

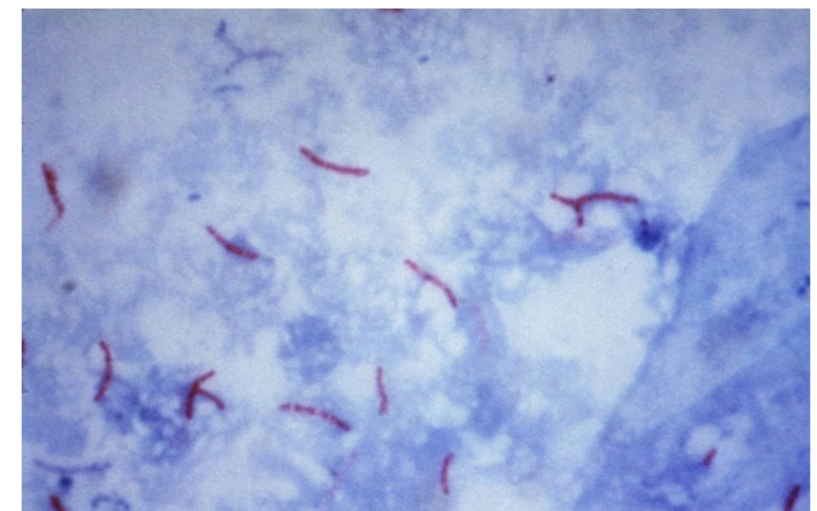
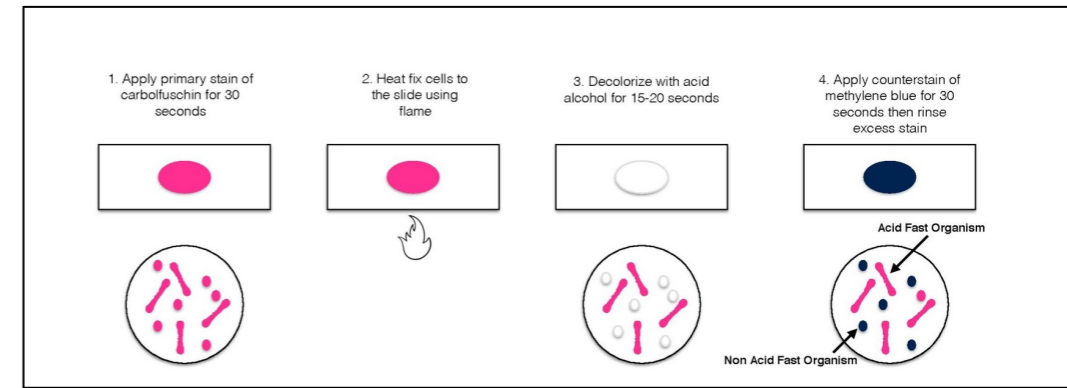
TB Diagnosis

Passive versus active case finding

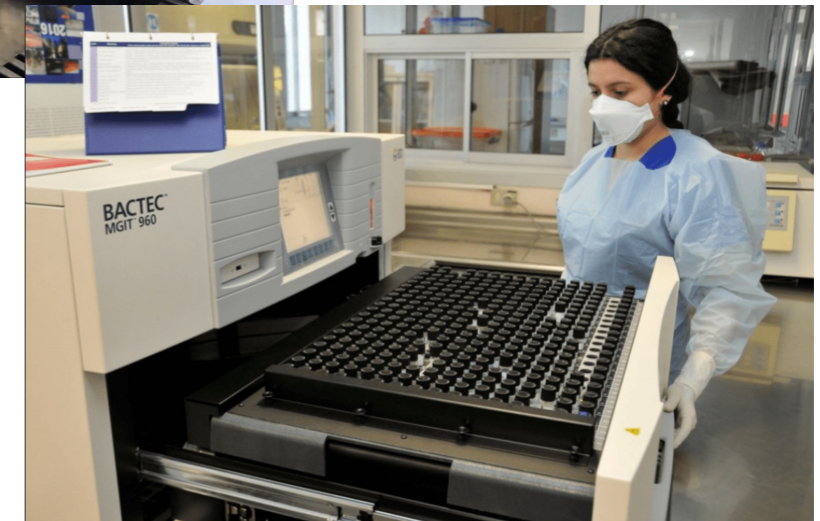
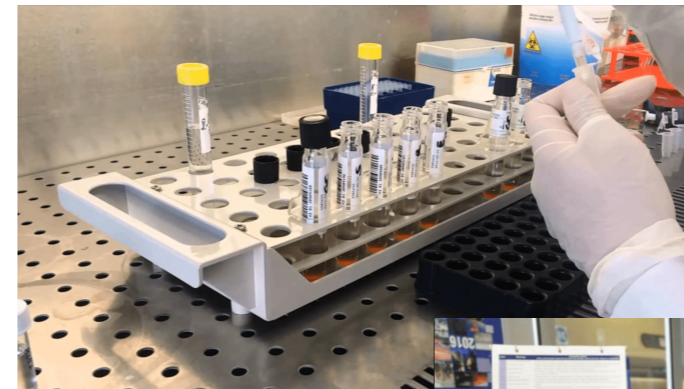
- Current guidelines recommend ACF only in high risk groups: HIV, HHCs, prisoners, silica exposed, urban slums, homeless, migrants.
- Passive case finding in people who “present” with 2 weeks cough, fever, night sweats, weight loss.



