Approach to Diagnosis of Tuberculosis in Children

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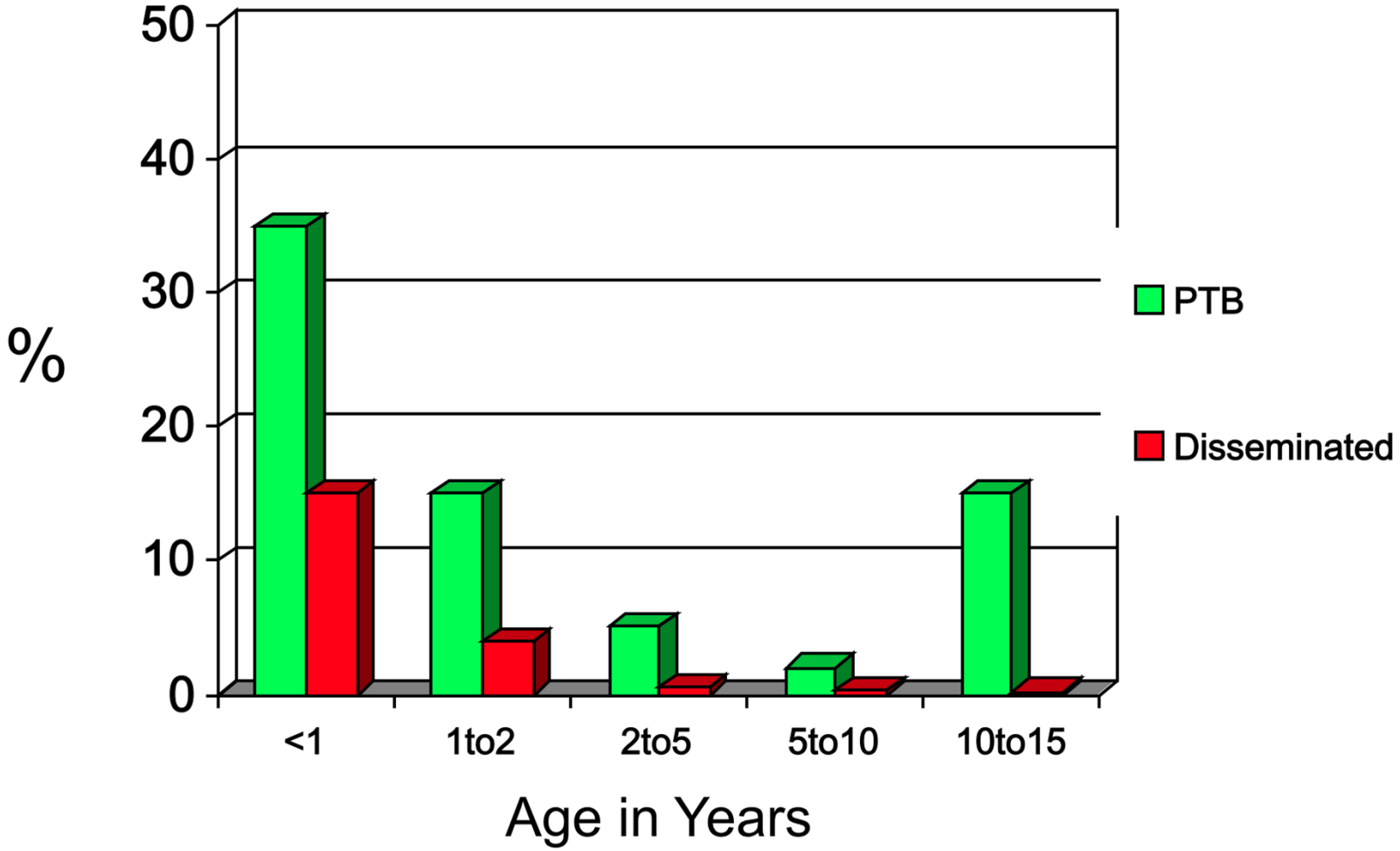
Objectives

- To discuss current approaches in the diagnosis of tuberculosis in children as per WHO/NTP protocol.
- To highlight differences in the current approach with previous TB diagnostic approaches.
- To emphasize the importance of proper diagnosis to facilitate treatment and cure of tuberculosis.

- Diagnosis of TB refers to the recognition of an active case of TB disease, i.e. a patient with current disease due to M. tuberculosis.

