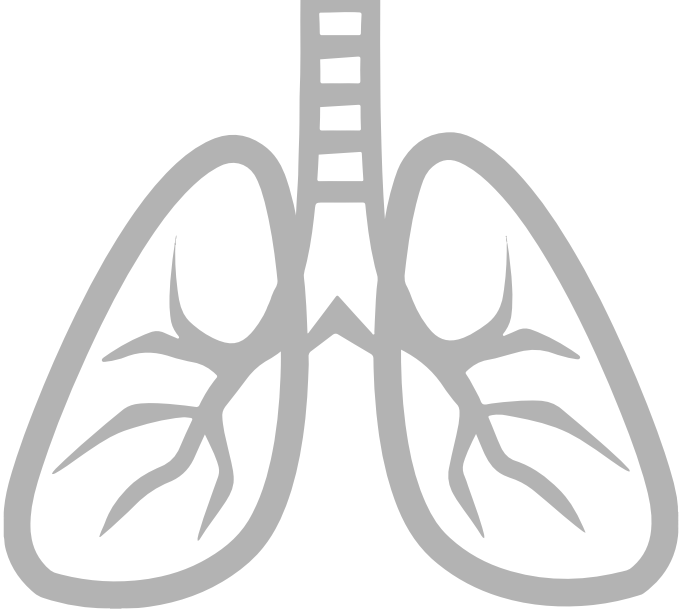
Clinical Practice Guidelines for the DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL OF TUBERCULOSIS in Adult Filipinos

2016 Update



Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos

2016 UPDATE

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Abbreviations

ACCP	American College of Chest Physicians
AD	After dialysis
ADR	Adverse drug reaction
AFB	Acid fast bacilli
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ATS	American Thoracic Society
BCG	Bacille Calmette Guerin
BMI	Body mass index
BSC	Biological safety cabinets
BTS	British Thoracic Society
BUN	Blood urea nitrogen
CDC	Center for Disease Control and Prevention (US)
CI	Confidence interval
CKD	Chronic kidney disease
CLD	Chronic liver disease
CMV	Cytomegalovirus
CNS	Central nervous system
CPG	Clinical practice guidelines
CPGTB	Clinical Practice Guidelines for TB
CXR	Chest x-ray
DM	diabetes mellitus
DOH	Department of Health
DOT	Directly observed treatment
DOTS	Directly observed treatment short course strategy
DRTB	Drug-resistant tuberculosis
DSSM	Direct sputum smear microscopy
DST	drug susceptibility test
ELISpot	Enzyme-linked immunospot
EMB or E	Ethambutol
EPTB	Extra-pulmonary tuberculosis
ETON	ethambutol-related toxic optic neuropathy

FBS	Fasting blood sugar
FDC	Fixed Dose Combination
FLD	First line drugs
FM	Fluorescent Microscopy
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRADE	Grades of Recommendations, Assessment, Development and Evaluation
HBA1c	Hemoglobin A1c or glycosylated hemoglobin
HD	Hemodialysis
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
HSP	Hepatology Society of the Philippines
IDSA	Infectious Diseases Society of America
IFG	impaired fasting glucose
IGRA	interferon gamma release assay
INH or H	Isoniazid
IPT	Isoniazid prophylaxis therapy
IRIS	Immune reconstitution inflammatory syndrome
ISTC	international standards for tuberculosis care
LAI	Laboratory-acquired infection
LAM	Lipoarabinomannan
LCP	Lung Center of the Philippines
LED	Light-emitting diode
LFT	Liver function tests
LPA	Line probe assay
LTBI	latent tuberculosis infection
MDH	Manila Doctors Hospital
MDR-TB	Multi-drug resistant tuberculosis
MODS	Microscopic observation drug susceptibility
MOP	Manual of Procedures
MTB	Mycobacterium tuberculosis
NAAT	Nucleic acid amplification test
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Clinical Excellence (UK)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor

NTM	Non-tuberculosis mycobacterium
NTRL	National Tuberculosis Reference Laboratory
NTP	National Tuberculosis Control Program
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAFP	Philippine Academy of Family Physicians
PCCP	Philippine College of Chest Physicians
PCOM	Philippine College of Occupational Medicine
PCP	Philippine College of Physicians
PCP	Pneumocystis pneumonia
PCR	Philippine College of Radiology
PCT	Patient-centered treatment
PD	Peritoneal dialysis
PGH	Philippine General Hospital
PICT	Provider-initiated counseling and testing
PhilCAT	Philippine Coalition Against Tuberculosis
PLHIV	Persons living with HIV
POGS	Philippine Obstetrical and Gynecological Society
PR	Paradoxical response
PRA	Philippine Rheumatology Association
PSAAI	Philippine Society of Allergy, Asthma and Immunology
PSEDM	Philippine Society of Endocrinology, Diabetes,and Metabolism
PSMID	Philippine Society for Microbiology and Infectious Diseases
PSMO	Philippine Society of Medical Oncology
PSN	Philippine Society of Nephrology
PMDT	programmatic management of drug-resistant TB
PPD	Purified protein derivative
PTB	Pulmonary Tuberculosis
PTOU	Previous treatment outcome unknown
PTSI	Philippine Tuberculosis Society, Inc
PZA or Z	Pyrazinamide
QFT-GIT	Quantiferon-Gold-in-Tube
QI	Quezon Institute
RBS	Random blood sugar
RCT	Randomized controlled trial

RIF or R	Rifampicin
RITM	Research Institute of Tropical Medicine
RR	Relative risk
RR-TB	Rifampicin-resistant tuberculosis
SDF	single drug formulations
SGD	Small group discussions
SGPT	Serum glutamic pyruvic transaminase
SLD	Second line drugs
SOT	Solid organ transplant
SRDR	Standardized regimen drug resistant
STC	satellite treatment center
TALF	Treatment after lost to follow-up
TASC	Technical Assistance Support to Country
TB	Tuberculosis
TC	treatment center
TST	Tuberculin skin testing
TWC	technical writing committees
ULN	Upper limit of normal
UPS	Unable to produce sputum
USAID	United States Agency for International Development
UST	University of Santo Tomas
WHO	World Health Organization
WRD	WHO-approved rapid diagnostic test
XDR-TB	Extensive drug resistant tuberculosis

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Executive Summary

This document is intended for practicing clinicians and other healthcare professionals involved in the holistic care of adult patients with presumptive or confirmed tuberculosis (TB), updating the 2006 Philippine Clinical Practice Guidelines on the Diagnosis, Treatment, Prevention and Control of Tuberculosis. Its timely release comes after the recent revision of the National Tuberculosis Control Program (NTP) Manual of Procedures (MOP) 5th Edition of the Department of Health (DOH), the 2014 International Standards for Tuberculosis Care (ISTC) and recent TB policies and statements released by the World Health Organization (WHO) since 2006.

This document has the following objectives:

1. To update the 2006 Philippine CPG on TB in Adults with recent medical evidence (2005-2015) in light of new developments at the global level, further localized in the Philippine setting, which will serve as useful tool to assist clinicians and other TB personnel to standardize diagnosis and management of TB among adult Filipinos;
2. To harmonize with and complement the NTP-MOP by providing medical evidence to support its policies, with focus on local data where available, in order to facilitate acceptance and compliance among private healthcare providers; and
3. To identify new and relevant TB-related issues and areas for future research in the diagnosis, treatment, prevention and control of TB among immunocompetent and high risk clinical groups in the Philippine setting.

Methodology

A Task Force of TB experts, clinicians, epidemiologists, academicians and program implementers was convened and oriented on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Clinical questions on diagnosis, treatment, drug-resistance, TB-HIV and other high risk clinical groups, prevention and control were identified, approved in plenary and assigned to Technical Writing Committees (TWCs) who appraised available published or unpublished local and foreign medical evidence from 2005 to 2015.

Quality of evidence was assessed to be high, moderate, low or very low based on study design and estimate of effect (Table 1).

TABLE 1 Quality of Evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Framework

QUALITY OF EVIDENCE		STUDY DESIGN	LOWER IF:	HIGHER IF:
High	Further research is very unlikely to change confidence in the estimate of effect	Randomized controlled studies (RCTs)	***Study quality:*** Poor quality of implementation of RCT ***Inconsistency of results:*** ***Indirectness:*** Different population, intervention, outcomes ***Imprecise results:*** High probability of reporting bias	***Stronger association:*** Large magnitude of effect, no plausible confounders ***Very large magnitude of effect,*** no major threats to validity ***Dose response gradient***
Moderate	Further research is *likely* to have impact on the confidence in the estimate of effect	Downgraded RCTs or upgraded observational studies		
Low	Further research is *very likely* to have an important impact on the confidence in the estimate of effect	Observational studies		
Very Low	Any estimate of effect is *very uncertain*	Case series or expert opinion		

Reference: Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336:924-926

Strength of statements developed after series of small group discussions (SGDs) with relevant experts and technical advisers at the committee level was assessed by a 27-member voting panel based on the balance between desirable and undesirable effects, quality of evidence, patients' values and preferences, cost and access to tests or interventions, and largely guided by its potential implications to patients, clinicians and policy makers as outlined in the GRADE approach (Table 2).