- Sputum smear microscopy with Ziehl Neelson stain for acid fast bacilli.
- 2 samples per WHO
- Requires 10k bacilli/ml to visualize so low accuracy in HIV, children
- Does not distinguish atypicals from Mtb or DR from DS
- Sensitivity 46%, Specificity 99%



Mycobacterial culture and drug susceptibility testing



Done in National reference labs or tertiary facilities

Requires BSL3

Average time to growth:
4-6 weeks solid culture
1-2 weeks MGIT

“Gold standard” for diagnosis but “unculturable TB” may exist.



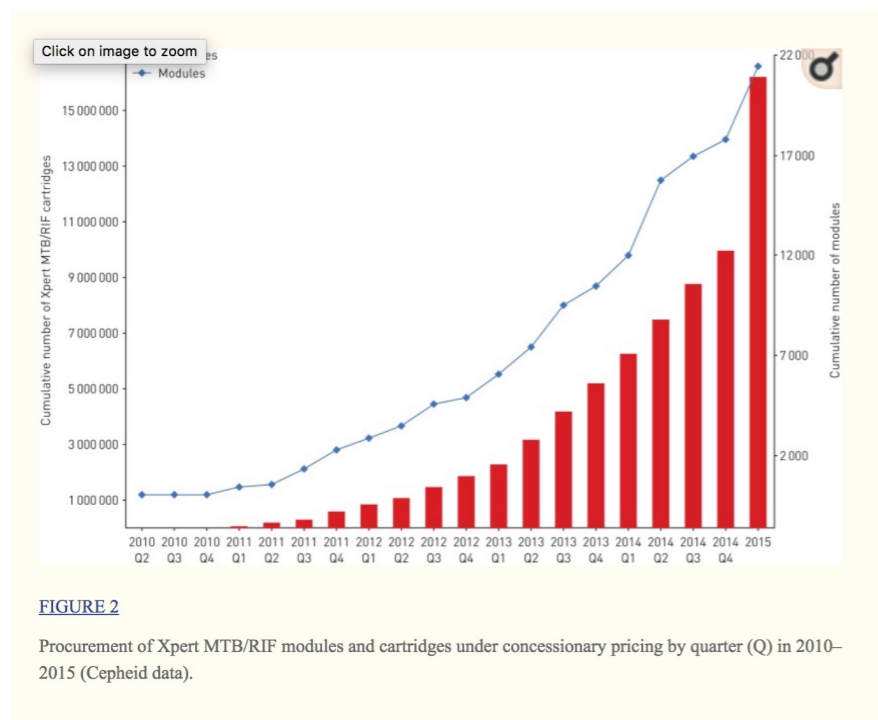
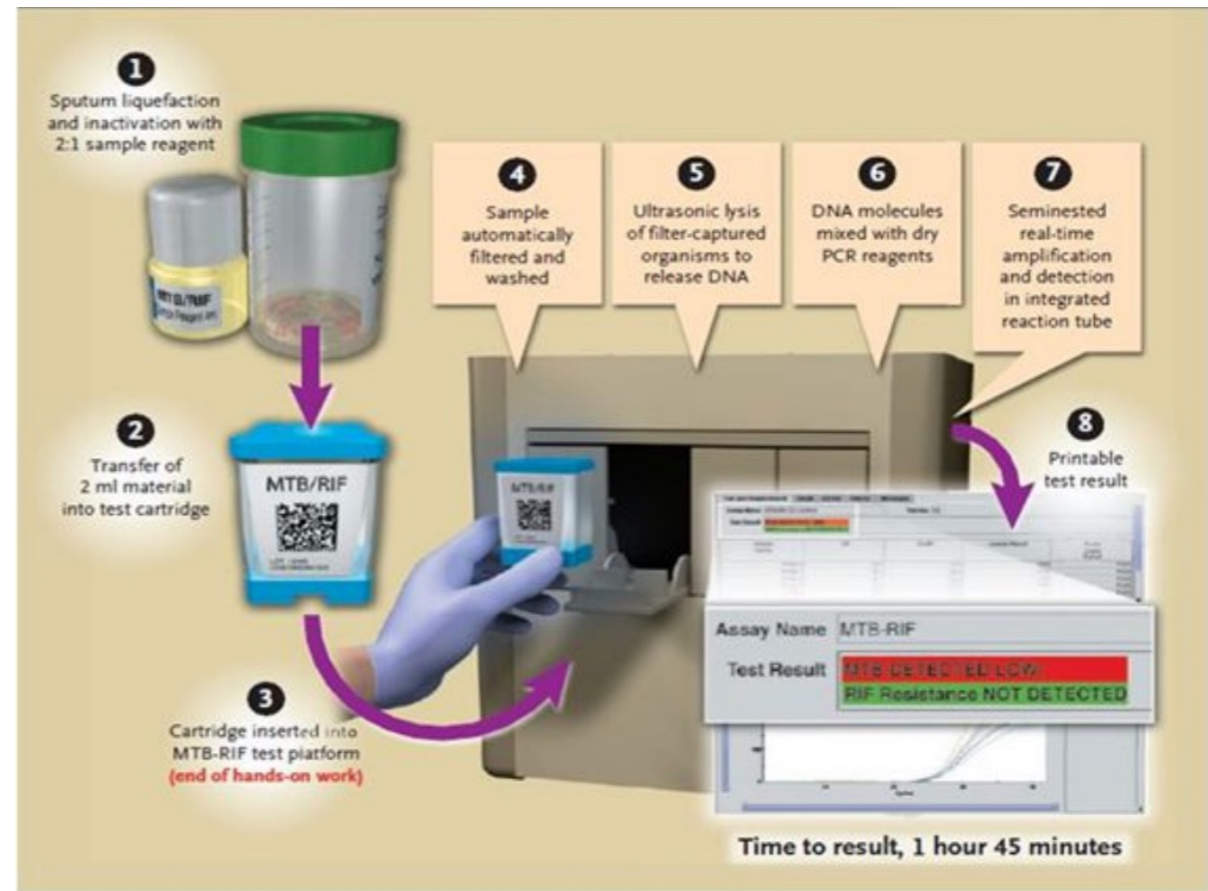
Gene Xpert