- Early diagnosis reduces morbidity and mortality and is critical in high-risk patients

Risk of TB disease following infection by age

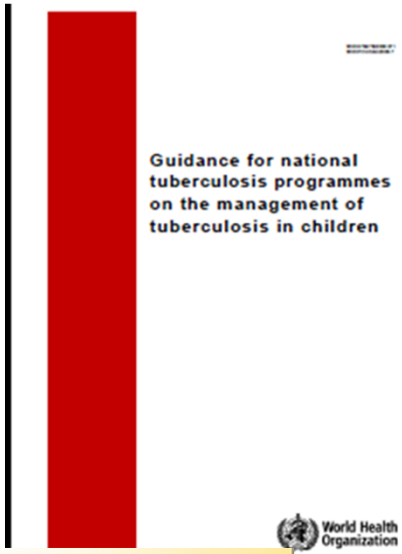


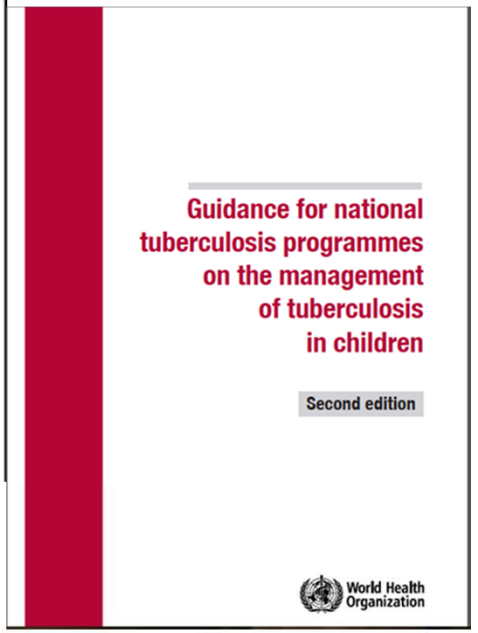
Adapted from Marais B, et al. Int J Tuberc Lung Dis 2004

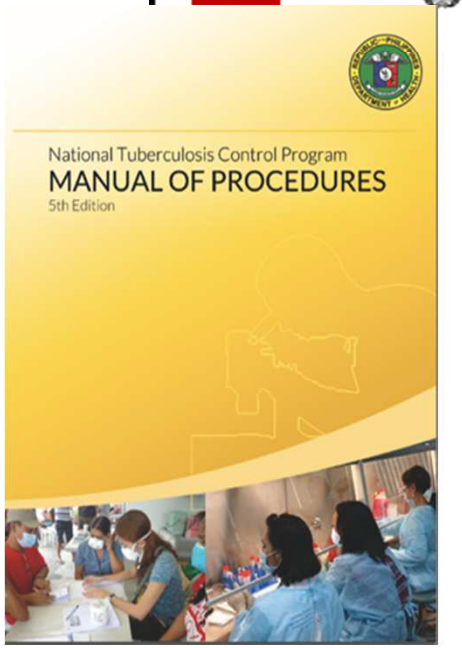
References

- *Guidance for national tuberculosis programmes on the management of tuberculosis in children, (2006 & 2014)*

- *NTP Manual of Procedures (2013)*







Recent Improvement in Diagnostics: Xpert MTB/RIF

- Automated amplification of MTB DNA
- Detects MTB & rifampicin resistance
- Test procedures take 2 hours
- Endorsed in 2010 by WHO

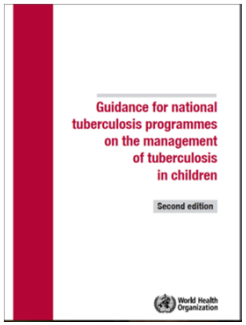
WHO recommendations for Xpert MTB/RIF

1. For diagnosis of pulmonary TB and rifampicin resistance in children

2. For diagnosis of extra-pulmonary TB in children.

- especially in severely ill children when rapid diagnosis is crucial.

- a negative Xpert MTB/RIF result does not exclude TB in children and a clinical decision should be made in all such cases.



WHO recommendations

Xpert MTB/RIF for diagnosis of pulmonary TB and rifampicin resistance in children

Recommendation 1

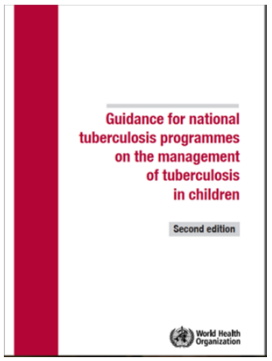
- Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

  (Strong recommendation, very low quality of evidence)

Recommendation 2

- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

  (Conditional recommendation acknowledging resource implications, very low quality of evidence)



WHO recommendations
Xpert MTB/RIF for diagnosis of EPTB in children

Recommendation 3

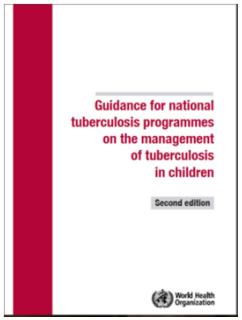
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having EPTB

  (Conditional recommendation, very low quality of evidence)

Recommendation 4

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis

  (Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)



Recommendations for Serodiagnosis

Recommendation 5

- IGRAs should not replace TST in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children suspected of TB disease in these settings

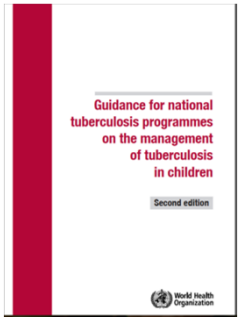
  (Strong recommendation, low quality of evidence)

