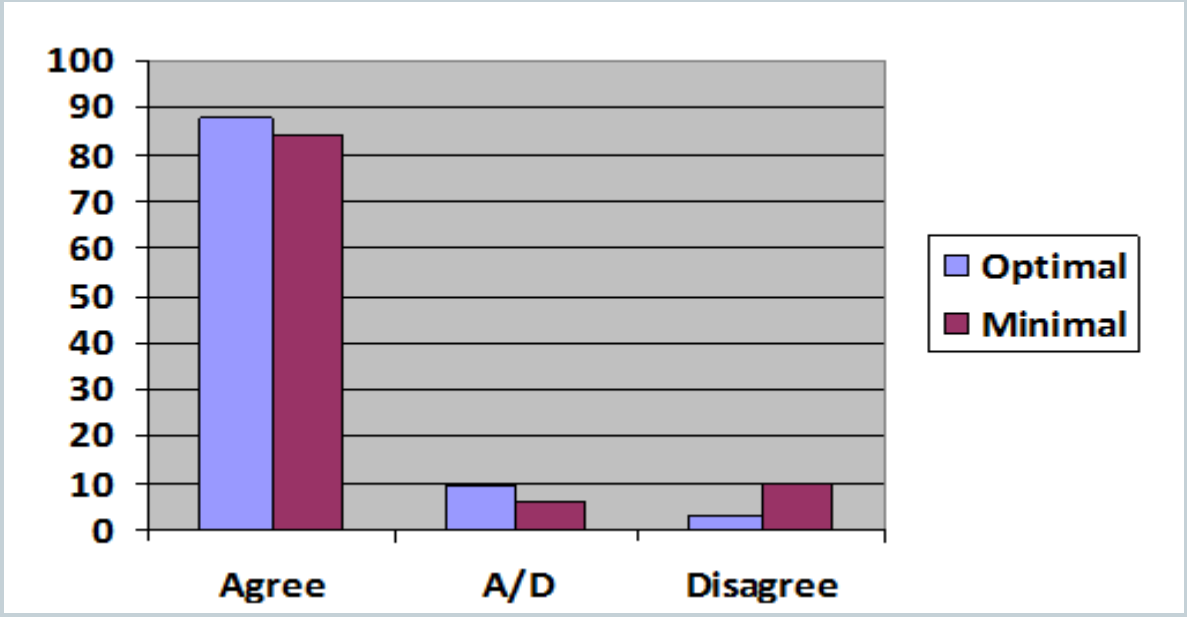


Q1: Goal of test/intended use

- **Optimal:** Biomarker-based test that can be used to predict the risk of progression from TB infection (TBI) to active TB within the next 2 years, with the ability to rule out active TB. Ideally, the test result should decrease or revert to negative with treatment and thus enable an assessment of treatment success or cure and consequentially also reinfection.

- **Minimal:** Biomarker-based test that can be used to predict the risk of progression from TBI to active TB within the next 2 years. The test would likely be positive in patients with active TB, therefore the presence of active TB needs to be ruled out by another highly sensitive test for active TB. Please rate your level of agreement with the above statements.

Results Question 1



	Disagree	Somewhat disagree	Neither agree nor disagree	Mostly agree	Fully agree	Total
Optimal	1,32% 1	7,89% 6	2,63% 2	32,89% 25	55,26% 42	76
Minimal	4,05% 3	2,70% 2	9,46% 7	41,89% 31	41,89% 31	74

