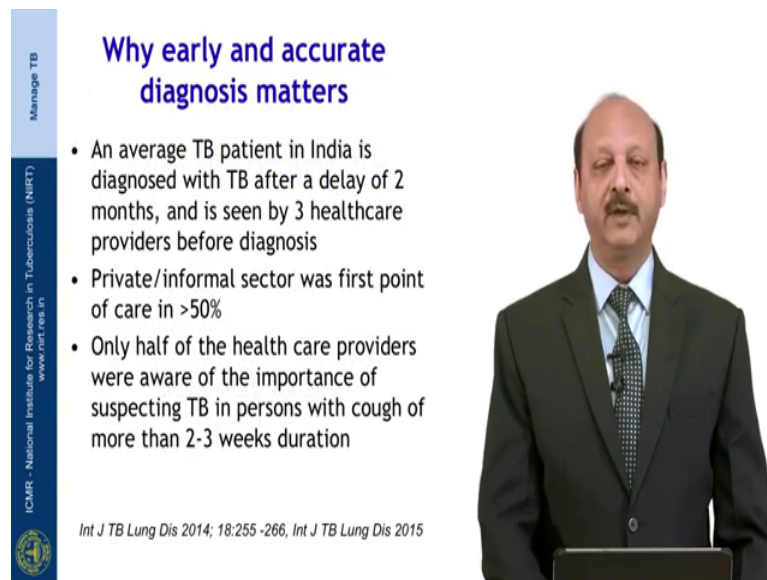


**Manage TB**  
**Prof. Rupak Singla**  
**Department of TB & Respiratory Diseases**  
**National Institute for Research in Tuberculosis & Respiratory Diseases, New Delhi**

**Lecture – 20**  
**Approach to diagnosis of Pulmonary TB**

Dear friends, very Good morning. In today's session we are going to talk about Approach to diagnosis Pulmonary Tuberculosis. I am Dr. Rupak Singla, I am heading the department at National Institute of Tuberculosis and Respiratory Diseases; New Delhi.

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**Why early and accurate diagnosis matters**

- An average TB patient in India is diagnosed with TB after a delay of 2 months, and is seen by 3 healthcare providers before diagnosis
- Private/informal sector was first point of care in >50%
- Only half of the health care providers were aware of the importance of suspecting TB in persons with cough of more than 2-3 weeks duration

Int J TB Lung Dis 2014; 18:255-266, Int J TB Lung Dis 2015

The slide features a vertical blue bar on the left with the text 'Manage TB' and 'ICMR - National Institute for Research in Tuberculosis (NIRT) www.nirt.res.in'. To the right of the text is a photograph of Dr. Rupak Singla, a man in a dark suit and tie, standing behind a podium.

You see if you look at the private sector in India the TB diagnosis; an average TB patient in India is diagnosed TB after delay of 2 months and is seen by 3 healthcare professionals before the diagnosis of TB is made. And not only that the private sector was the first point of care in more than 50 percent of cases in several studies. And on top of that only half of the healthcare providers were aware of the importance of suspecting TB in person with cough more than 2 to 3 weeks, which we all know is the commonest symptom of pulmonary tuberculosis.

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## Substantial under-testing for TB, and empirical Rx, in private sector

Point-of-care testing in India: missed opportunities to realize the true potential of point-of-care testing programs

Treatment as diagnosis and diagnosis as treatment: empirical management of presumptive tuberculosis in India

Use of standardized patients to assess quality of tuberculosis care: a pilot, cross-sectional study

Barriers to Point-of-Care Testing in India: Results from Qualitative Research across Different Settings, Users and Major Diseases

How Do Urban Indian Private Practitioners Diagnose and Treat Tuberculosis? A Cross-Sectional Study in Chennai

Alternative medicine: an ethnographic study of how practitioners of Indian medical systems manage TB in Mumbai

Multiple-test approach to the laboratory diagnosis of tuberculosis - perception of medical doctors from Ujjain, India

Several studies across the country have shown that in the private sector there is substantial under testing for tuberculosis and medical treatment is being started.