- In 2011, WHO published recommendations against the use of commercial serodiagnostics, and included specific policy to discourage the use of IGRAs in low- and middle-income setting, including in children

Recommendation 6

- Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status

  (Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)



Recommendation for HIV Test

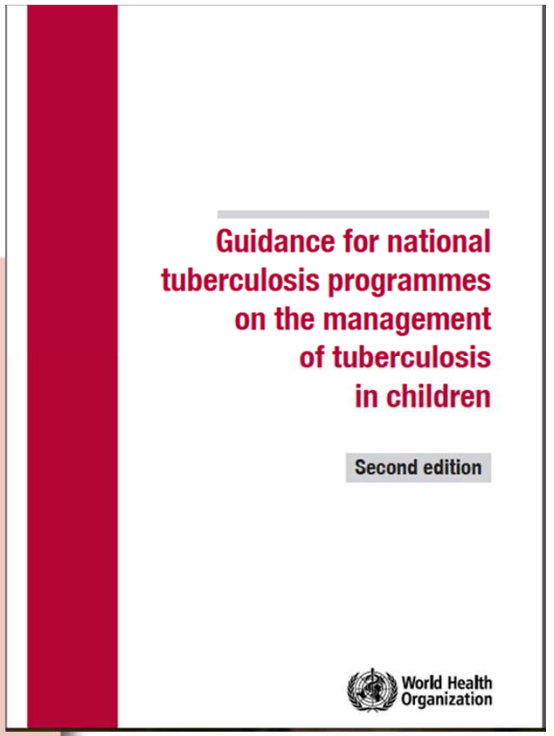
Recommendation 7 (This recommendation has not changed from the 2006 edition.)

- Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB

  (Strong recommendation, low quality of evidence.)

Box 1. **Guidance on approach to diagnosis of TB in children**

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin testing
- Chest X-ray (if available)
- Bacteriological confirmation whenever possible
- Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
- HIV testing



Careful History

1. **Contact**
   - Infants and young children are likely to have contracted TB at home.
   - Contact with the source case is usually recent because children who develop TB usually do so within 1 year following exposure and infection.
   - Evaluate the child who has been in close contact with a TB case
   - Find the source of infection

2. **Symptoms**
   - chronic unremitting symptoms
   - Cough, fever, poor appetite, weight loss or failure to thrive, fatigue, reduced playfulness, decreased activity
   - Check child's growth chart
   - Other or additional symptoms will be present in various forms of extrapulmonary TB (i.e. TB of organs other than the lungs) and will depend on the site of disease (e.g. enlarged lymph nodes, back swelling, seizures).

Clinical examination
(including growth assessment)

- No specific clinical examination findings can confirm pulmonary TB.
- Physical signs highly suggestive of extra-pulmonary TB:
  - gibbus, especially of recent onset (resulting from vertebral TB)
  - non-painful enlarged cervical lymphadenopathy, with or without fistula formation.
  - meningitis not responding to antibiotic treatment, with a subacute onset and/ or raised intracranial pressure
  - pleural effusion
  - pericardial effusion
  - distended abdomen with ascites
  - non-painful enlarged lymph nodes without fistula formation
  - non-painful enlarged joints.

Tuberculin skin test

- a positive TST indicates that a person is or was infected with M. tuberculosis but does not necessarily indicate TB disease.
- measures immune response, not the presence/absence of bacteria.
- a useful tool in the assessment of a child with suspected TB, especially when there is no positive history of TB contact, because a positive TST indicates that the child has been infected at some point.
- use as an adjunct in diagnosing TB in children with signs and symptoms of TB and in conjunction with other diagnostic tests.
- use to screen children exposed to TB (such as household contact with TB)

Bacteriological confirmation

- Every effort should be made to confirm diagnosis of TB
- Appropriate specimens from the suspected sites of involvement should be obtained for
  - microscopy
  - culture
  - molecular test
  - histopathological exam

Chest radiography

- Good-quality chest radiographs (including lateral view, if and where possible) are essential and should preferably be read by a radiologist trained in their reading.
- Chest radiography
  - In most cases, children with pulmonary TB have radiographic changes suggestive of TB
  - the commonest picture is one of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands.
  - A miliary pattern of opacification in HIV-negative children is highly suggestive of TB.
- Adolescent patients with TB have radiographic changes similar to adult patients
  - with large pleural effusions and apical infiltrates
  - cavity formation being the most common forms of presentation

Investigations relevant for suspected extra-pulmonary TB

Table 2. **Common forms of extrapulmonary TB in children**

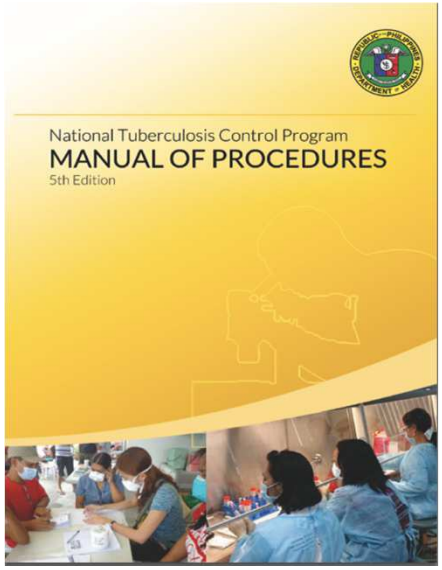
Note: All fluid (CSF, pleural, ascetic, joint or pericardial) must be subjected to biochemical analysis (protein and glucose concentrations), cell count, AFB stain and culture whenever possible.