Sensitive and specific, fully automated, commercial nucleic acid amplification test for use with sputum and other body specimens.

Closed cartridge system of rt-PCR to detect TB marker and rifampicin resistance (RpoB).

Minimal processing, 2 hour turn-around time.

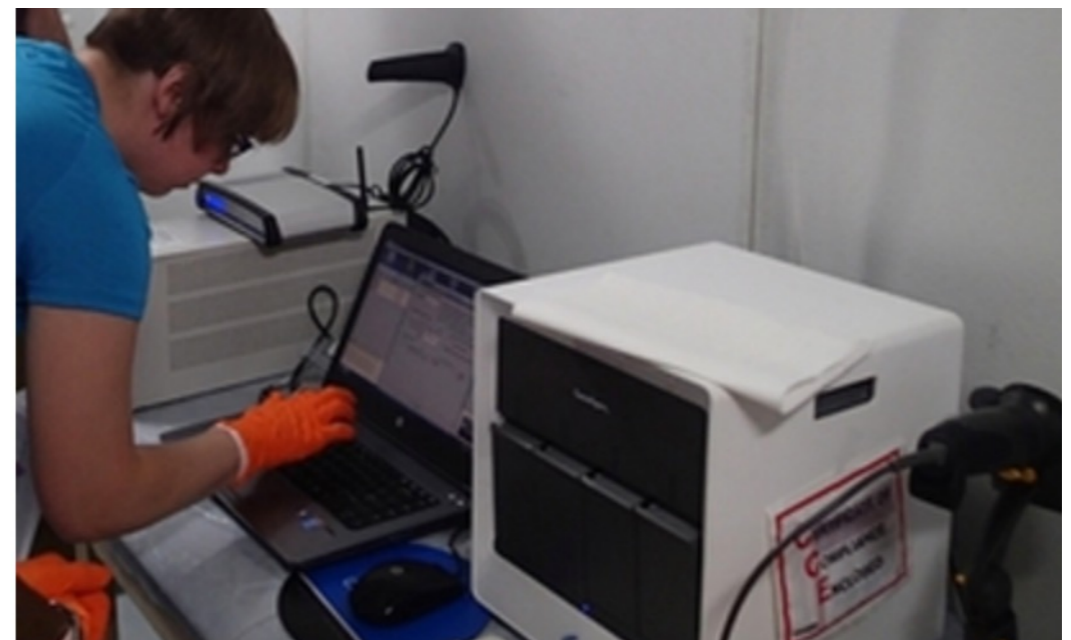
As of 2013, recommended by WHO as initial test for all TB.