Members of the consensus panel voted as follows: A=accept completely; B=accept with some reservations; C=accept with major reservations; D= reject with some reservations; and E= reject completely. Statements reached consensus if 80% voted A or B; rejected if less than 80% was reached or at least one (1) member voted D or E. Major or minor reservations were noted and addressed by the TWCs. Statements that reached consensus were presented in annual medical conventions for initial feedback and comments; while those that were not accepted were sent back to the TWCs for either revision or further literature review as recommended by the voting panel. The Second Draft was finalized in a writeshop by the TWCs

TABLE 2 Implications of Strength of Recommendations to Patients, Clinicians and Policy Makers using GRADE Approach

STRENGTH OF RECOMMENDATION		IMPLICATIONS OF THE RECOMMENDATIONS		
		TO PATIENTS	*TO CLINICIANS*	*TO POLICY MAKERS*
Strong	The benefits outweighed the harm. There are no cost or access issues for the general population	Most people in the situation would want the recommended course of action and only very few would not; request for discussion if the intervention is not offered	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Weak	Best available evidence is very low to low quality; Magnitude of benefits or risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting; Benefits may not warrant the cost or resource requirements in all settings	Most people in the situation would want the recommended course of action, but many would not	Different choices are appropriate for different patients, and clinician must help patients arrive at a management decision consistent with patient's values and preferences	Policy making will require substantial debate and involvement of any stakeholders

Reference: Guyatt GH et al. Going from evidence to recommendations. BMJ. 2008 May 10; 336(7652):1049-1051.

and presented to the consensus panel for final voting. Statements that did not reach consensus but were not rejected by the consensus panel were reviewed, revised and elevated to the Steering Committee for final review and consideration.

Summary of Highlights of the CPGTB 2016 Recommendations

The 2016 Update contains 24 recommendations on Diagnosis, 29 recommendations on Treatment, 4 recommendations on Drug-Resistant TB, 17 recommendations on TB-HIV and other High Risk Clinical Groups, and 10 recommendations on Prevention and Control. Throughout the document, the updated WHO case definitions, policies and procedures are used, with major reference to the ISTC 2014 and the DOH's latest NTP Manual of Procedures.

Comparison Between the 2016 and 2006 CPG Recommendations

A. DIAGNOSIS OF TB IN THE GENERAL POPULATION

QUESTION/ISSUE	2016 CPG	2006 CPG
Identifying Presumptive PTB	**Presumptive TB** replaces the term *TB Symptomatic* or *TB Suspect* • Adopts the cut-off of 15 years old to refer to adults (based on WHO and NTP MOP) For patients 15 years old and above, a presumptive TB has any of the following: • Cough of at least 2-weeks duration; unexplained cough of any duration in a close contact of a known active TB case; or CXR findings suggestive of PTB with or without symptoms ***(Strong recommendation, low quality evidence)*** • ANY of the following symptoms: cough of any duration, significant and unintentional weight loss, fever, bloody sputum or hemoptysis, chest pains not referable to any musculoskeletal disorders, easy fatigability or malaise, night sweats, shortness of breath or difficulty of breathing ***(Weak recommendation, low quality evidence)***	**TB Symptomatic** was defined as a patient exhibiting cough of 2 weeks or more with or without accompanying symptoms • Cough of 2 weeks should make any healthcare worker suspect PTB (Grade A recommendation) • Cough with or without the following: night sweats, weight loss, anorexia, unexplained fever and chills, chest pain, fatigue and body malaise, is suggestive of TB
Tests for bacteriologic confirmation of PTB	• Direct sputum smear microscopy (DSSM), TB culture or WHO-approved rapid diagnostic tests specifically Xpert® MTB/Rif • Emphasis to pursue bacteriologic confirmation versus clinical diagnosis alone	• Sputum microscopy and TB culture
Role of Direct Sputum Smear Microscopy (DSSM)	• DSSM remains as the primary diagnostic test for diagnosing TB • If available, fluorescent light-emitting diode (LED-FM) microscopy is preferred over light microscopy ***(Strong recommendation, moderate quality evidence)***	• DSSM is the initial work-up of choice for a TB symptomatic; still the most efficient way of identifying cases of tuberculosis
Sputum collection for DSSM	• 2 specimens, either spot-spot one-hour apart or spot-early morning collection submitted to a quality-assured laboratory ***(Strong recommendation, moderate quality evidence)*** • Spontaneous expectoration preferred ***(Strong recommendation, moderate quality evidence)***	• Should preferably have 3, at least 2 specimens *(Grade A recommendation)* • *Spot-early AM-spot* collection *Grade C recommendation)*