Comments Question 1

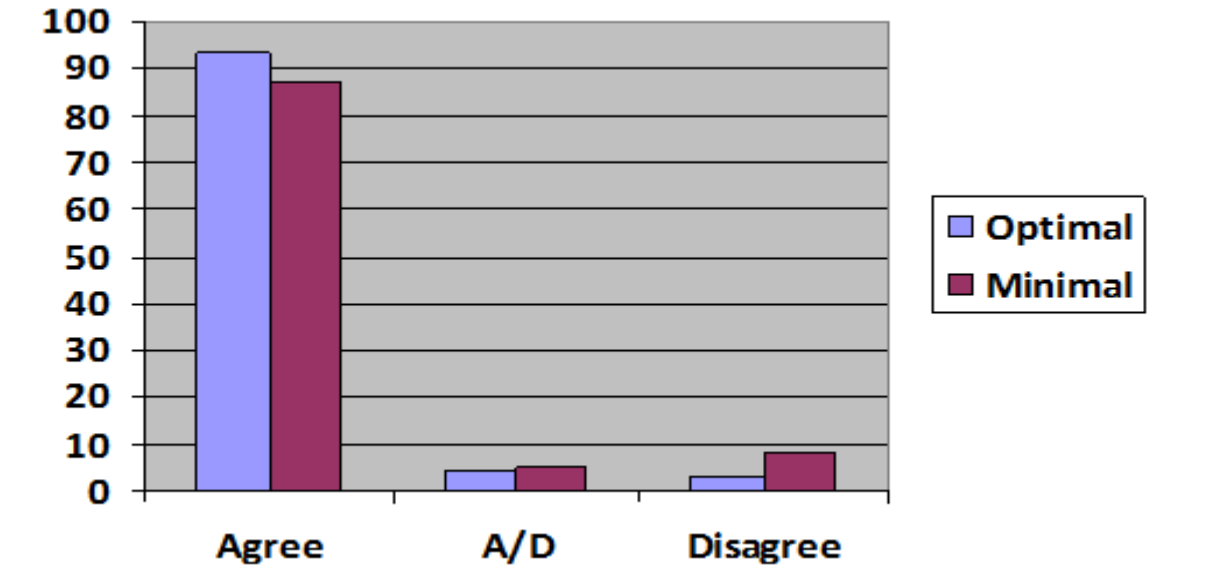
- “Biomarkers positive only for LTBI”
- “Differentiate from active TB: too ambitious, not feasible”
- “Two years too long → an arbitrary number?”
- “Complicated in HIV patients: HIV promotes progression to active TB”
- “The "optimal" test provides risk assessment on progression and tells you when the infection is gone. Ideally in a people life time”.

Q2: Type of test

- **Optimal:** single or multiple biomarker-based test, providing quantitative results that correlate with the risk of progression as well as qualitative results (positive/negative).

- **Minimal:** single or multiple biomarker-based qualitative test (positive/negative).

Results question 2



	Disagree	Somewhat disagree	Neither agree nor disgaree	Mostly agree	Fully agree	Totale
Optimal	0,00% 0	2,63% 2	3,95% 3	30,26% 23	63,16% 48	76
Minimal	1,35% 1	6,76% 5	5,41% 4	39,19% 29	47,30% 35	74

