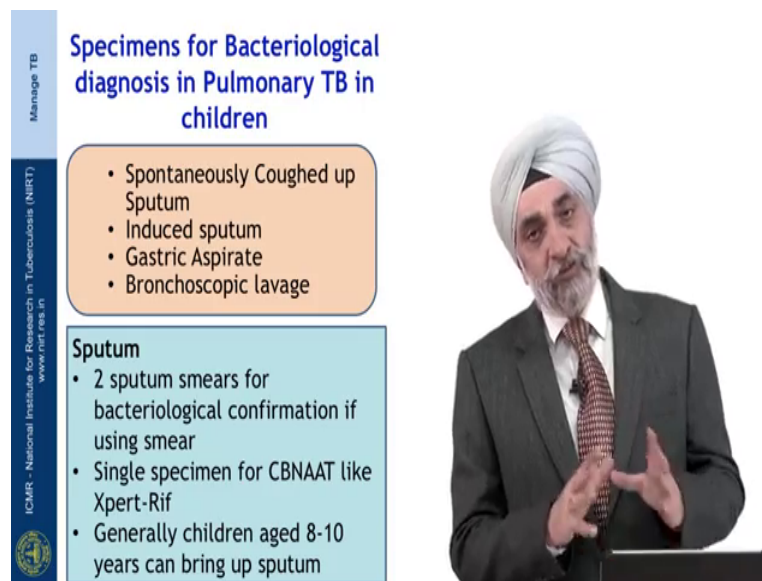


Manage TB
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Lecture – 27
Diagnosis of Childhood Tuberculosis
Session 02

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Specimens for Bacteriological diagnosis in Pulmonary TB in children

- Spontaneously Coughed up Sputum
- Induced sputum
- Gastric Aspirate
- Bronchoscopic lavage

Sputum

- 2 sputum smears for bacteriological confirmation if using smear
- Single specimen for CBNAAT like Xpert-Rif
- Generally children aged 8-10 years can bring up sputum

So, we understood the algorithm it is equally important for us to understand the specimens for diagnosis, why is it important? In an adult it is easy to combine because they can voluntarily give you sputum, children cannot. One, they may not produce sputum at all; two even if they do produce sputum they are not able to expectorate at will.

And young children cannot even be told to expectorate or throw ups sputum out, they tend to swallow it. And that makes the specimen learning about specimen in childhood TB more important. So, as I said you could have a spontaneously coughed up sputum which is good to combine an older child say above 7, 8 or 9 years of age or you could have a child at any age; who is just having dry cough you could induce his sputum and we learn about it how we do it. Or you could have a situation where child is just not bringing up that sputum and you could use alternatively gastric aspirate.

I will explain to you why gastric aspirate is important and rarely like I said for persistent pneumonias, where you refer this child to an expert you may have to record to bronchoscopic lavage; this is not what we use routinely.

For sputum you need 2 sub specimen; if it is for smear and if it is CBNAAT; a single specimen is needed generally children up to 8 to 10 years can bring up sputum.

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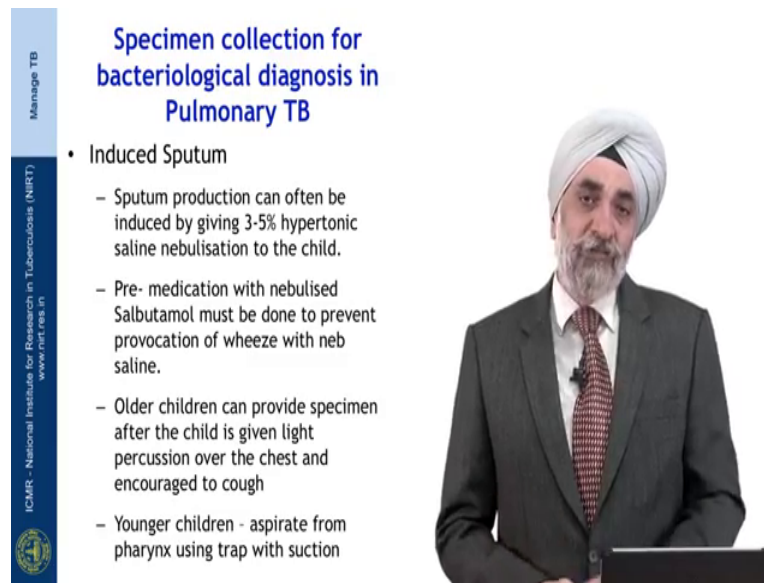