QUESTION/ISSUE	2016 CPG	2006 CPG
DSSM interpretation	• At least 1 sputum smear positive is considered bacteriologically confirmed TB ***(Strong recommendation, moderate quality evidence)***	• At least 2 out of 3 sputum smear positive to be considered ***smear positive***
Role of sputum TB Culture	• If available, requested in the diagnostic work-up of TB cases, specifically in ruling out NTM. The long turnaround time of results, limited access and cost of test, limit its routine use. • Culture-positive for *Mycobacterium tuberculosis* (MTB) is considered *bacteriologically confirmed PTB.*	Recommended for: • All smear-positive patients: retreatment, treatment failure, suspected to have one or multi-drug resistant TB, household contacts of MDR-TB, patients who may be infected with HIV *(Grade A recommendation)* • All smear-negative TB symptomatic patients whenever resources permit *(Grade A recommendation)*
Role of sputum TB culture with drug susceptibility testing (DST)	• Previous recommendations maintained • Also for known contacts of MDR-TB, PLHIV • DST not routinely performed among new cases of PTB	• For all cases of retreatment, treatment failure, MDR suspects • All smear-negative TB symptomatic who have risk factors for drug-resistant TB *(Grade A recommendation)*
Patients who cannot expectorate sputum	• Sputum induction ***(Strong recommendation, low quality evidence)*** • NTP recognizes "Sputum Not Done" in the following situations: a. Mentally incapacitated as decided by a specialist b. Debilitated or bedridden c. Patients unable to produce sputum (UPS) despite sputum induction	• Sputum induction *(Grade B recommendation)*
Additional work-up for smear-negative patients	• CXR should be performed for all smear-negative presumptive PTB ***(Strong recommendation, moderate quality evidence)*** • If available, Xpert® MTB/Rif should be requested among smear-negative, CXR-positive presumptive TB patients with no risk for DR-TB or HIV-TB ***(Strong recommendation, high quality evidence)***	For smear-negative TB symptomatic: • CXR *(Grade A recommendation)* • TB culture when available, with DST if at risk for drug-resistant TB *(Grade A recommendation)* • Repeat sputum AFB after adequate nebulization *(Grade C recommendation)*

QUESTION/ISSUE	2016 CPG	2006 CPG
	• No recommendation on TBDC	• Referral to TB Diagnostic Committee (TBDC) *(Grade C recommendation)*
Role of CXR in PTB diagnosis	• Patient with CXR findings suggestive of PTB with or without symptoms is a Presumptive TB ***(Strong recommendation, low quality evidence)*** • Although a good screening test to identify presumptive PTB, a single CXR film cannot accurately confirm active PTB by this modality alone ***(Strong recommendation, high quality evidence)*** • No radiologic findings considered specific for active TB. Clinical correlation, together with bacteriologic confirmation, is required to assess activity BEFORE initiation of treatment ***(Strong recommendation, high quality evidence)*** • A good quality CXR film is needed to initially guide clinician in identifying presumptive PTB for further bacteriologic confirmation ***(Strong recommendation, moderate quality evidence)*** • CXR can be done in parallel or sequential to DSSM	• Not routinely necessary in the management of a smear+ TB symptomatic *(Grade C recommendation);* may be helpful if other concomitant diseases or life-threatening conditions are being considered *(Grade B recommendation)* • Smear-negative TB symptomatic should have a CXR *(Grade A recommendation)* • Together with clinical history, CXR can be a powerful basis for decision-making in the diagnostic approach to smear-negative PTB patients
Role of chest CT in PTB diagnosis	• Same recommendations • Clinical correlation and bacteriologic confirmation should still be done. ***(Strong recommendation, moderate quality evidence)***	• As adjunctive tool in selected cases to establish diagnosis of PTB and evaluate differential diagnosis that may mimic or co-exist with PTB. Routine use of chest CT cannot be recommended at the moment.
Diagnostic work-up for Extra-PTB	• Same recommendation • Now includes Xpert® MTB/Rif using specimens from *selected* extra-pulmonary sites	• Appropriate specimens from the suspected sites of involvement should be obtained and processed for microbiologic, both microscopy and culture, as well as histopath examinations.