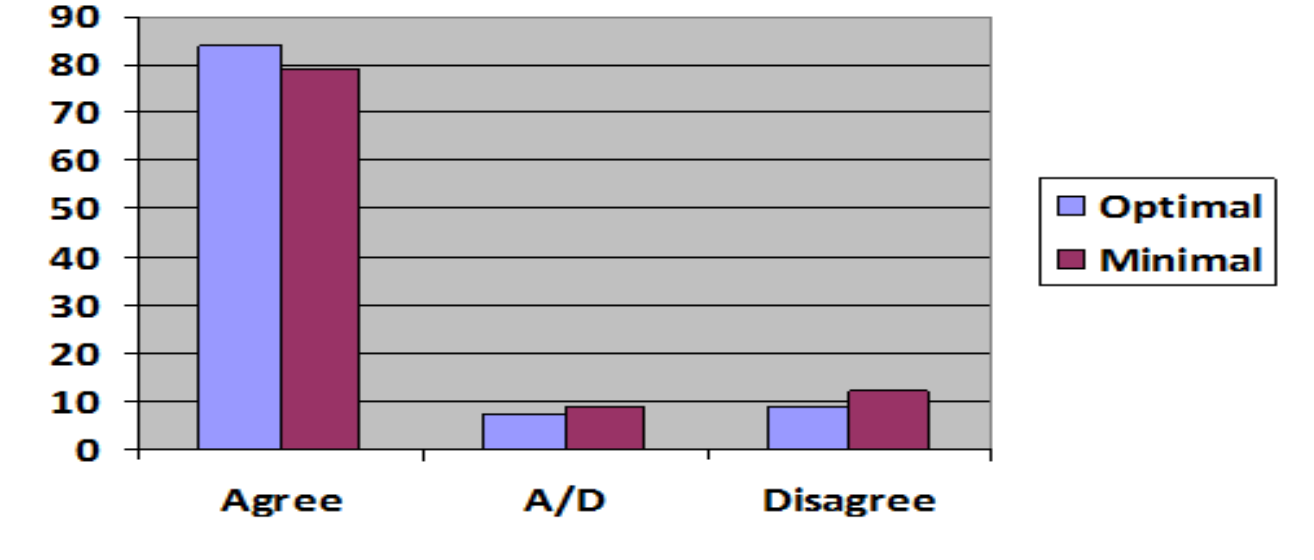
Comments Question 2

- “A qualitative test will probably not be sufficient in view of the spectrum of TB infection”
- “Not sure of the value of the quantitative result that will require a lot of data to validate”
- “A qualitative result is not necessary, as depending on the immune system of the subject. As with the TST, both false negative and false positive results can occur with tests such as QFT-GIT due to various reasons”

Q 3: Target user of the test

- **Optimal:** health care workers with no or minimal laboratory training (e.g. nurses).
- **Minimal:** health care workers with laboratory training (e.g. skilled laboratory technicians).

Results Question 3



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	0,00% 0	9,33% 7	6,67% 5	30,67% 23	53,33% 40	75
Minimal	6,67% 5	5,33% 4	9,33% 7	28,00% 21	50,67% 38	75

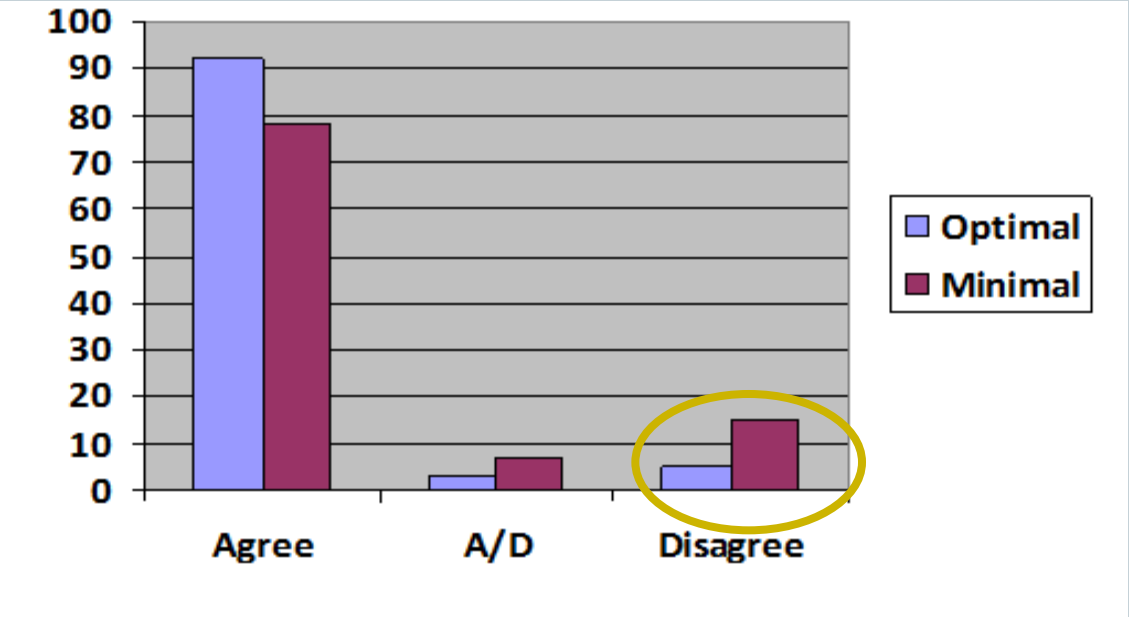
Comments Question 3

- “An ideal test should be POC and community-based, bedside laboratory independent.”
- Target user should be the patient/candidate himself”
- “The interpretation needs health care workers with good training”

Q4: Diagnostic sensitivity for progression to active TB

- **Optimal:** ≥ 90% sensitivity.
- **Minimal:** ≥ 75% sensitivity.