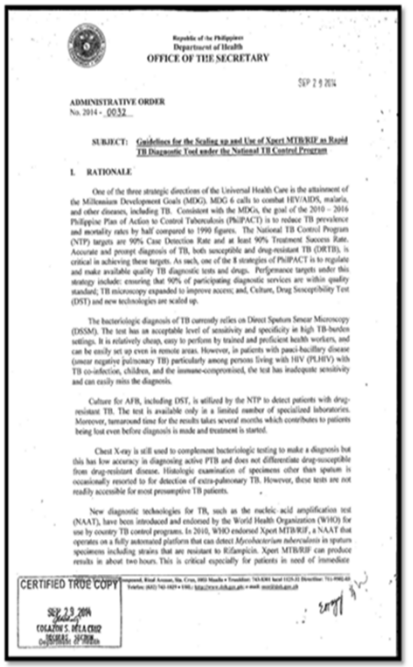
Site	Practical approach to diagnosis
Peripheral lymph t (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest radiograph and lumbar puncture (to test for meningitis)
Tuberculous meningitis	Lumbar puncture (and imaging where available)
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound (3) and ascitic tap
Osteoarticular	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

DOH - National TB Control Program (NTP)

- NTP Manual of Procedures (2013)

- DOH Policy: *Guidelines for the scaling up and use of Xpert MTB/RIF as rapid diagnostic tool under the NTP*




Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

SEP 2 9 2014

ADMINISTRATIVE ORDER
No. 2014 - 0032

SUBJECT: Guidelines for the Scaling up and Use of Xpert MTB/RIF as Rapid TB Diagnostic Tool under the National TB Control Program

I. RATIONALE

One of the three strategic directions of the Universal Health Care is the attainment of the Millennium Development Goals (MDG). MDG 6 calls to combat HIV/AIDS, malaria, and other diseases, including TB. Consistent with the MDGs, the goal of the 2010 – 2016 Philippine Plan of Action to Control Tuberculosis (PhilPACT) is to reduce TB prevalence and mortality rates by half compared to 1990 figures. The National TB Control Program (NTP) targets are 90% Case Detection Rate and at least 90% Treatment Success Rate. Accurate and prompt diagnosis of TB, both susceptible and drug-resistant TB (DRTB), is critical in achieving these targets. As such, one of the 8 strategies of PhilPACT is to regulate and make available quality TB diagnostic tests and drugs. Performance targets under this strategy include: ensuring that 90% of participating diagnostic services are within quality standard; TB microscopy expanded to improve access; and, Culture, Drug Susceptibility Test (DST) and new technologies are scaled up.

The bacteriologic diagnosis of TB currently relies on Direct Sputum Smear Microscopy (DSSM). The test has an acceptable level of sensitivity and specificity in high TB-burden settings. It is relatively cheap, easy to perform by trained and proficient health workers, and can be easily set up even in remote areas. However, in patients with paucibacillary disease (smear negative pulmonary TB) particularly among persons living with HIV (PLHIV) with TB co-infection, children, and the immune-compromised, the test has inadequate sensitivity and can easily miss the diagnosis.

Culture for AFB, including DST, is utilized by the NTP to detect patients with drug-resistant TB. The test is available only in a limited number of specialized laboratories. Moreover, turnaround time for the results takes several months which contributes to patients being lost even before diagnosis is made and treatment is started.

Chest X-ray is still used to complement bacteriologic testing to make a diagnosis but this has low accuracy in diagnosing active PTB and does not differentiate drug-susceptible from drug-resistant disease. Histologic examination of specimens other than sputum is occasionally resorted to for detection of extra-pulmonary TB. However, these tests are not readily accessible for most presumptive TB patients.

New diagnostic technologies for TB, such as the nucleic acid amplification test (NAAT), have been introduced and endorsed by the World Health Organization (WHO) for use by country TB control programs. In 2010, WHO endorsed Xpert MTB/RIF, a NAAT that operates on a fully automated platform that can detect *Mycobacterium tuberculosis* in sputum specimens including strains that are resistant to Rifampicin. Xpert MTB/RIF can produce results in about two hours. This is critical especially for patients in need of immediate

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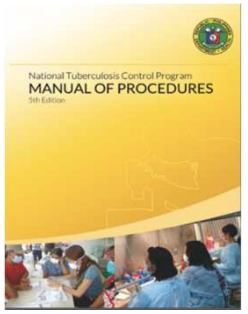
NTP Manual of Procedures
Chapter 2: Casefinding Policies

Objective

- Early identification and diagnosis of TB cases

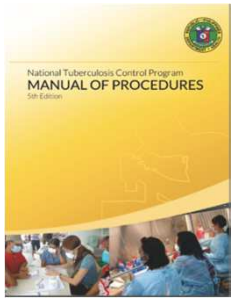


Definition of Terms

- **DOTS facility**
- **Passive Case Finding**
- **Active Case Finding**

- **Turnaround time** –collection of first sputum sample to initiation of treatment for TB.