The slide features a blue vertical header on the left with the text 'Manage TB' and 'ICMR - National Institute for Research in Tuberculosis (NIRT) www.nirt.res.in'. The main title is 'Gastric aspirate for Bacteriological confirmation'. Below the title is a bulleted list: '• Gastric aspiration (GA) - technique used to collect gastric contents to confirm TB diagnosis as children children unable to expectorate sputum may swallow it.', '• Swallowed sputum contains M. tb and can be retrieved from the stomach as GA', and '• Gastric aspiration is performed after at least 4 hours of fasting (3 hours for infant) on 2 consecutive mornings to be performed'. A small WHO reference 'WHO/HTM/TB/2006.371' is at the bottom left. A speaker overlay of a man in a grey turban and suit is on the right side of the slide.

What is gastric aspirate? Gastric aspirate is a technique which is used to collect gastric contents to confirm TB diagnosis, as children often are unable to expectorate sputum and they tend to swallow it. Once they swallowed it; that swallowed sputum which may contain M. tb can be retrieved from the stomach content because it stays there for right, but it will stay there if only this child remains fasting.

That means, a gastric aspiration is always performed after some period of fasting which we say it is about 4 hour to 6 hours in an older child. And you in an infant perhaps you will not be able to keep them fasting longer than 3 hours and; it is performed on 2 consecutive mornings if you are looking at smear and a single if you have CBNAAT available.

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Specimen collection for bacteriological diagnosis in Pulmonary TB

- Induced Sputum
 - Sputum production can often be induced by giving 3-5% hypertonic saline nebulisation to the child.
 - Pre- medication with nebulised Salbutamol must be done to prevent provocation of wheeze with neb saline.
 - Older children can provide specimen after the child is given light percussion over the chest and encouraged to cough
 - Younger children - aspirate from pharynx using trap with suction



Induced sputum is an alternative therapy which is alternative method of collecting the specimen which is there. Sputum production can often be induced by giving 3 to 5 percent hypertonic saline. So, you nebulize 3 to 5 percent hypertonic saline and child expectorates that sputum there after once it is induced. Since hypertonic saline sometimes can cause wheeze it is important that we premedicate this child with nebulized salbutamol.

So, you first give a course of salbutamol, followed by 3 to 5 percent hypertonic saline. So, you give one dose and thereafter you give 3 to 5 percent hypertonic saline to the patient. This older child after inducing sputum may be able to provide this specimen at you know by you give light percussion after inducing sputum and ask the child to expectorant they are able to throw up.

But in a younger child who does not understand these instructions, this will be again swallowed and what you can do is in that situation we can attach a mucus trap to wall suction and put that through the nose into the nasal pharynx; when it tickles in nasal pharynx the child it will provoke cough and that induced sputum which has been loosened by percussion by use chest percussion would come up. And because of the suction it will be trapped into the mucus trap before the child is able to swallow it and that is a nasopharyngeal collection of the deep respiratory sputum which has been induced by giving hypertonic saline and that is why it is called induced sputum.

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Specimen collection for bacteriological diagnosis in Pulmonary TB

REMEMBER

- Sputum induction is an aerosol generating procedure
 - Adequate infection control precautions have to be ensured
- Children with the following characteristics should not undergo sputum induction:
 - Severe respiratory distress
 - Reduced level of consciousness
 - Intubation
 - Bleeding
 - Current acute asthma