	All	All	HIV+	HIV+
	Smear	Smear	Smear	Smear
	+	-	+	-
GenXpert MTB/Rif	90/98%	98/99	67/99	97/99
GenXpert Omni				
GenXpert Ultra	88/98	63/98	90/98	

Issues with Xpert

- Pricing
 - 17k for 4 module instrument
 - 10\$ for concessionary price for cartridges
- Training
 - 1-2 days officially, 1-2 months by report
- Infrastructure
 - Targeted to district health facilities. Requires stable power, temperature, humidity, no dust.
- Maintenance
 - Higher than expected rates of module failure, up to 10%
- Supply Chain
 - Stock outs of cartridges
 - Expiration of cartridges
- IT/Reporting



Chest Radiography

- CXRs
- Digital CXRs
- Chest CT
- PET/CT

- Myriad possible presentations
- High sensitivity, low specificity
- Role for AI?



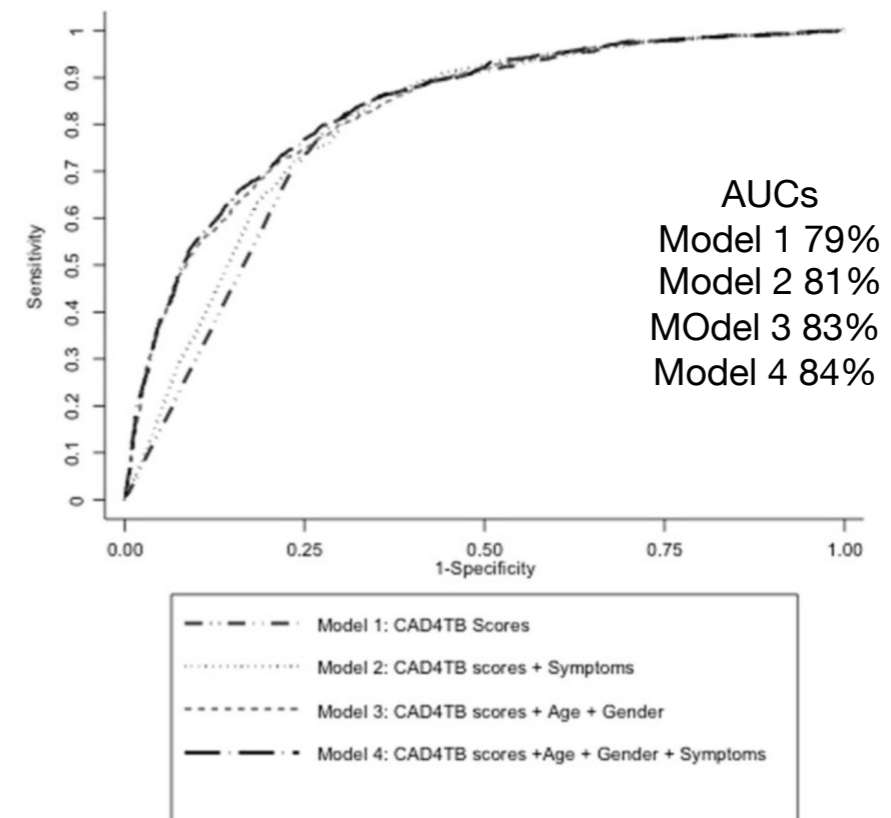
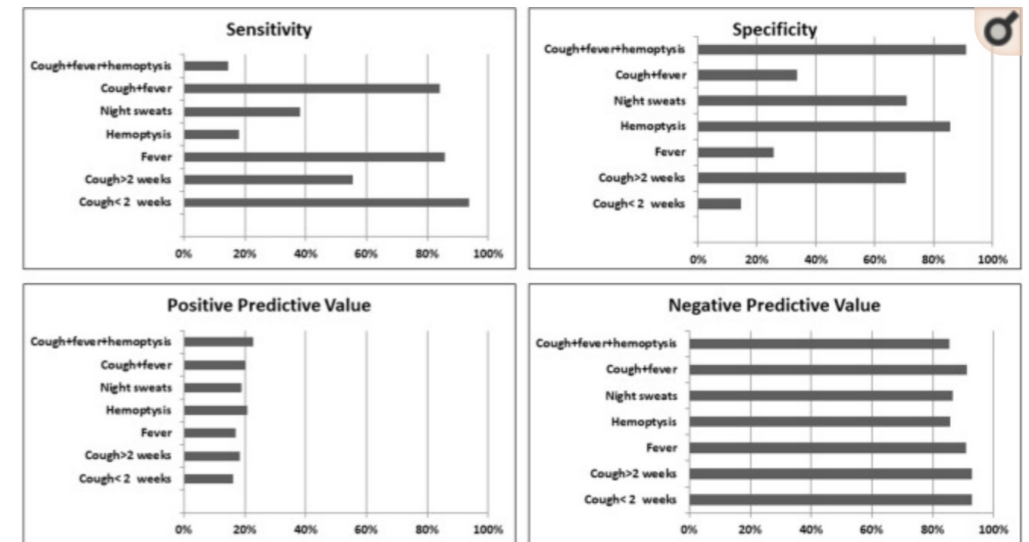
Consolidation