Results Question 4



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	0,00% 0	5,26% 4	2,63% 2	26,32% 20	65,79% 50	76
Minimal	2,70% 2	12,16% 9	6,76% 5	47,30% 35	31,08% 23	74

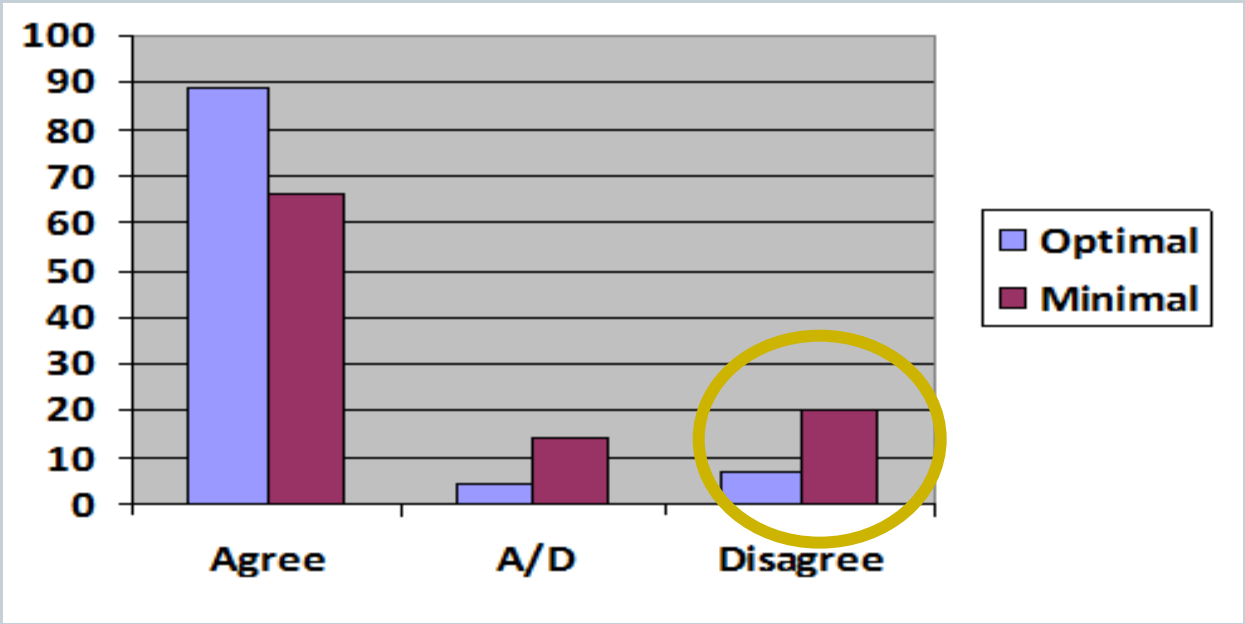
Comments Question 4

- “Optimal sensitivity should be at least 95%. Missing 1 in 10 isn't going to be an acceptable risk for many providers/patients”
- “The minimal standard is too low, at least 85%”.
- “The IGRAs set a very low bar to improve on. Anything better than 25% would be a major advance and much”
- “I think we need to look at PPV and NPV as well, based on expected prevalence, and what the treatment decision implications would be with a positive test. Both 75% and 90% sound low as minimal/optimal”.

Q5: Diagnostic specificity for risk of progression to active TB

- **Optimal** ≥90%.
- **Minimal**≥75%.