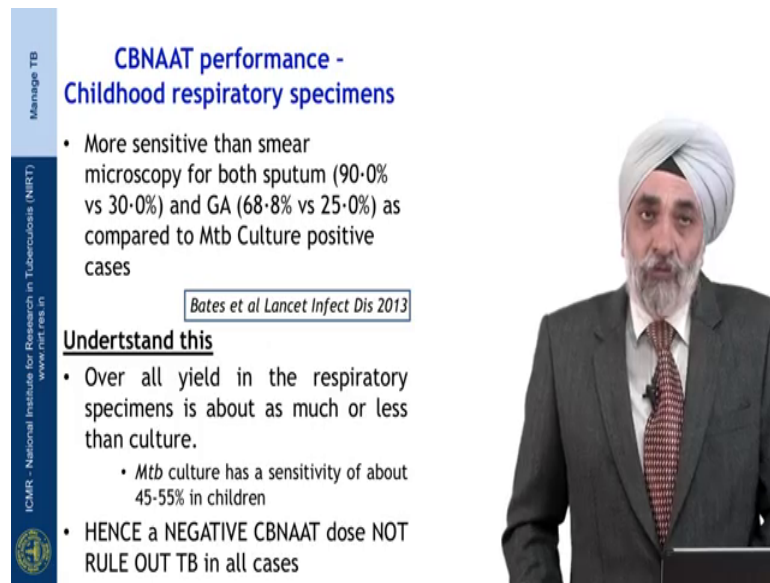


So, these are important ways we can collect the sputum what is important to remember is sputum induction is an aerosol generating procedure in a potentially infected child.

And therefore, for the safety of the health worker it is important that adequate infection control precautions are ensured; some of these there should be a negative pressure, there should be a N 95 mask which is used. So, that there is enough safety for the health worker in there.

What is also important is that if this child is having severe respiratory distress or has a low level of consciousness or has is intubated or is bleeding or in his current wheezing, then inducing sputum may not be a good idea because their distress may increase. So, with these caveats it is possible to use induced sputum in younger children who are not able to expectorate or give you sputum directly.

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CBNAAT performance - Childhood respiratory specimens

- More sensitive than smear microscopy for both sputum (90.0% vs 30.0%) and GA (68.8% vs 25.0%) as compared to Mtb Culture positive cases

Bates et al Lancet Infect Dis 2013

Understand this

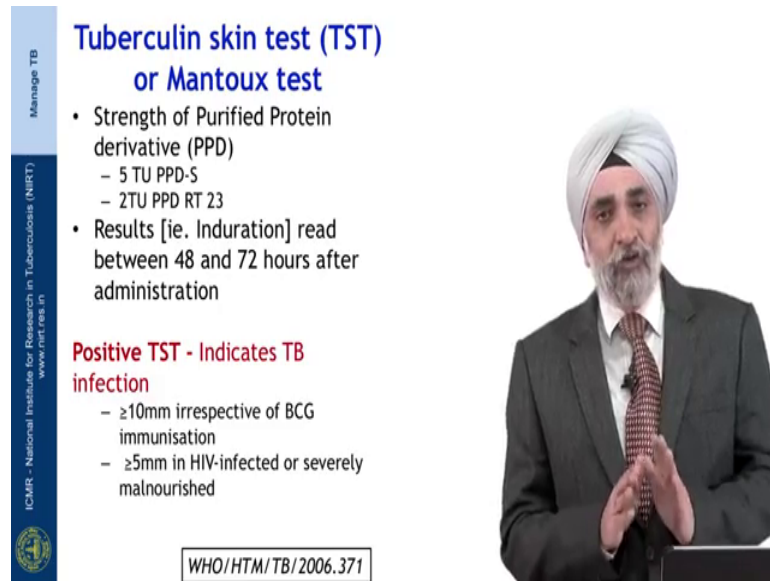
- Over all yield in the respiratory specimens is about as much or less than culture.
 - Mtb culture has a sensitivity of about 45-55% in children
- HENCE a NEGATIVE CBNAAT dose NOT RULE OUT TB in all cases

Now, once you have collected this sputum; the other difficulty we always had in children was that because it is a paucibacillary disease; it is a primary disease this smear positivity was very poor. Smear positive range about 10 to 15 percent in pediatric TB which in younger children; in older adolescent it may be about 40 percent.