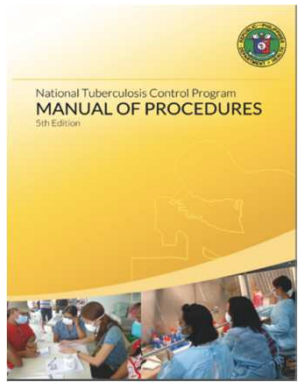
- **Intensified case finding** – active case finding among ***individuals belonging to special or defined populations***



Definition of Terms
(vulnerable groups)

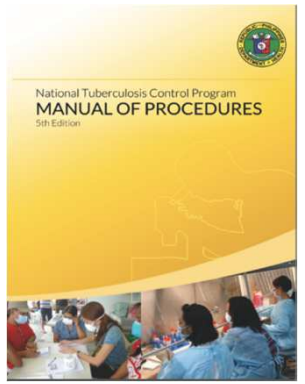
- **Close contact** –a person who ***shared an enclosed space*** for extended periods within the day ***with the index case***

- **High-risk Clinical groups** – with clinical conditions that puts them ***at risk of contracting TB disease***, particularly those with ***immunocompromised states***



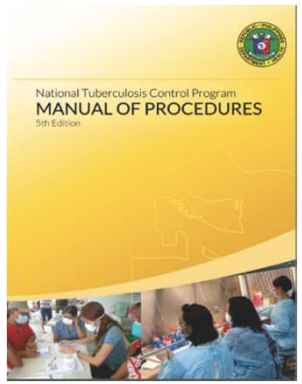
Definition of Terms
(vulnerable groups)

- **High-risk Clinical groups**
  - HIV/AIDS
  - Diabetes
  - end-stage renal disease
  - Cancer
  - connective tissue diseases
  - autoimmune diseases
  - Silicosis
  - gastrectomy
  - solid organ transplantation
  - prolonged systemic steroids



Definition of Terms
(vulnerable groups)

- **High-risk populations** –persons with known high incidence of TB, particularly those **in closed environments or living in congregate settings** that promote easy disease transmission
  - Inmates
  - Elderly
  - Indigenous People
  - Urban/rural poor



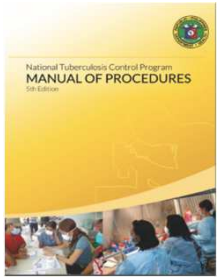
Definition of Terms

- **Presumptive TB, Presumptive DRTB**

- **TB exposure**
  - close contact with an active adult TB case
  - without any signs and symptoms of TB
  - with negative TST reaction
  - no radiologic and laboratory findings suggestive of TB.

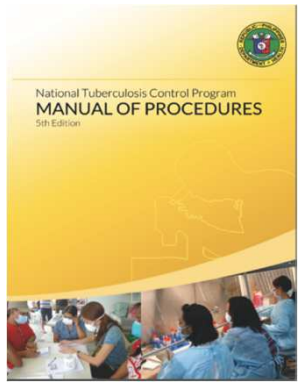
- **TB infection or latent TB infection (LTBI)**
  - as above ***BUT with a positive TST reaction***.

- **TB disease –** A presumptive TB who after clinical and diagnostic evaluation is confirmed to have TB.

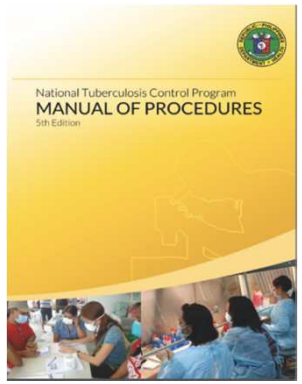


Identification of Presumptive TB

- **For 15 years old and above,**
  - **Cough of at least 2 weeks duration** with or without other symptoms
  - **Unexplained cough of any duration in:**
    - a close contact of a known active TB case
    - high-risk clinical groups
    - high risk populations
  - **Chest x-ray findings suggestive of PTB, with or without symptoms**