Results Question 5



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	0,00% 0	6,58% 5	3,95% 3	26,32% 20	63,16% 48	76
Minimal	5,41% 4	14,86% 11	13,51% 10	43,24% 32	22,97% 17	74

Comments Question 5

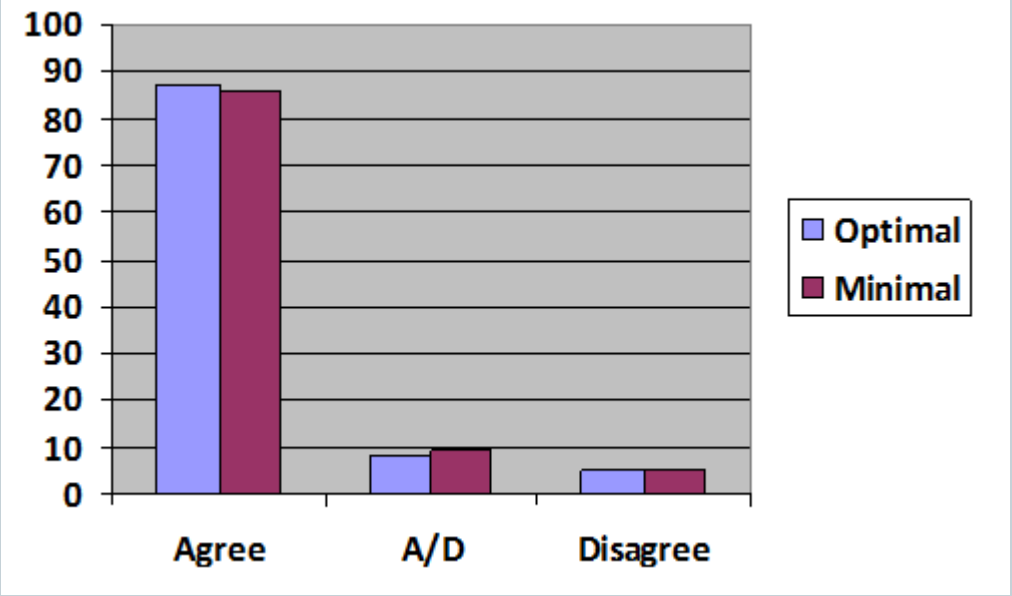
- “Test should maximize true negatives: 95% specificity optimal, 90% minimal”
- “Minimal specificity too low→ non meaningful risk stratification”
- “The test should be of high specificity to rule out BCG and NTM”
- “Specificity of =>75% is only acceptable when sensitivity is at the higher end of the range. Sens & spec should be presented to have sufficient high PPV”

Q6: Results capturing, documentation, data display

- **Optimal:** ideally instrument-free test but should allow for attaching or scanning results to the reader to have the ability to save and print the results.

- **Minimal:** ability to save the results either via instrument or via a separate reader (or alternative).When instrument is used the test menu should be simple with integrated LCD screen; simple key paid or touch screen.

Results Question 6



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	0,00% 0	5,33% 4	8,00% 6	36,00% 27	50,67% 38	75
Minimal	0,00% 0	5,33% 4	9,33% 7	44,00% 33	41,33% 31	75