Cavity

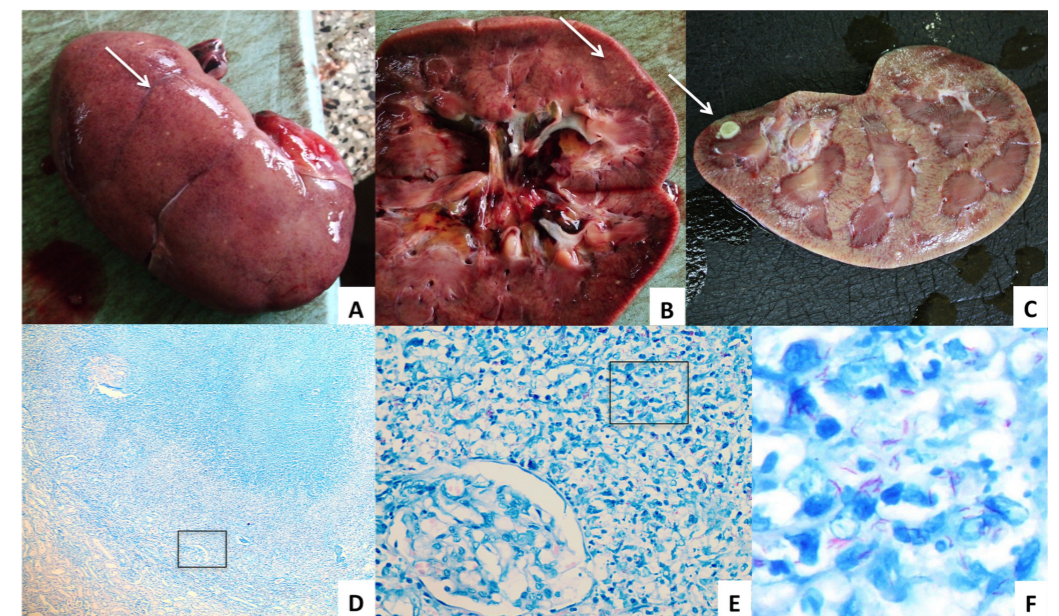
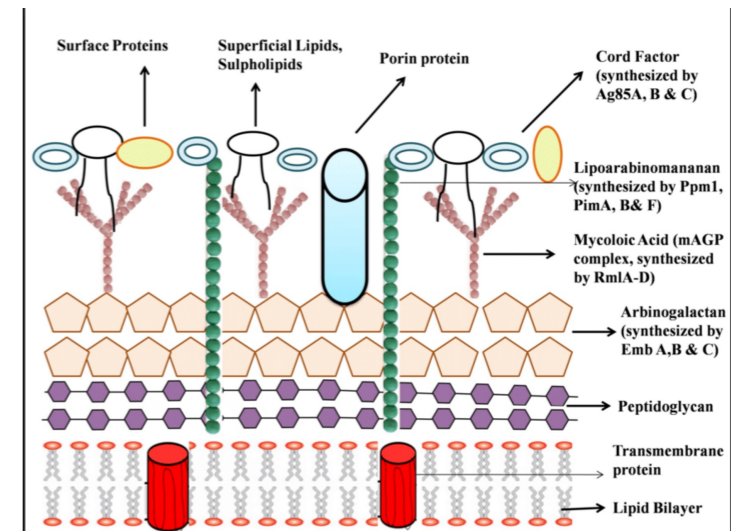


Miliary



Urine LAM

- Lipoaribinomannan, Cell wall liposaccharide specific to Mtb.
- Measured in urine with ELISA or *Determine TB-LAM test strip*
 - 3.50\$, 3 minutes
 - High Specificity in HIV, Specificity increases as CD4 decreases:
 1. Cd4<200 39%
 2. Cd4<100 51.7%
 3. Cd4<50 66.7%
- Renal TB explains most positive results.



TB LAMP

- LAMP = loop mediated isothermal amplification
- Isothermal nucleic acid amplification technique. (in contrast to [PCR](#) which is carried out with a series of alternating temperature steps or cycles, requiring a [thermal cycler](#)).
- Typically, 4 different primers used to identify 6 regions on the target gene, improving specificity. "loop primers" further accelerate the reaction. Amount of DNA produced in LAMP than [PCR](#) based amplification.
- Detection of amplification product determined via photometry for turbidity caused by an increasing quantity of magnesium [pyrophosphate](#) precipitate in solution as a byproduct of amplification, allowing easy visualization by the naked eye. Dyes can be used to create a visible color change - Dye molecules directly label the DNA and can be correlated to the number of copies initially present.