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## Importance of TB case finding and diagnosis

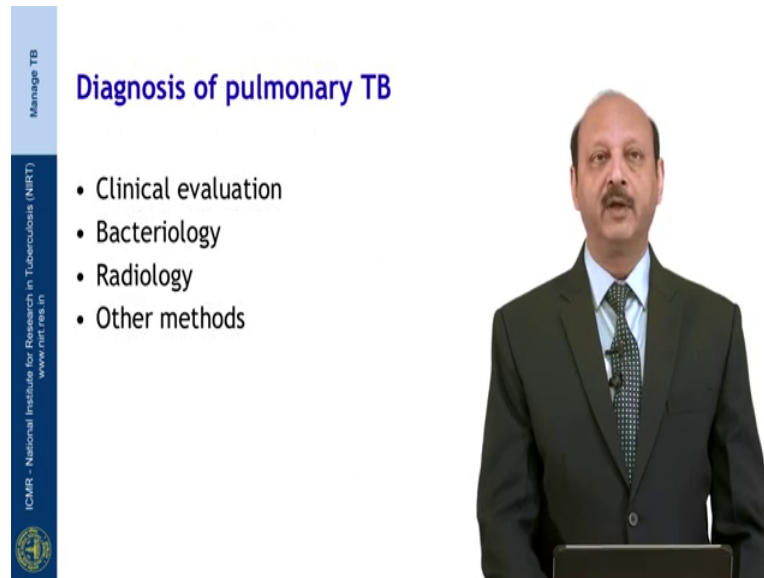
- Identification of presumptive TB cases at first point of care, linking them to best available diagnostic tests is important
- Can be done by:
  - Universal access to early accurate diagnosis of TB
  - Enhancing case finding efficiency
- Early & accurate diagnosis:
  - Good outcome of treatment
  - Interrupt transmission of TB

The man is a middle-aged man with a mustache, wearing a dark suit, a light-colored shirt, and a patterned tie. He is standing behind a dark podium, looking directly at the camera.

The importance of TB case finding and diagnosis cannot be over emphasized. Their identification presumptive TB cases at the first point of care and linking them to the best available diagnostic test; it can be done and can be done by universal access to the early and accurate diagnosis of TB and enhancing the case finding efficiency. The early and

accurate diagnosis of TB once we achieve it; it will lead to good often of treatment and also interrupt the transmission of TB to the others in the community.

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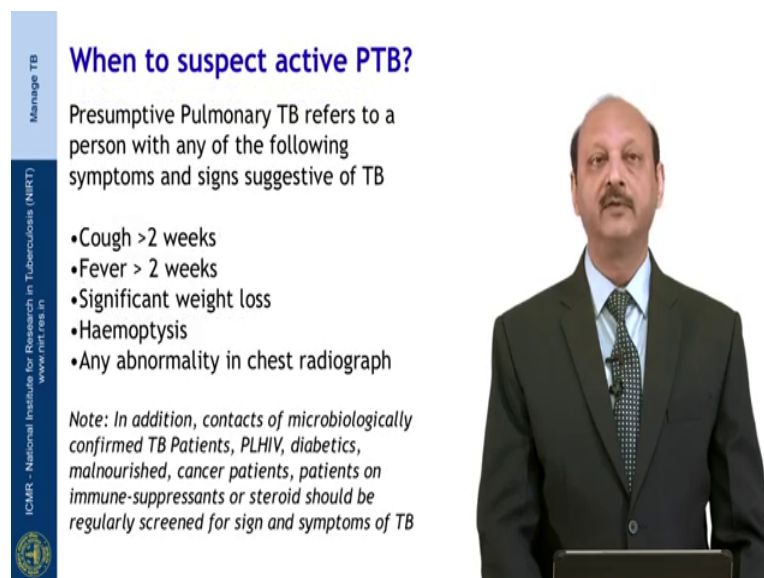
### Diagnosis of pulmonary TB

- Clinical evaluation
- Bacteriology
- Radiology
- Other methods



When we talk about diagnose pulmonary tuberculosis; always the initial thing is clinical evaluation, then bacteriology, radiology and other methods they come in to picture. .

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### When to suspect active PTB?

Presumptive Pulmonary TB refers to a person with any of the following symptoms and signs suggestive of TB

- Cough >2 weeks
- Fever > 2 weeks
- Significant weight loss
- Haemoptysis
- Any abnormality in chest radiograph

*Note: In addition, contacts of microbiologically confirmed TB Patients, PLHIV, diabetics, malnourished, cancer patients, patients on immune-suppressants or steroid should be regularly screened for sign and symptoms of TB*



First thing is when to suspect permanent tuberculosis? So, they are called presumptive pulmonary TB it refers to a person with any of the following symptoms and signs which suggestive of tuberculosis; which includes cough for more than 2 weeks, fever for more

than 2 weeks, significant weight loss, haemoptysis or any abnormality in the chest radiograph suggesting tuberculosis. In addition, we need to remember that contacts of microbiological confirmed TB patients, people living with HIV, diabetics, malnourished, cancer patients, patients on immunosuppressive drugs or steroids they should be regularly screened for symptoms and signs of tuberculosis.