So, as a thumb rule the whenever you have a paucibacillary disease the yield is less, but this is increased tremendously by use of CBNAAT. And these are many studies which have shown that a CBNAAT can pick almost as two third or as much as a culture a from respiratory specimen and there are enough to do that. But having said that it is very important to tell here at this point of time the culture positivity in pediatric TB is not more than 50 percent.

So, understand this very clearly overall yield in the respiratory specimen is less than culture or equal to culture with gene xpert, but which is about 50 percent overall which means a negative CBNAAT does not rule out TB. So, it is a good ruling test, but it is not a very good rule of test that is something important to remember. Because are you know looking up for a test which is very effective in children still continues despite the improvement provided by CBNAAT.

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Tuberculin skin test (TST) or Mantoux test

- Strength of Purified Protein derivative (PPD)
 - 5 TU PPD-S
 - 2TU PPD RT 23
- Results [ie. Induration] read between 48 and 72 hours after administration

Positive TST - Indicates TB infection

- ≥ 10 mm irrespective of BCG immunisation
- ≥ 5 mm in HIV-infected or severely malnourished

WHO/HTM/TB/2006.371



Let me now change that and talk about the third test which I introduced to you in the algorithm and that is the tuberculin skin test or mantoux. Now tuberculin skin test again what strength you use? If you will read the western textbook most textbooks say for 5 TU;, but what is important to remember is they say 5 TU of PPD-S.

PPD-S is not something which is available in our country; what is available to us is PPD RT 23; an equal dose of PPD RT 23; to a 5 TU of PPD-S is 2 TU. So, therefore, what you need is 2 to tuberculin unit of PPD RT 23 forgoing this test that is something very important to remember because 5 TU PPD RT 23 is much higher dose right.

So, having know that you give it I will just show you the method of giving PPD remember; what you read it is you read the induration and a positive test which is considered positive when it is more than 10 millimeter just indicates TB infection it does not indicate a presence of TB disease. This is how you give TT PPD test or to between skin test also called as a mantoux test.

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You would need to give it intra dermal making an angle of about 50 percent or in the skin and you are able to raise a wheel of about 6 millimeter ok. Once you have raised that wheel you take out this 26 gauge needle and this child comes back to you after 48 to 72 hours and you read the induration and not the rhythm; that means, you do heat the hardness of skin; which can be sometimes as raised and as dramatic as this, but in malnourished children can be better felt than seen.

So, induration is what you measure in children after giving tuberculin and a positive test is 10 millimeter.

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Causes of false negative and false positive TST

False negative TST	False positive TST
Incorrect administration or interpretation of test	Incorrect interpretation of test
Improper storage of tuberculin	Infection with Non-Tuberculous mycobacteria
HIV infection	
Viral infections (e.g. measles, varicella)	
Vaccinated with live viral vaccines (within 6 weeks)	
Malnutrition	
Bacterial infections (e.g. typhoid, leprosy, pertussis)	
Immunosuppressive medications (e.g. corticosteroids)	
Neonatal patient	
Primary immunodeficiencies	
Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukaemia, sarcoidosis)	
Low protein states	
Severe TB	

WHO/HTM/TB/2006.371

You could have several situations where you could have a false negative tuberculin skin test even in an infected child. One of the commonest reason being incorrect administration or could be an improper storage of tuberculin or it could be because of any immune deficiency which could be either HIV or a primary immunodeficiencies or use of immunosuppressive drugs or are severe malnutrition.

Severe disease bacterial viral or micro bacterial can also give rise to false negative tuberculin skin disease; this tuberculin skin test. You could have a false positive test one because of incorrect interpretation; if we read arrhythmia which may sometimes be more than the induration or because of the infection by the non tuberculosis mycobacteria.

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Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	FNAC/ Lymph node biopsy, Aspirate for CBNAAT
Miliary TB (e.g. disseminated)	Chest X-ray and lumbar puncture (to test for meningitis)
TB meningitis	CSF analysis including CBNAAT and Neuroimaging (CECT)
Pleural effusion (older children and adolescents)	Chest X-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	X-ray / Ultrasound

(WHO/HTM/TB/2014.03)

This is how; what we what are the tests which are used for pulmonary TB. Now, quickly let me take you through with the other tests which are specific or specific investigations for diagnosis of extra pulmonary TB. So, for extra pulmonary TB like peripheral lymphadenopathy; tubercular lymph adenopathy what you need is a fine needle aspiration psychology which is seen by a pathologist or you could do a lymph node biopsy, if your psychopathology does not give you the answer.