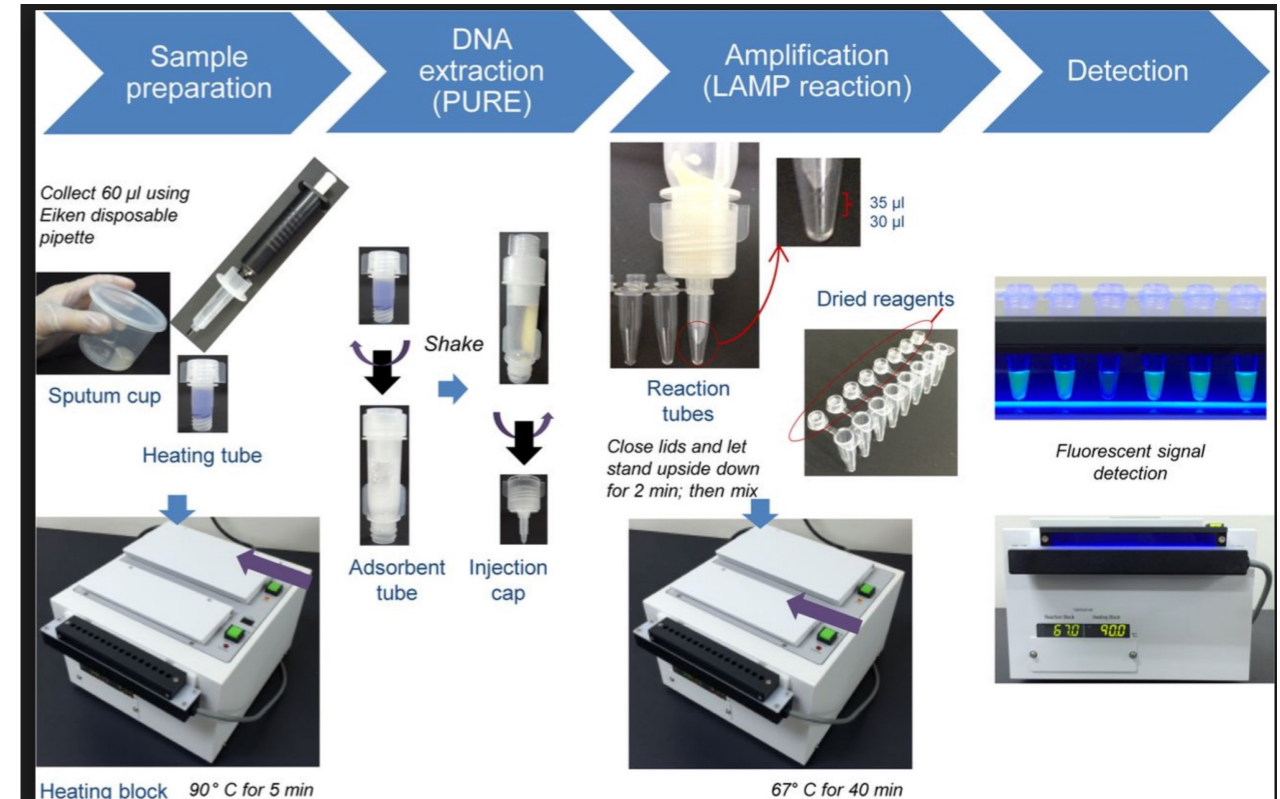


Table 1. Comparison of TB-LAMP positive rates according to smear grade

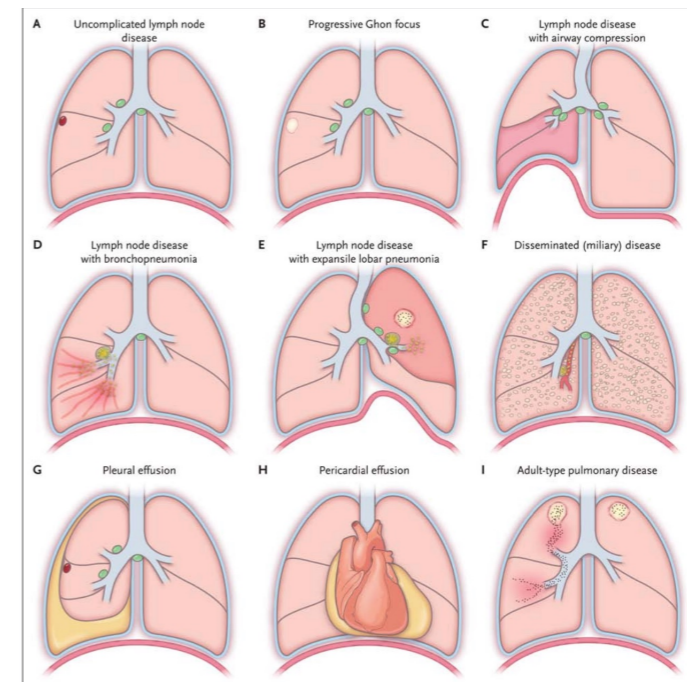
Smear	TB-LAMP		Total	% Agreement (95% CI)	κ (95% CI)
	Positive (%)	Negative (%)			
Negative	14 (7.5)	172 (92.5)	186	83.8 (79.1–87.6)	0.63 (0.54–0.73)
Scanty	3 (17.6)	14 (82.4)	17		
1+	39 (73.6)	14 (26.4)	53		
2+	13 (81.3)	3 (18.8)	16		
3+	16 (88.9)	2 (11.1)	18		
Total	85 (29.3)	205 (70.7)	290		

For assessing agreement, the smear results were divided into positive and negative regardless of grade.

Diagnosis in Children

Issues

- Several different child TB phenotypes:
 - Age 2-3 and under, Age 4-10 or 11, Age >11
- Kids can't expectorate sputum easily.