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### Recommended diagnostic options for TB

- See the bacilli [smear microscopy]
- Grow the bacilli [Phenotypic methods eg. cultures]
- Use genetic information [Genotypic methods eg. NAATs]



Once you suspect tuberculosis the recommended diagnostic options for tuberculosis are that we see the bacteria; that is smear microscopy or we grow the bacteria called phenotypic like cultures or we use is the genetic information they are called genotypic methods.

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Tests endorsed by RNTCP		
<b>Sputum Smear Microscopy (for AFB)</b>	<b>Culture and Drug Sensitivity Testing (DST)</b>	<b>Rapid molecular diagnostics</b>
<ul style="list-style-type: none"><li>• Zeihl-Neelson Staining</li><li>• Fluorescence staining</li></ul>	<ul style="list-style-type: none"><li>• Solid (Lowenstein Jensen) media</li><li>• Automated Liquid culture systems e.g. BACTEC MGIT 960, BactiAlert or Versatrek etc.</li><li>• DST: Modified PST for MGIT 960 system (for both first and second line drugs)</li><li>• Economic variant of Proportion sensitivity testing (1%) using LJ medium (as a back up when indicated)</li></ul>	<ul style="list-style-type: none"><li>• Line Probe Assay for MTB complex and detection of RIF + INH resistance and resistance to second line drugs</li><li>• Xpert MTB/Rif testing using the GeneXpert system</li></ul>

The test which have been endorsed by our national program that is revised national TB control program include sputum smear microscopy for AFB that is zeihl-neelson staining and fluorescent staining.

The culture and DST include the solid that is Lowenstein Jensen media. The automated liquid culture system that is BACTEC MGIT 960 or Bactialert or Versatrek; the DST includes modified PST for MGIT 960 system for both first line drugs as well as second line drugs or we can use economic variant of proportion sensitivity testing that is 1 percent using LJ media as a backup whenever indicated.

Among the rapid molecular test we have line probe assay for MTB complex, which helps in the detection of resistance against INH plus RIF remphasin and also against resistance to the second line drugs. Then we have expert MTB Rif testing using the genexpert system.

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### Direct smear microscopy

- Technique of choice: simple, rapid, low cost, operational feasibility
- Differentiates active vs. healed TB
- Specificity: 96-99%

**Major Drawback:**

- Low sensitivity: can miss upto 50% cases  
(In cavitory lesion: high sensitivity)




Coming to the direct smear microscopy; it is a technique of choice because it is simple, it is rapid, has a low cost and operational feasibility. It differentiates between active and healed tuberculosis and the specificity is very high to the tune of 96 or 99 percent, but it has some drawbacks; it has a low sensitivity and can miss up to 50 percent of cases although in cavitory lesions, the sensitivity is very high it can go up to 80 or 90 percent.

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### WHO-endorsed strategy for optimized microscopy: fluorescence staining, LED microscope, two samples, read by a trained technician with EQA



**Public Health Action** International Union Against Tuberculosis and Lung Disease  
Health solutions for the poor

**LED-Fluorescence Microscopy for Diagnosis of Pulmonary Tuberculosis under Programmatic Conditions in India**

LED fluorescence microscopy increases the detection of smear positive pulmonary tuberculosis in medical colleges of India

**LED-FM pick up 20% more cases than conventional microscopy**

The WHO endorsed strategy for optimized microscopy includes fluorescent staining, LED microscope using 2 samples read by trained technician with the external quality

assurance. And it has been shown that led fluorescence microscopy it can pick up 20 percent more cases than the conventional microscopy.

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### Liquid cultures for PTB diagnosis

- “Gold Standard” and WHO-endorsed
- High Sensitivity
- Isolate Available for DST and molecular typing
- Ideal test for smear-negative and EPTB
- -2 week turn-around time **MGIT system**
- Very helpful for treatment monitoring

**Major disadvantage:**

- ✓ Can't wait for culture result to start treatment
- ✓ Require expertise and infrastructure



The liquid culture for the PTB diagnosis it is a gold standard and WHO endorsed, they have high sensitivity and the isolates are available for DST and molecular test typing as well and their ideal test for smear negative an extra-pulmonary tuberculosis.

However, they have 2 week turnaround time and they are very helpful in treatment monitoring also because you want to know whether the bacteria are dead or monitoring or not; however, they have some disadvantages that, most of the time treating position cannot wait for the cultural result to start the treatment and it can take 2 2 3 to 4 weeks and also the liquid culture they require expertise and infrastructure.