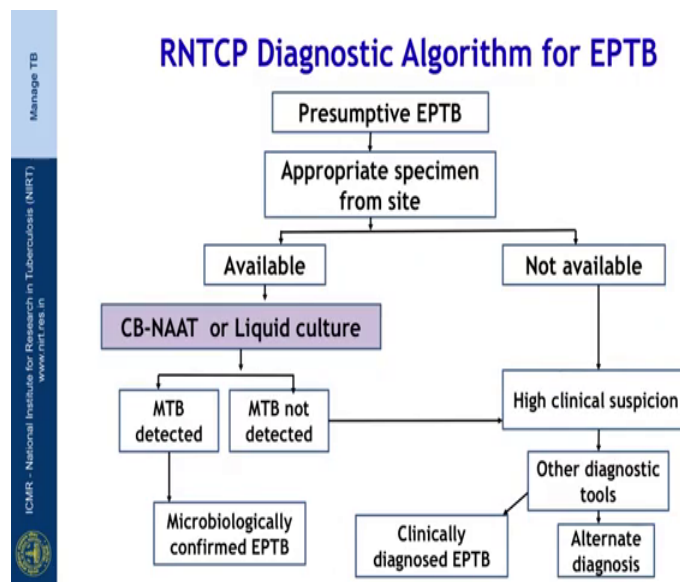
However a very important test which can be done on this aspirate is either a smear or CBNAAT and as I all as I said in the past also CBNAAT gives you much better sensitivity. So, remember if you aspirate pass or cell sap from or lymph node; this is a very good material which can be used for a microbiological diagnosis also. So, if you are in a smaller place where a trained histopathology just may not be available, a cytopathologist may not be available you can still do aspiration and send that for microbiological diagnosis which cause a very good yield for peripheral lymphadenopathy.

Miliary TB again we because it rest of the thing it are just like pulmonary TB, but because it is miliary it spread, disseminated all over body you may like to do a CSF to pick up in early meningitis. Pleural effusion is something else which was comes in TB as a manifestation of TB in children.

This is where you would need to do a pleural tap to differentiate from other causes of global effusion in children which can be bacterial not always micro bacterial. And what helps you here is the biochemical tests that it is an exudates, which is more than 3 gram proteins and it has usually lymphocytic cells and it is usually not pus cultures may help.

However, CBNAAT is something which is very poor yield for pleural TB for abdominal TB abdominal ultrasound, ascitic tap may be useful when there is (Refer Time: 11:15); for osteoarticular again appropriate biological specimen like joint tap synovial biopsy may be used. For pericardial again you could do you do a pericardial tap and you pick them up by bioradio measure.

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So, for algorithm when it comes to accept pulmonary TB, it is about collecting an appropriate specimen from the site which may not always be available, but if it is available; you subject that to microbiology through CBNAAT or liquid culture depending on this what is available to you one any one of these 2.

It would either detect an MTB or not if it detects it gives you a confirmed diagnosis which will be in a relatively small proportion. A larger proportion 50 to 60 percent sometimes even higher would be where you would not be able to detect MTB; in those gateway situations it does not rule out TB if you still have a high clinical suspicion. You do other diagnostic tools as I said I referred to some of them in the previous; slide and then make a clinically diagnosed EPTB.

And remember imaging like neuroimaging for TBM looking at the biochemistry and cytology for effusions may be supportive or the other diagnostic tools which may help you to make a diagnosis of EPTB or they may confirm an alternative diagnoses.