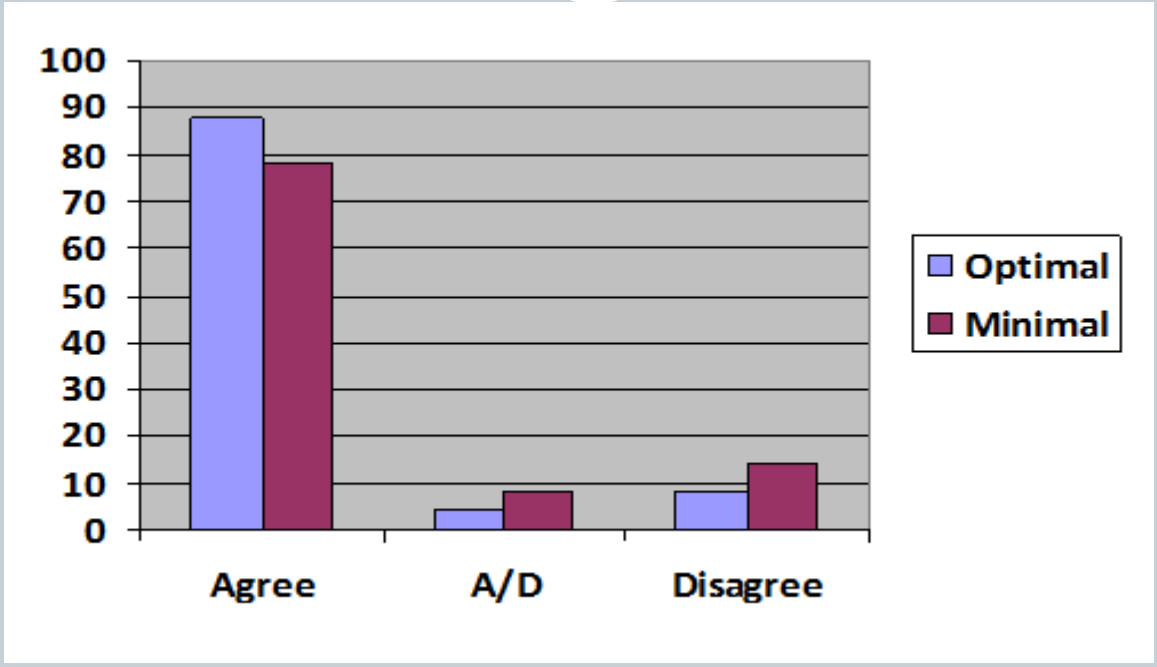
Comments on Question 6

- “Add 'mobile-phone application based reader→ wireless transmission of results to tablet or smart phone”
- “Linkage to TB program data collection require that test data are uploaded and captured. Instrument-free/paper results are likely to be lost to analysis”
- “Scanning /attaching results is not important as point of care test → could be recorded in patient notes or logged on a computer”

Q7: Training

- **Optimal:** < 1 day dedicated training for non laboratory trained health-personnel.
- **Minimal:** 3-7 days dedicated training for a laboratory trained health-personnel.

Results Question 7



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	1,33% 1	6,67% 5	4,00% 3	26,67% 20	61,33% 46	75
Minimal	4,05% 3	9,46% 7	8,11% 6	40,54% 30	37,84% 28	74

Comments Question 7

- “3-7 days is too much: <2 days minimal, < 4 hours optimal”
- “The more complex the test the more detailed training will be required: at least between 1-3 days training”
- “ Test automated, little reason to keep staff away from work for such a long time. The training can be reduced as much as possbile”

Q8: Number of steps to be performed by the operator

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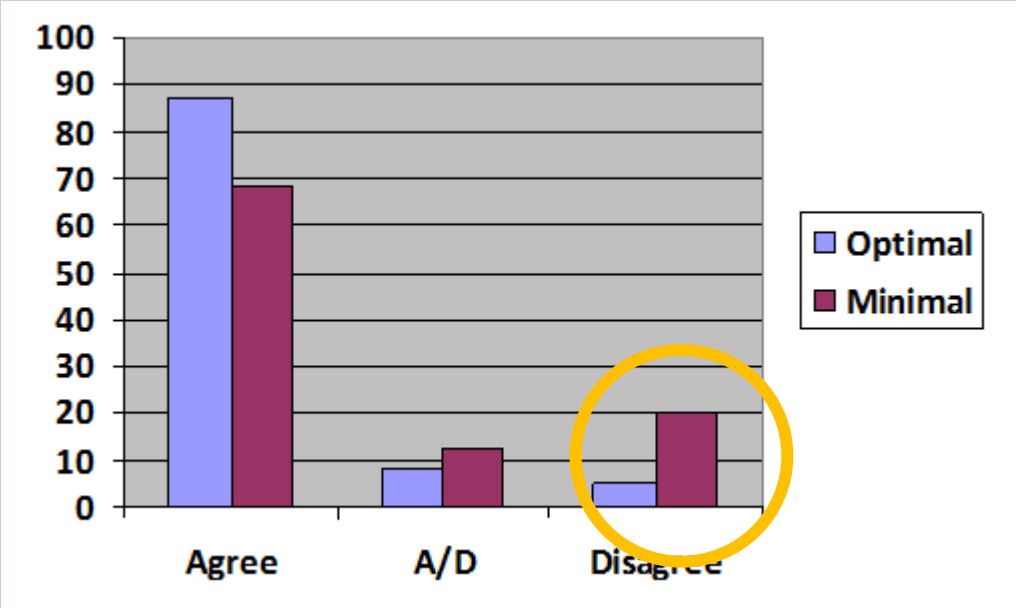
- **Optimal:** <2, no timed steps.
- **Minimal:** <10, 1-2 timed steps