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### Genotypic Tests

- Detect genetic mutations linked with drug resistance
- Xpert MTB/RIF (CBNAAT)
- Line probe assay (LPA)
  - Genotype MTBDR Plus Assay (Hain's test)
- Results within 1-2 days
- Do not distinguish between live and dead bacilli



Coming to the genotypic test; they detect the genetic mutations which are linked with the drug resistance. And in this category we have export MTB RIF that is cartridge space, nucleic acid amplification called CBNAAT and line probe assay called LPA and the genotypic MTBDR plus assay is also called hain test and the results are available within 1 or 2 days but they do not distinguish between live and dead bacteria.


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### LPA (Genotype MTBDR Plus assay)

- Detects both H (*katG*, *inhA*) and R (*rpoB*) resistance
- Results available within 1-2 days
- Good sensitivity and specificity
  - RIF: Sensitivity: 98.1%; Specificity: 98.7%
  - INH: Sensitivity 84.3%; Specificity: 99.5%
- Limitations:
  - Lab. infrastructure and skilled personnel



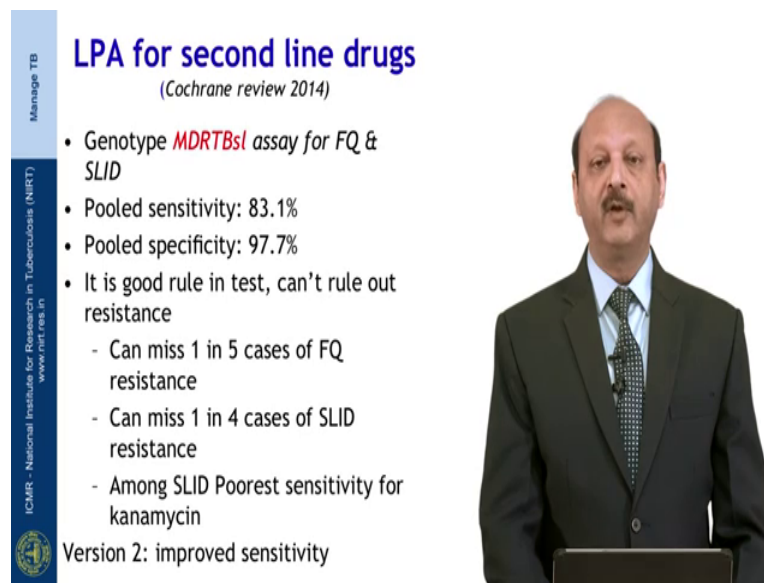
Coming to the LPA that is genotype MTBDR plus assay it detects both INH as well as RIF resistance INH based on the cardigan *inhA* mutations and RIF resistance based on



the rpoB gene mutations; the results of the available within 1 or 2 days the good sensitivity and good specificity, for rifampicin sensitive strains to the tune of 98 percent and specificity also almost 99 percent.

For INH this sensitivity was low to the tune of around 84 percent with a very high specificity almost reaching 99.5 percent, but the limitations are that the LPA it needs lab, infrastructure as well as skilled personnel.

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The slide features a vertical blue bar on the left with the text 'Manage TB' at the top, 'ICMR - National Institute for Research in Tuberculosis (NIRT)' in the middle, and 'www.nirt.res.in' at the bottom. The main title is 'LPA for second line drugs' in blue, with '(Cochrane review 2014)' in smaller text below it. The bullet points are: 'Genotype *MDR TBsI* assay for FQ & SLID', 'Pooled sensitivity: 83.1%', 'Pooled specificity: 97.7%', and 'It is good rule in test, can't rule out resistance'. Under the last point, there are three sub-points: '- Can miss 1 in 5 cases of FQ resistance', '- Can miss 1 in 4 cases of SLID resistance', and '- Among SLID poorest sensitivity for kanamycin'. At the bottom left of the slide content, it says 'Version 2: improved sensitivity'. On the right side of the slide, there is a photograph of a man in a dark suit and tie, standing behind a podium.

Then we also have a LPA for this second line drugs the cochrane reviews 2014; it showed that this LPA for second line drugs also called MDRTB second line assay for fluoroquinolones and second line injectable drug that pooled sensitivity of 83 percent and pooled specificity of almost 100 percent.

It is a good role in test, but cannot rule out the resistance; that means, in case LPA is tells it is resistance it is resistance, but if it says it is sensitive; it may not be sensitive. DLP can miss 1 and 5 cases of product non resistance, it can miss 1 in 4 cases of second line injectable resistance and among the second line ejectibles the poorest sensitivity is for the kanamycin. And there is version 2 now available in the market and our national program using version 2, it has improved sensitivity to the tune of up to 90 percent.