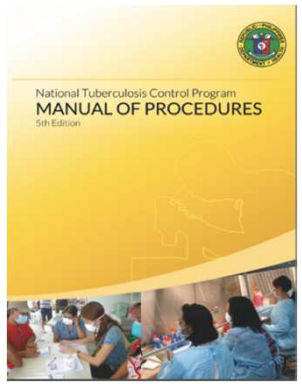
Identification of Presumptive TB



- **For below 15 years old**
  - at least three (3) of the following clinical criteria:
    1. Coughing/wheezing of 2 weeks or more
    2. Unexplained fever of 2 weeks or more
    3. Loss of weight/ failure to gain weight/ weight faltering/ loss of appetite;
    4. Failure to respond to 2 weeks of appropriate antibiotic therapy
    5. Failure to regain previous state of health 2 weeks after a viral infection
    6. Fatigue, reduced playfulness, or lethargy (child has lost his/her normal energy)

Identification of Presumptive TB

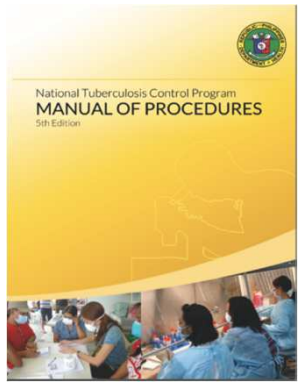
- **For below 15 years old**
  - **Any of the above in a child who is a close contact of a known active TB case**
  - **Chest x-ray findings suggestive of PTB, with or without symptoms**



Identification of Presumptive Drug Resistant-TB (DRTTB)

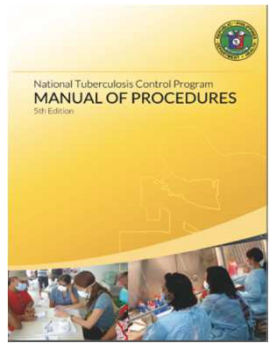
Any person whether adult or child, who belongs to any of the DR-TB high-risk groups, such as:

- re-treatment cases
- new TB cases that are contacts of confirmed DR-TB cases or non-converter of Category
- people living with HIV with signs and symptoms of TB.



Identification of Presumptive TB

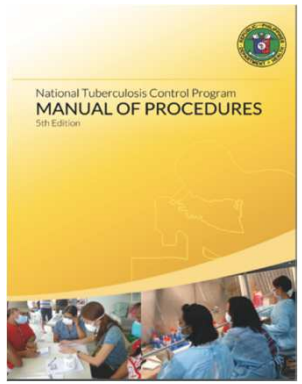
- **Presumptive extrapulmonary TB**
  - Gibbus, especially of recent onset (resulting from vertebral TB);
  - Non-painful enlarged cervical lymphadenopathy with or without fistula formation;
  - Nuchal rigidity and/or drowsiness suggestive of meningitis that is not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure;
  - Pleural effusion;
  - Pericardial effusion;
  - Distended abdomen (i.e., big liver and spleen) with ascites;
  - Non-painful enlarged joint; and



Definition of Terms

Classification

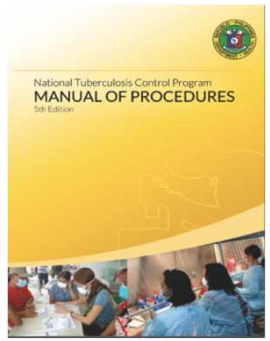
- Anatomic site
  - Pulmonary TB
  - Extra-pulmonary TB



Definition of Terms

Classification

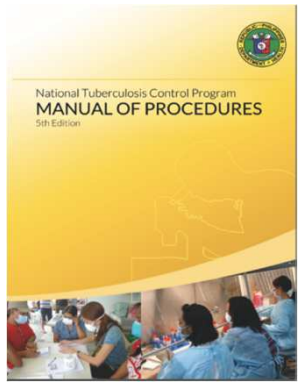
- **Bacteriological status**
  - **Bacteriologically confirmed** - a biological specimen is ***positive by smear microscopy, culture or rapid diagnostic tests*** (Xpert MTB/RIF).
  - **Clinically diagnosed** – A PTB patient who ***does not fulfil the criteria for bacteriological confirmation*** but has been diagnosed with active TB



Definition of Terms

Classification

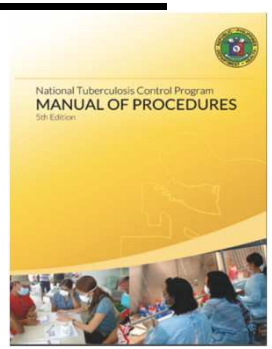
- History of previous treatment
  - New case
  - Retreatment case



Definition of Terms

Classification

- Drug-susceptibility test result
  - Monoresistant TB
  - Polydrug resistant TB
  - Multidrug resistant TB (MDRTB)
  - Extensive drug-resistant TB (XDRTB)
  - **Rifampicin resistant TB (RR-TB)** - ***resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs***.