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Diagnosis of EPTB using Xpert MTB/RIF
(INDEX -TB guidelines, 2016)

Type of EPTB	Recommendation
Lymph node TB	✓ Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture and cytology in FNAC specimens. <i>(Strong recommendation)</i>
Meningeal TB	<ul style="list-style-type: none"> ✓ Xpert MTB/RIF may be used as an adjunctive test ✓ A negative Xpert MTB/RIF result on CSF does not rule out TBM ✓ The decision to treat for TB should be based on clinical features & CSF profile <i>(Conditional recommendation)</i>
Pleural TB	✓ Xpert MTB/RIF should not be routinely used to diagnose pleural TB. <i>(Strong recommendation)</i>

low quality evidence for sensitivity estimate, high quality evidence for specificity estimate

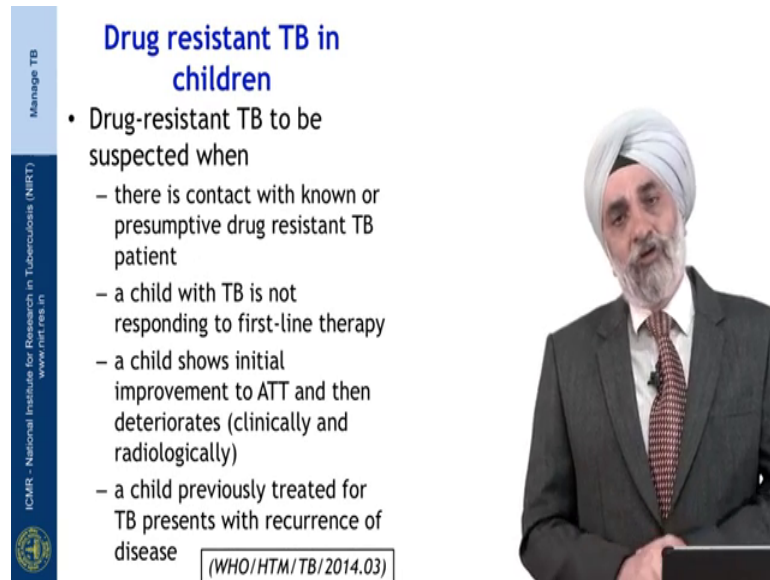
The index TB guidelines from our country they I have they have made very strong recommendations about usage of these tests based on the currently available evidence. For lymph node TB they strongly recommend using expert TB as an additional test; in addition to FNAC or if FNAC not available; this can be used as a sole test. For meningeal again expert TB can be an adjunctive test; however, here CSF and neuroimaging play a very important role.

Because it is a very serious illness you need an early diagnosis and CBNAAT may not come positive in about 60 pursuant of case equation therefore, you would use this as an adjunctive test and not the sole test. But it is an important test to do anyway because you will get a confirmation in about 45; 40, 50 percent cases. Pleural TB is where expert TB does not help you; CBNAAT does not help you that is where you would need alternative diagnosis methods.

One of the methods recommended is ADA or adenosine deaminase levels; however, these are not a good distinct for pediatric cases; they may be good distinct are in adults where your differential is a malignancy, but in children usually the differential diagnosis

for a pleural effusion is other infections, which are not very clearly delineated by ADA and therefore, it is not recommended for pediatric meningeal TB.

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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 (NIIRT)' in the middle, and 'www.nirt.res.in' at the bottom. The main title is 'Drug resistant TB in children'. The content includes a bulleted list of criteria for suspecting drug-resistant TB in children, a citation '(WHO/HTM/TB/2014.03)', and a photograph of a man in a grey suit and white turban speaking.

Drug resistant TB in children

- Drug-resistant TB to be suspected when
 - there is contact with known or presumptive drug resistant TB patient
 - a child with TB is not responding to first-line therapy
 - a child shows initial improvement to ATT and then deteriorates (clinically and radiologically)
 - a child previously treated for TB presents with recurrence of disease