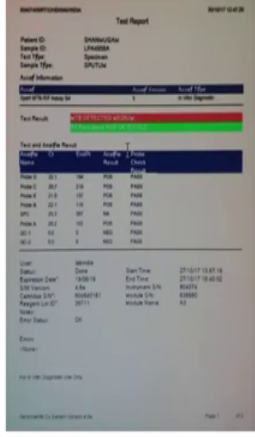

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### Xpert MTB/RIF (GeneXpert)

- Automated nested RT-PCR
- Simple 1-step specimen preparation
- Can be used at the point-of-treatment
- Results in 2 hours
- Detects TB and RIF resistance



>800 GeneXpert machines, all over India

The Xpert MTB RIF is also called GeneXpert it is a automated nested RT-PCR. It is a simple one test specimen preparation that can be used at the point of treatment that is wherever the treatment is being planned, it can be used there. The results are available within 2 hours and detects TB and RIF resistance, but does not tell us about the INH resistance.

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### How good is Xpert MTB/RIF for PTB diagnosis?

Cochrane review: Systematic review with 27 studies, 9558 participants

- Reference standard for detecting pulmonary TB was solid/liquid culture
- Reference standard for Rif resistance was phenotypic DST

**For S+ C+ TB**


- Pooled sensitivity: **98%**; Specificity **99%**

**For S- C+ TB**

- Pooled sensitivity: **68%**; Specificity **98%**

Used as an initial test replacing phenotypic DST, Xpert detected 95% of rifampicin-resistant TB cases with specificity of 98%

Steingart KR et al. Cochrane Database of Systematic Reviews, 2014

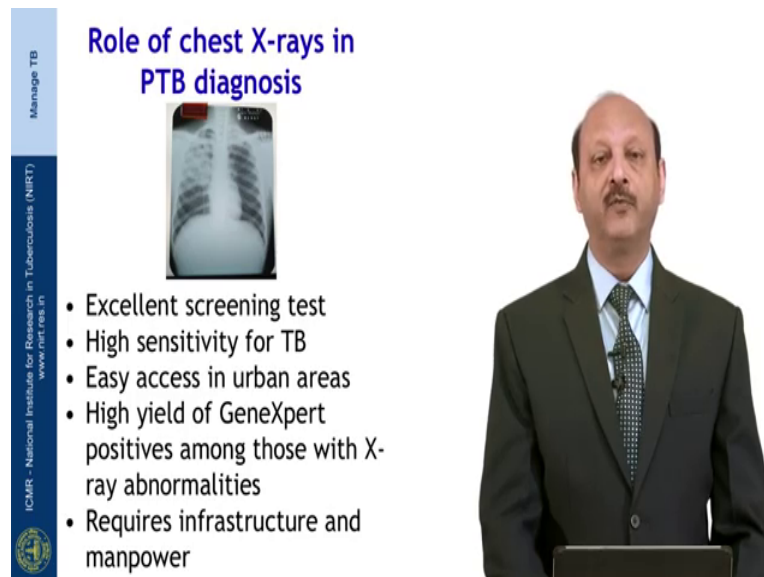


Then looking at the how good is GeneXpert for PTB diagnosis, a cochrane review including 27 studies and almost 9500 patients, it showed that using the reference

standard for detecting TB as a liquid culture. And reference standard for RIF resistance as a phenotypic DST for smear positive and culture plus tuberculosis the pooled sensitivity are 98 percent and specificity 99 percent.

Even amongst smear negative culture positive cases, the sensitivity was 68 percent specificity 98 percent. So; that means, even if person is sputum smear negative where LPA cannot be used it could detect up to 70 percent of patients and used as an initial test replace in phenotypic DST, Xpert detected 95 percent of rifampicin resistance TB cases with specificity of 98 percent.


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### Role of chest X-rays in PTB diagnosis

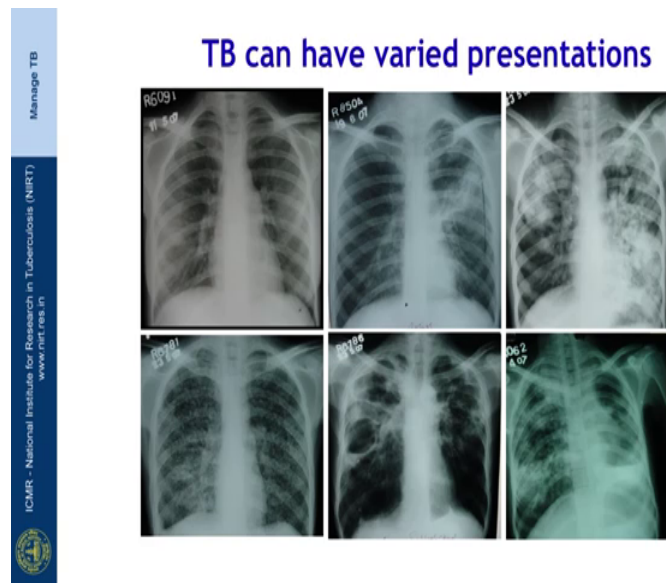


- Excellent screening test
- High sensitivity for TB
- Easy access in urban areas
- High yield of GeneXpert positives among those with X-ray abnormalities
- Requires infrastructure and manpower



Coming to the role of X-ray in the PTB diagnosis; it is an excellent screening tool it has a high sensitivity for the tuberculosis and has easy access in the urban areas. And among those with X-ray abnormalities the gene expert can have very high yield; however, as we all know it required infrastructure and manpower.