Classification

Bacteriological status	Definition of Terms	
Bacteriologically confirmed	Smear-positive	A patient with at least one (1) sputum specimen positive for AFB, with or without radiographic abnormalities consistent with active TB
	Culture-positive	A patient with positive sputum culture for MTB complex, with or without radiographic abnormalities consistent with active TB
	Rapid Diagnostic test-Positive	A patient with sputum positive for MTB complex using rapid diagnostic modalities such as Xpert MTB/RIF, with or without radiographic abnormalities consistent with active TB

Classification

Anatomical Site	Bacteriological status	Definition of Terms
Pulmonary (PTB)	Clinically diagnosed	A patient with 2sputum specimens negative for AFB or MTB, or with smear not done due to specified conditions but with radiographic abnormalities consistent with active TB; and there has been no response to a course of empiric antibiotics and/or symptomatic medications; and who has been decided (either by the physician and/or TBDC) to have TB disease requiring a full course of anti-TB chemotherapy OR A child (<15 years old) with 2 sputum specimens negative for AFB or with smear not done, who fulfills 3 of the 5 criteria for disease activity; and who has been decided (either by the physician and/or TBDC) to have TB disease requiring a full course of anti-TB chemotherapy OR

Classification

Anatomical Site	Bacteriological status	Definition of Terms
Pulmonary (PTB)	Clinically diagnosed	OR A patient with laboratory or strong clinical evidence for HIV/AIDS with 2 sputum specimens negative for AFB or MTB or with smear not done due to specified conditions but who, regardless of radiographic results, has been decided (either by physician and/or TBDC) to have TB disease requiring a full course of anti-TB chemotherapy.

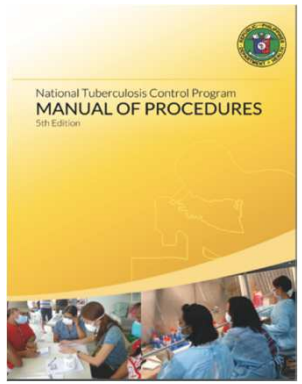
Classification

Anatomical Site	Bacteriological status	Definition of Terms
Extra-pulmonary (EPTB)	Bacteriologically confirmed	A patient with a smear/culture/rapid diagnostic test from a biological specimen in an extra-pulmonary site (i.e., organs other than the lungs) positive for AFB or MTB complex
	Clinically diagnosed	A patient with histological and/or clinical or radiologic evidence consistent with active extra-pulmonary TB and there is a decision by a physician to treat the patient with anti-TB drugs

Policies

A. Both passive and **intensified case finding** activities shall be implemented

B. Intensified case finding shall be done among **close contacts, high risk clinical groups and high-risk populations**.

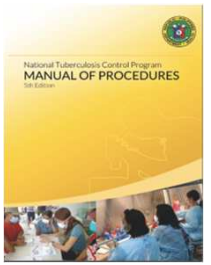


Policies

C. Direct Sputum Smear Microscopy (DSSM) by light **or fluorescence microscopy**, shall be the primary diagnostic tool in NTP case finding.

D. All presumptive TB should undergo **DSSM unless** it is **not possible** due to the following situations:

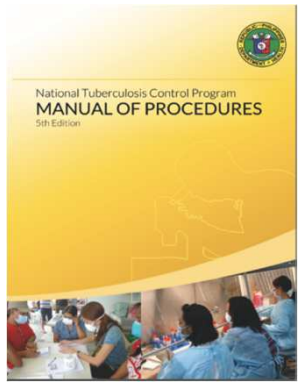
- mentally incapacitated as decided by a specialist or medical institution
- debilitated or bedridden
- children unable to expectorate
- patients unable to produce sputum despite sputum induction



Policies

E. Two sputum specimens of good quality shall be collected, either as **frontloading** (i.e., spot-spot one-hour apart) or **spot – early morning** specimens, based on the patient's preference.

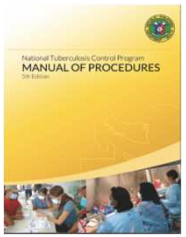
– *The two specimens should be collected at most within 3 days.*



Policies

F. Available rapid diagnostic test (e.g., Xpert MTB/RIF) shall be used for TB diagnosis among
   - presumptive DRTB
   - persons living with HIV (PLHIV) with signs and symptoms of TB
   - ***smear negative children***
   - ***smear negative adults with CXR findings suggestive of TB.***

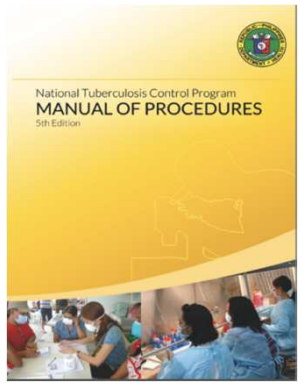
G. If Xpert MTB/RIF **is inaccessible**….**evaluated by the DOTS physician who shall decide using his/her best clinical judgment.**



Policies

H. Tuberculin skin test (TST) shall not be used as sole basis for TB diagnosis. It shall be used as a screening tool for children.

– A 10mm induration is considered a positive TST reaction.



Policies

I. All DOTS facilities, whether public or private are encouraged to establish their own in-house microscopy unit.

J. All municipalities and cities shall ensure access to quality-assured microscopy services.
   - One microscopy center shall cater to at most 100,000 population.
   - In difficult to access areas, remote smearing stations (RSS) manned by trained volunteers could be established.