- Often have LN disease rather than parenchymal consolidation.
- More pleural disease in adolescents.
- Relies heavily on CXR, Chest CT



Tests



Host based tests

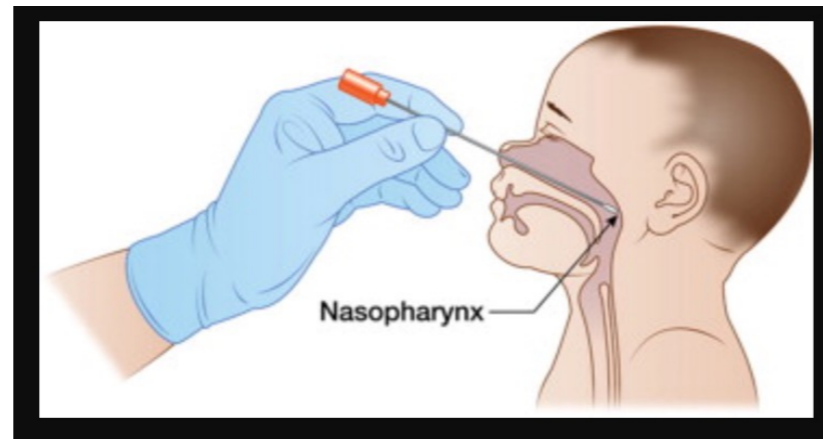
- Radiography
- Biomarkers



Bug based tests

- Gastric aspiration
- Sputum induction
- Naso-pharyngeal swab
- String test

- Stool
- Urine
- Biopsy of LN or pleura



Tests that should not be used to diagnose active TB


- Serology (antibody tests)
- TST
 - Can be negative in very sick people
 - Can lead to necrosis with strong positive response.
- IGRA



TABLE 4.

Overall sensitivities, specificities, and likelihood ratios for antigens evaluated for serodiagnosis of pulmonary TB with assays detecting IgG and/or IgA antibodies