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And we know the TB can have varied presentation it can be minimum involvement, it can have consolidations, it can have bilateral (Refer Time: 09:34) consolidation with fibroses, it can have miliary shadows, it can have cavitary shadows, it can have also involve the pleura with (Refer Time: 09:42) and we all need to remember TB can be make anything and anything make tuberculosis.

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The slide is titled "RNTCP recommendation on chest X-ray" in blue text. It features a vertical sidebar on the left with the text "Manage TB" at the top, "ICMR - National Institute for Research in Tuberculosis (NIRT)" in the middle, and the ICMR logo at the bottom. The main content is a bulleted list of recommendations. To the right of the list is a photograph of a man in a dark suit and tie, standing behind a podium.

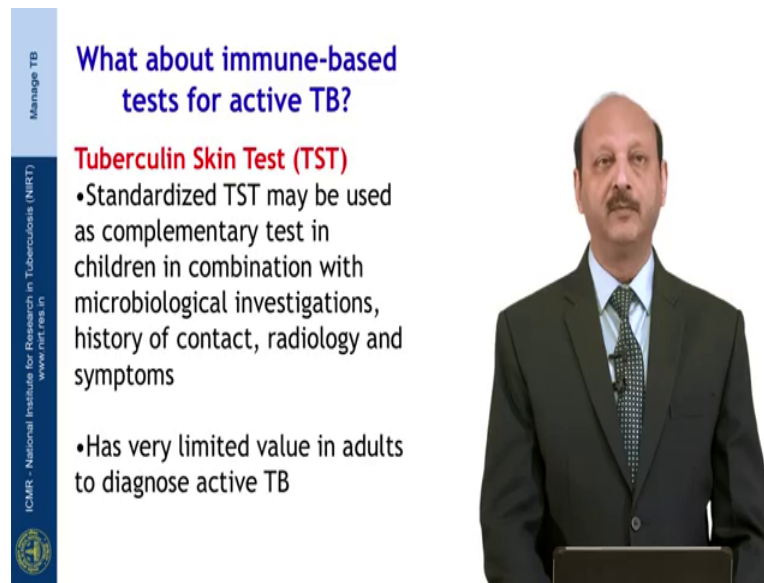
- Chest X-ray to be used as screening tool (to increase sensitivity of the diagnostic algorithm)
- Any abnormality in chest X-ray should further be evaluated for TB including microbiological confirmation
- **Diagnosis based ONLY on X-ray can result in significant over diagnosis and some underdiagnosis**
- In the absence of microbiological confirmation, careful clinical assessment for TB diagnosis should be done
- Diagnosis of TB based on X-ray will be termed as clinically diagnosed TB

The RNTCP recommendation on chest X-ray use are that the chest X-rays to be used as screening tool; to increase sensitivity of the diagnostic algorithm. And any abnormality

in chest X-ray should further be evaluated for TB including the microbiological confirmation. And diagnosis based only on the X-ray can result in significant over diagnosis and some amount of under diagnosis as well.

In the absence of microbiological confirmation, we require a careful clinical assessment for TB diagnosis and diagnosis of TB based on X-ray is labeled as clinically diagnose tuberculosis.

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### What about immune-based tests for active TB?

#### Tuberculin Skin Test (TST)

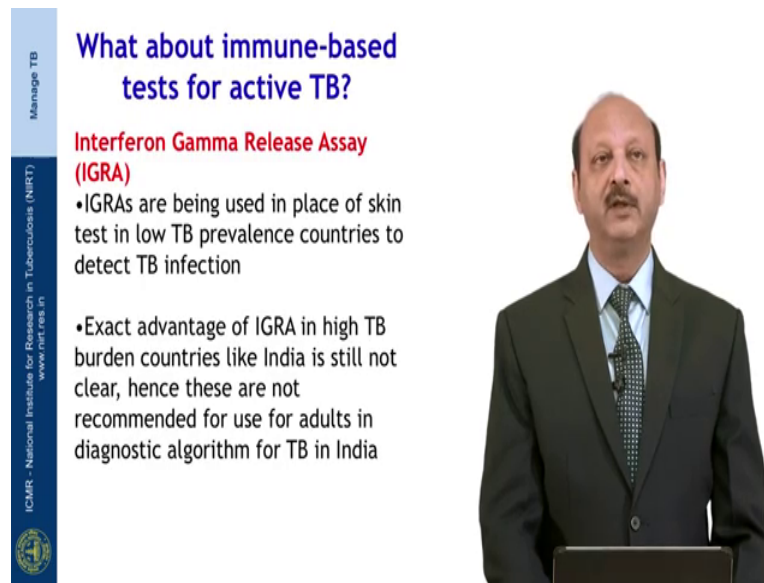
- Standardized TST may be used as complementary test in children in combination with microbiological investigations, history of contact, radiology and symptoms
- Has very limited value in adults to diagnose active TB