Results Question 8



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	1,33% 1	4,00% 3	8,00% 6	32,00% 24	54,67% 41	75
Minimal	8,11% 6	12,16% 9	12,16% 9	44,59% 33	22,97% 17	74

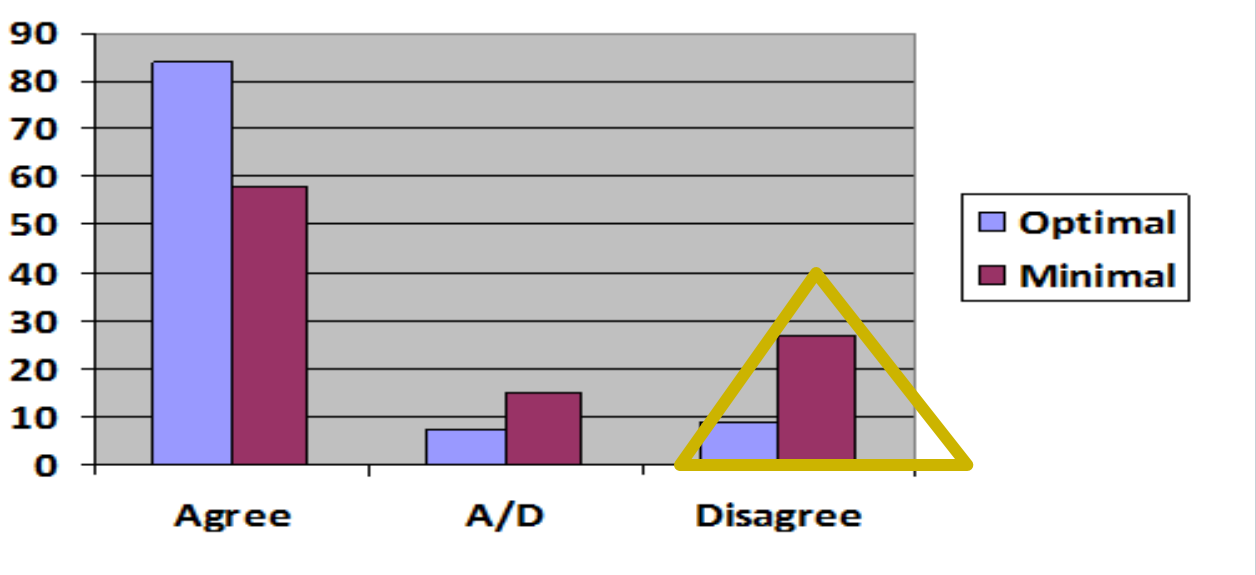
Comments Question 8

- “Laboratory heavy → end up in ZN method fate where intra and inter operator performance and results vary greatly because of multiple steps”
- “If the test meets all the other requirements but is of high complexity who cares about the number of steps? “
- “Current tests such as TST and IGRA have many steps→ optimal too ambitious”
- “The less steps, the more user friendly and the higher the chances of it being correctly done.”

Q9: cost of equipment

- **Optimal:** <500 USD.
- **Minimal**:<5000 USD.