Type of compound	Antigen name	Rv designation	No. of studies	Smear status	HIV status	Sensitivity (%) ^a	Specificity (%) ^a	Likelihood ratio positive ^a	Likelihood ratio negative ^a
Recombinant	38 kDa	0934	12	Positive	+/-	47 (39-55)	94 (86-98)	8.22 (3.41-24.85)	0.56 (0.48-0.65)
	Malate synthase	1837c	8	Positive	+/-	73 (58-85)	98 (95-100)	40.78 (14.43-155.7)	0.27 (0.16-0.42)
	MPT51	3803c	5	Positive	-	59 (38-76)	94 (77-99)	10.50 (2.70-69.69)	0.44 (0.26-0.67)
	MPT51	3803c	4	Positive	+	58 (30-82)	97 (84-100)	19.03 (3.73-172.3)	0.44 (0.19-0.73)
	CFP-10	3874	6	Positive	+/-	48 (29-68)	96 (83-99)	12.11 (3.20-64.63)	0.55 (0.35-0.73)
	TbF6 ^b		4	Positive	-	70 (37-90)	93 (69-99)	9.61 (2.23-53.99)	0.33 (0.13-0.66)
	TbF6, DPEP ^c		4	Positive	-	75 (50-91)	95 (86-99)	14.97 (5.43-56.66)	0.26 (0.10-0.53)
Native protein	38 kDa	0934	13	Positive	+/-	49 (37-61)	97 (94-99)	15.73 (8.84-31.55)	0.53 (0.41-0.65)
	38 kDa	0934	7	Negative	-	31 (15-52)	97 (92-99)	9.13 (3.88-24.05)	0.72 (0.51-0.87)
	Ag 85B	1886c	4	Positive	-	53 (20-83)	95 (78-99)	9.36 (2.52-53.81)	0.51 (0.20-0.84)
	Ag 85B	1886c	4	Positive	+	62 (19-92)	97 (89-99)	17.83 (4.04-62.32)	0.39 (0.08-0.84)
	α-Crystallin	2031c	6	Positive	+/-	54 (32-75)	96 (83-99)	13.23 (3.52-66.61)	0.48 (0.28-0.71)
Lipid	DAT		7	Positive	+/-	63 (45-78)	81 (50-96)	3.32 (1.32-13.35)	0.47 (0.30-0.74)
	TAT		4	Positive	+/-	81 (21-99)	44 (24-67)	1.44 (0.42-2.31)	0.42 (0.03-1.71)
	SL-1		4	Positive	+/-	80 (56-93)	59 (8-96)	1.94 (0.89-20.90)	0.34 (0.14-2.22)
	Cord factor		5	Positive	+/-	69 (28-94)	91 (78-97)	7.03 (2.44-20.65)	0.35 (0.06-0.80)



Let Us Stop Malpractices in TB Diagnosis

Inaccurate Serological Blood Tests for Diagnosis of TB banned by the Government of India in Public Interest

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)
NOTIFICATION
New Delhi, the 7th June, 2012

G.S.R. 432(E). - Whereas the Central Government is satisfied that the use of the serodiagnostic test kits for diagnosis of tuberculosis are giving inconsistent and imprecise results leading to wrong diagnosis and their use is likely to involve risk to human beings and whereas safer alternatives are available:
And whereas the Central Government is satisfied that it is necessary and expedient to prohibit the manufacture, sale, distribution and use of the said test kits in public interest:
Now, therefore, in exercise of the powers conferred by Section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby prohibit the manufacture for sale, distribution and use of the following test kits with immediate effect:
"Serodiagnostic test kits for diagnosis of tuberculosis"

Frequently asked questions on the notification
Q. What is the reason behind the ban?
ANS: There is proven scientific evidence that serodiagnostic tests for TB provide inconsistent and imprecise results despite high claims of its accuracy

**No More Deaths From TB
Together We Can Make India TB Free**
Free Diagnosis and Treatment for TB is Available
For More Details Please Contact Concerned District TB Officer

Q. What is the consequence of inconsistent and imprecise results?
ANS: The dependence on such unreliable tests can be harmful as many patients will end up undergoing TB treatment without any need for it as they are wrongly diagnosed as TB. At the same time, the test also misses many TB patients thus denying treatment at the right time. Such patients will continue to suffer and even spread the infection to other healthy individuals.

Q. What is meant by "serodiagnostic test kits" for tuberculosis?
ANS: Serodiagnostic tests for tuberculosis are tests that detect the antibody response to tuberculosis causing bacteria in blood samples of suspected tuberculosis patients.

Q. Is the ban applicable to Indian as well as imported TB serodiagnostic kits?
ANS: Yes, the ban is applicable to all kits manufactured in India as well as all types of imported kits.

Q. How can TB be detected if all blood tests have been banned? Are there any alternative tests available?
ANS: Government of India has approved the following tests for diagnosis of TB:
• Sputum examination under microscope
• Culture tests
• Newer molecular tests.

Q. What are Interferon-gamma release assays (IGRAs)?
ANS: IGRAs are laboratory blood test that measure the cell-mediated immune response of TB in infected individuals.

Q. In which situation should IGRAs not be used?
ANS: IGRAs blood tests have limited use as they cannot differentiate between active pulmonary TB disease and latent TB infection. Hence IGRAs should not be used as stand alone tests to detect active TB disease.

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM
Ministry of Health and Family Welfare, Government of India

Promising approaches

Holy Grail = Urine dipstick test

Breath test for volatiles

Blood for biomarkers, Mtb

Urine for lipids, glycolipids, proteins or Mtb DNA

Stool for Mtb or microbiome profile consistent with TB

Oral or buccal swab for Mtb



Breathalyser detects tuberculosis

Coughing into a breathalyser could be the new way to detect the most common form of tuberculosis.

The portable device, developed by Rapid Biosensor Systems, would be quicker and easier to use than the current screening method, called the Heaf test.

The Heaf test involves an injection of tuberculin into the skin. The patient has to wait one week to see if a reaction develops, which would indicate exposure to infection.



A simple breath test could detect tuberculosis