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What about the immunological based test for a active tuberculosis? First coming to the tuberculin skin test also called as TST. In children this standardized TST may be used as a complementary test in combination with microbiological investigations, history of contact, radiology and other symptoms by it is limited value in adults to diagnose active tuberculosis.

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**What about immune-based tests for active TB?**

**Interferon Gamma Release Assay (IGRA)**

- IGRAs are being used in place of skin test in low TB prevalence countries to detect TB infection
- Exact advantage of IGRA in high TB burden countries like India is still not clear, hence these are not recommended for use for adults in diagnostic algorithm for TB in India

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Talking about the interferon gamma release assay is called IGRAs they are being used in place of skin test in low TB progress countries to detect TB infection not the disease is an exact advantage of IGRAs in high TB burden countries like our country. It is still not clear and hence these are not recommended for use for adults in diagnostic algorithm for TB in India.

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**Serological tests are banned for TB diagnosis**

- The Government of India issued Gazette notification (vide 433E, 7<sup>th</sup> June 2012) and banned the manufacture, importation, distribution and use of currently available commercial serological tests for diagnosing TB



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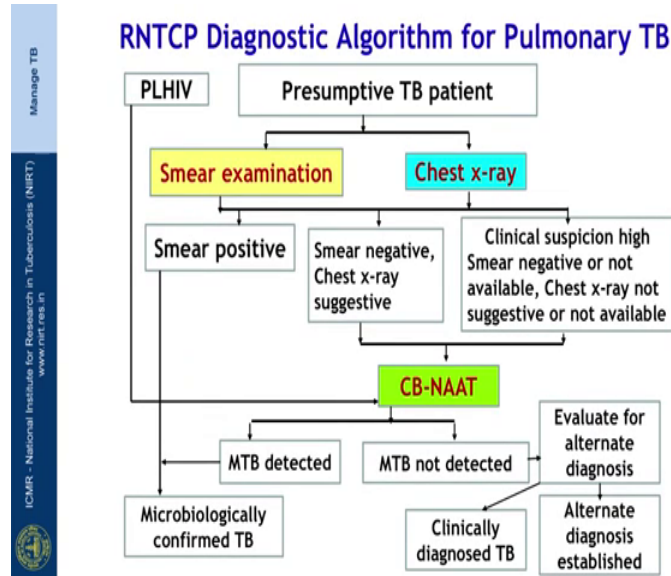
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And in India the serological test are banned for TB diagnosis in 2012 the Government of India released a gazette notification where they banned the manufacture, importation,

distribution and use of currently available commercial serological test for diagnosis of tuberculosis.

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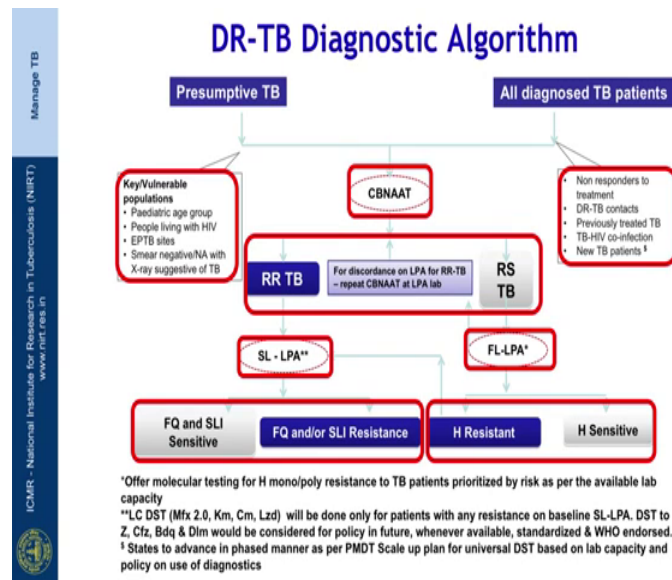


Coming to the RNTCP our national program diagnostic algorithm for pulmonary tuberculosis; first step is the whenever we suspect tuberculosis on clinical ground that is called presumptive TB patient; we offer smear examination and chest X-ray whenever it is a variable. If the smear shows smear positive this patient is labeled as microbiologically confirm tuberculosis.