Results Question 9



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	6,67% 5	2,67% 2	6,67% 5	41,33% 31	42,67% 32	75
Minimal	18,92% 14	8,11% 6	14,86% 11	48,65% 36	9,46% 7	74

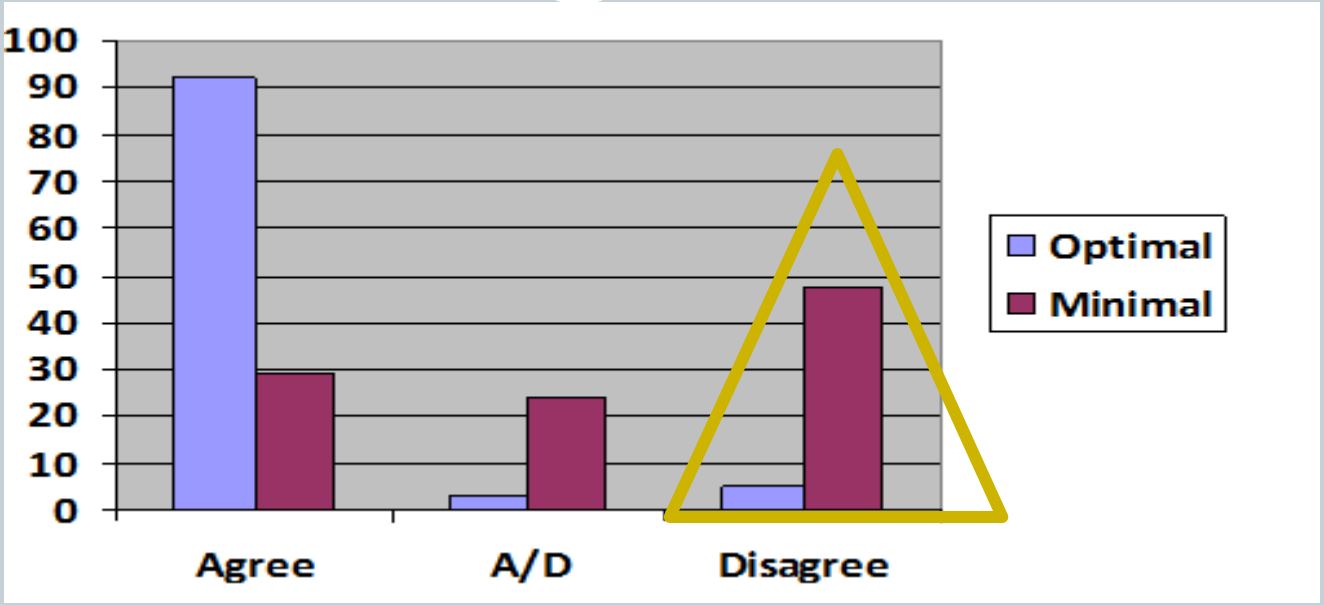
Comments Question 9

- “Must be cheap and affordable”
- “For optimal the cost of equipment would be $0 (no equipment). For minimal, similar to complexity, if we can get *something* that meets all the other requirements I think we'd rather have it than not”
- “The affected communities cannot afford high cost →low acquisition /under utilization→no impact on the global LTBI burden”

Q10: Cost of consumables (reagents/test strips)

- **Optimal:** < 5 USD/test.
- **Minimal:** < 150 USD/test.

Results Question 10



	1- Disagree	2- Somewhat disagree	3- Neither agree nor disagree	4- Mostly agree	5- Fully agree	Total
Optimal	0,00% 0	5,26% 4	2,63% 2	30,26% 23	61,84% 47	76
Minimal	33,78% 25	13,51% 10	24,32% 18	18,92% 14	9,46% 7	74

Comments Question 10

- “The cost of the test should be equal to or less than smear microscopy. < 1$ optimal /< 10$ minimal”
- “A test at <150 USD would not be a research tool: <20 USD in LMIC; much higher for research or in HIC”
- “<5 USD/test is unrealistic whereas 150 USD/test is really too much. Range suggested: 30 USD/test -100 USd/test”