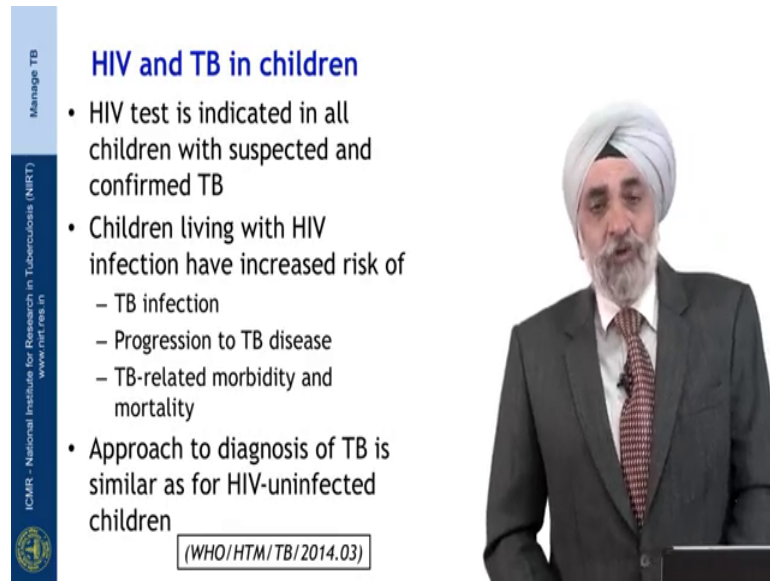
(WHO/HTM/TB/2014.03)

So, far we talked about drug sensitive TB, but we need to quickly also remember about when to suspect drug resistant TB where you would need a bigger effort to get a microbiological diagnosis.

The drug resistance TB should be suspected when the contact; there is a known contact with a presumptive or a known or confirmed case of drug resistant TB by with in this patient. Or if this child is not responding to the first line therapy if there is a failure to therapy or this child shows an initial improvement, but then starts deteriorating clinically as well as radiological he becomes a suspect or DRTB suspect.

So, remember somebody who has been exposed to a case with MDR TB or likely MDR TB or patient who does not respond to first line therapy or a patient who shows initial or a partial response and then deteriorates; are these situations where you should keep a possibility of DRTB as a strong alternative. And this is where you would start looking for a microbiological verification or presence of drug resistance.

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HIV and TB in children

- HIV test is indicated in all children with suspected and confirmed TB
- Children living with HIV infection have increased risk of
 - TB infection
 - Progression to TB disease
 - TB-related morbidity and mortality
- Approach to diagnosis of TB is similar as for HIV-uninfected children

(WHO/HTM/TB/2014.03)

The other comorbidity which should be identified and talked of is HIV TB in children. HIV test is indicated and that is the national policy in all children with suspected and confirmed TB.

Children living with HIV have a higher risk of having TB infection and have higher risk of progressing from infection to TB disease. And therefore, have a higher TB related morbidity and mortality and therefore, one must look at TB as a comorbidity in children who have HIV disease. Approach to diagnosis of TB remains quite similar to the; what I showed to you earlier.

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Key messages

- Diagnosis of TB in children is challenging
- Early diagnosis is important, especially in meningitis
- Efforts should be made for microbiological confirmation
- Xpert MTB/RIF has significantly improved the prospect of TB diagnosis in children
- In the absence of bacteriological confirmation, X-ray, ultrasound, CT and MRI may be helpful

So, what are the key messages at the end of my talk? I would say diagnosis of TB in children is challenging because microbiological diagnosis is not possible in all; where even it is possible the excess to specimen is difficult. While you need a early diagnosis because there can be serious involvement like CNS involvement or meningitis. We should always make an effort for microbiological confirmation even in pediatric TB; though you yield is lesser than adults. Xpert MTB or gene expert or CBNAAT has significantly improved the prospect of TB diagnosis in children.

And therefore, this should be used as early as possible depending on the facilities available to you, but this should be guided to you by presence of a lesion. So, when you have a presumptive case who has an X-ray suggestive; highly suggestive or an X-ray which was not highly suggestive, but has no response to antibiotic, in all this situation when you collect a respiratory specimen you should use CBNAAT as an important test for making diagnosis in children.

However, remember CBNAAT will not always be possible and you would have to make a diagnosis in the absence of bacteriological confirmation using other techniques like X-ray ultrasound CT and MRI which may be useful depending on the type of environment. Thank you so, much for your kind attention I hope you; I was able to describe the diagnosis of childhood TB to you well.

Thank you.