If smear is negative or the chest X-ray suggestive tuberculosis or another scenario technical suspicion is high, but smear is negative or not available and chest X-ray is not suggestive or is not available then they are offered the CB-NAAT. In people living with HIV then they are offered the CB-NAAT examination up front, after CB-NAAT either we can have MTB detected again the diagnosis microbiologically confirmed tuberculosis in case MTB is not detected these patients are offered other test and where were for alternative diagnosis. After these test we can have clinically diagnosed tuberculosis or we can have alternative diagnosis established.



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Coming to the algorithm diagnostic algorithm for drug resistance tuberculosis so one is the presumptive pulmonary tuberculosis cases where we offered the CB-NAAT upfront or we have clinically the all the diagnosis case tuberculosis. Among presumptive TB cases like paediatric age group, the people living with HIV or we have extra pulmonary tuberculosis or EPTB cases in these cases upfront CB-NAAT is offered or in other cases where the TB has been diagnosed.

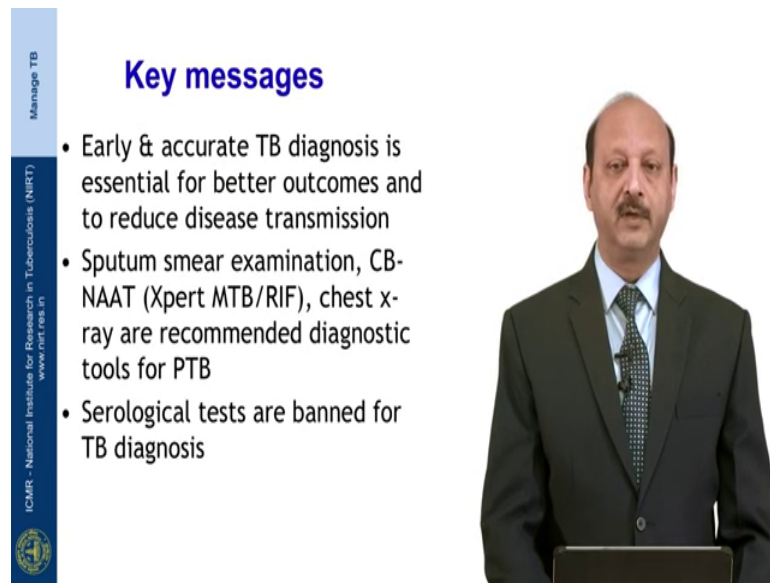
But these cases belong to the category of either they are DRTB contacts, they are previously treated TB cases, they are TB HIV cases or they are not responds to the TB treatment that is the fall of sputum positives. And sometimes the new TB patients which are in the higher scale of the PMDT implementation they can also be offered CB-NAAT upfront.

Once the CB-NAAT report is available we have either rifresistance tuberculosis or we can have rifsensitive tuberculosis and whenever there is a mismatch between the CB-NAAT and the LPA the repeat CB-NAAT is to be done. So, after the RIF resistance TB cases is diagnosed then we do the second line LPA test and is second line LPA test shows fluoroquinolones and or second line rejectible sensitive. Then we can further do the resistance pattern against injectables that is kanamycin and capreomycin and (Refer Time: 15:05) and in case the FQS and the SLI's are sensitive they may be offered short

MDR-TB regimen; however, in case you find resistance to the fluoroquinolones or second injectable resistance then DST guided treatment is to be offered to them.

On the other hand, suppose it is found to be rif-sensitive tuberculosis on CB-NAAT examination then we do the LPA. If LPA tells us it is H-resistant they are offered treatment for INH resistance cases and in case H is sensitive they are given standardized treatment for the new smear positive cases in the country.

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### Key messages

- Early & accurate TB diagnosis is essential for better outcomes and to reduce disease transmission
- Sputum smear examination, CB-NAAT (Xpert MTB/RIF), chest x-ray are recommended diagnostic tools for PTB
- Serological tests are banned for TB diagnosis

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So, dear friends the key messages for diagnostic algorithm for tuberculosis are been must keep in mind that early and accurate TB diagnosis is essential for better outcomes and to reduce disease transmission in the community. Sputum smear examinations, the CB-NAAT that is expert MTB RIF and chest X-ray are recommended diagnostic tools for pulmonary tuberculosis and serological tests are banned for TB diagnosis.

Thank you very much.