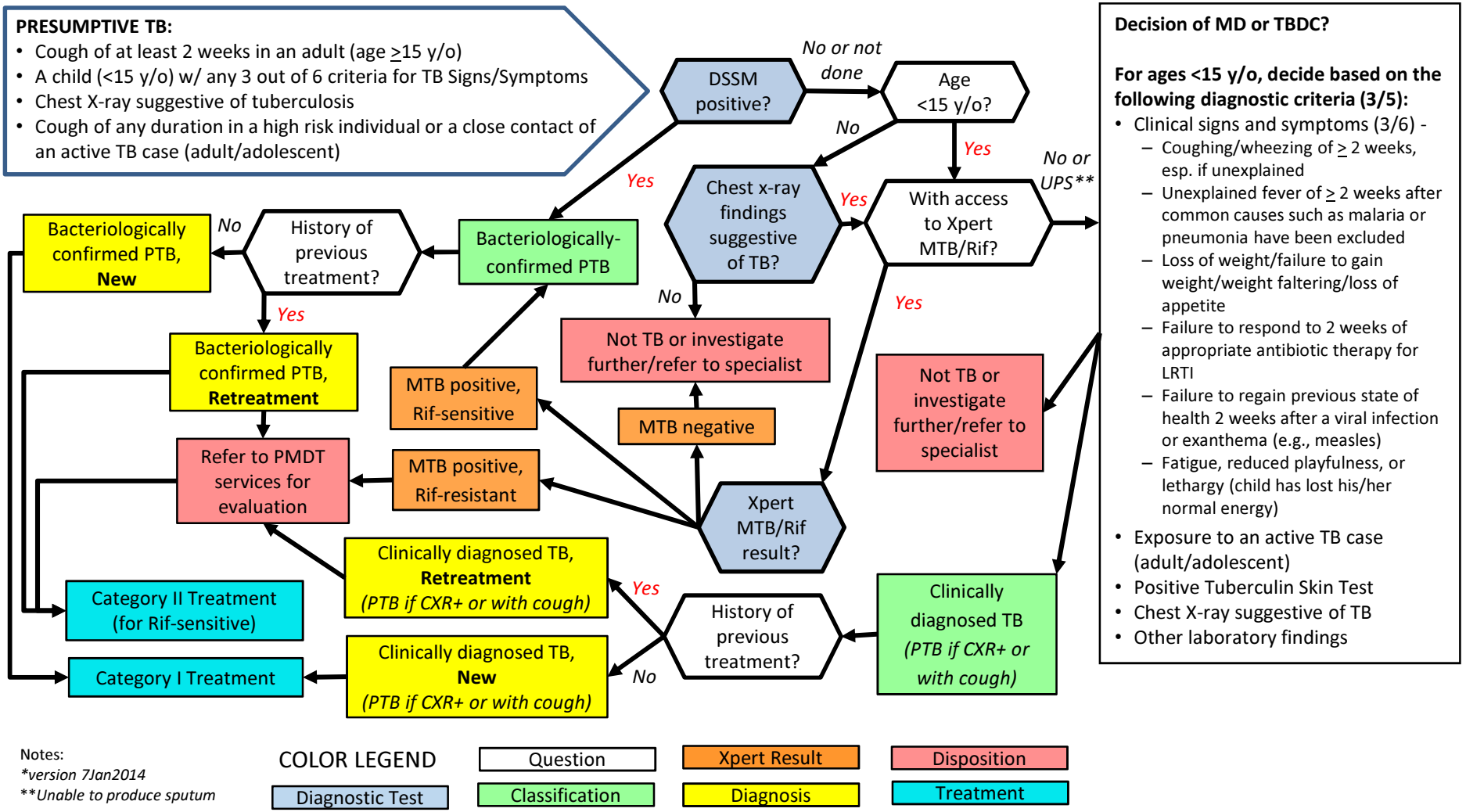
Policies

K. All laboratories providing DSSM services or other TB diagnostic tests, whether public or private, shall participate in the **External Quality Assessment (EQA)** system of the NTP.

L. All **presumptive DRTB --** referred to the nearest Programmatic Management of Drug-resistant TB (PMDT) facility for screening and management.

M. All Persons living with HIV (PLHIV) shall be screened for TB co-infection.

Decision on Diagnosis based on Laboratory Results



Summary

- intensified- case finding strategy – screen for TB among vulnerable groups: immunocompromised, contacts of TB cases
- 2-sputum collection and front-loading
- New terms: presumptive TB or DRTB, bacteriologically confirmed or clinically diagnosed, rifampicin resistant

Summary

- Use of Xpert MTB/RIF for the following:
  - DRTB
  - Smear negative but CXR (+)
  - Children
  - PLHIV with signs and symptoms
  - EPTB
- The basics still apply: careful assessment of the patient based on clinical history, physical examination, chest radiograph, TST, laboratory examinations

THANK YOU