Additional Recommendations on Diagnosis of TB:

- Inclusion of Xpert® MTB/Rif in the diagnostic algorithm for the work-up of new and retreatment cases, pulmonary and extra-pulmonary TB; review of its role and accuracy in the following clinical situations:
  - As initial diagnostic test in adults with presumptive TB *(Weak recommendation, high quality evidence)* with pooled sensitivity of 89%, specificity 99%. *(Strong recommendation, high quality evidence)*
  - As follow-on test to smear-negative patients with CXR findings suggestive of active PTB *(Weak recommendation, high quality evidence)* with pooled sensitivity of 67%, specificity of 99%. *(Strong recommendation, high quality evidence)*
  - As initial diagnostic test for presumptive drug-resistant TB *(Strong recommendation, high quality evidence),* with pooled sensitivity of 95% and specificity of 99% for rifampicin resistance detection. *(Strong recommendation, high quality evidence)*
  - In comparison with smear microscopy, Xpert® MTB/Rif increased TB detection among culture-confirmed cases by 23% *(Strong recommendation, high quality evidence).*
  - For smear-positive, culture-positive TB, Xpert® MTB/Rif pooled sensitivity was 98%; specificity was not reported (all smear positive considered TB positive). *(Strong recommendation, high quality evidence).*
- Results of Xpert® MTB/Rif, if available, should be interpreted along with clinical, radiologic, and/or other laboratory findings *(Strong recommendation, high quality evidence)*
- If available, digital imaging can be used in the diagnostic work-up of PTB similar to a chest film as long as appropriate standards are followed. *(Strong recommendation, moderate quality evidence).*
- For digitized radiographic films, the recommended minimum specifications are 2.5 lp/mm spatial resolution with an 8-bit pixel depth.
- The following CANNOT be used to diagnose active PTB and extra-PTB:
  - Nucleic Acid Amplification Testing (NAATs) other than Xpert® MTB/Rif as stand-alone test *(Strong recommendation, high quality evidence);* if available, can be a more sensitive and specific adjunct to diagnose PTB which requires clinical and radiographic correlation *(Weak recommendation, moderate quality evidence),* preferably commercial NAATs over in-house (home brew) assays *(Strong recommendation, high quality evidence)*
  - Quantiferon-Gold-in-Tube (QFT-GIT) *(Strong recommendation, low quality evidence)*

- Enzyme-linked immunospot (EliSpot) *(Strong recommendation, low quality evidence)*
- Interferon-gamma release assays (IGRAs), regardless of HIV status *(Strong recommendation, high quality evidence)*
- Microscopic Observation Drug Susceptibility (MODS) and Lipoarabinomannan (LAM) assay, mainly used for research purposes

B. TREATMENT OF TB:

QUESTION/ISSUE	2016 CPG	2006 CPG
Pre-treatment screening tests	• Baseline serum ALT and creatinine before starting anti-TB treatment. In resource-limited settings, baseline ALT and serum creatinine, at the least, should be requested for patients older than 60 years old, and those with risk factors for liver or kidney disease before starting TB treatment. ***(Strong recommendation, moderate quality evidence)*** • Provider initiated counseling and testing (PICT) for HIV for all patients with TB, specially with high-risk behavior for HIV and those from areas with high HIV prevalence ***(Strong recommendation, moderate quality evidence)*** • Screening for DM using FBS, RBS or 75g OGTT for all patients with TB ***(Strong recommendation, moderate quality evidence)***, HbA1c not routinely recommended due to standardization issues. ***(Strong recommendation, moderate quality evidence)*** • Serum uric acid testing **NOT** routinely recommended before starting anti-TB treatment. ***(Strong recommendation, moderate quality evidence)***	• Baseline kidney and liver function tests for patients with CKD and chronic liver disease • Routine testing for HIV not recommended for TB patients at this time
Registration Categories of TB Cases	• **New** – same definition retained	• **New** – no or less than 1 month of previous treatment for TB
	• **Retreatment -** patient who has received 1 month or more of anti-TB drugs in the past (excluding prophylaxis or treatment for latent TB infection	• **No mention**

QUESTION/ISSUE	2016 CPG	2006 CPG
	• **Relapse** - patient has previously been declared cured or treatment completed at the end of most recent course of treatment, and is now diagnosed with bacteriologically confirmed or clinically diagnosed TB	• **Relapse** – declared cured in the past after full course of anti-TB meds and now has become smear-positive
	• **Treatment after lost to follow-up (TALF)** – patient has previously been declared lost to follow-up after interruption of at least 2 consecutive months at the end of most recent course of treatment and is now bacteriologically confirmed or clinically diagnosed TB (previously known as *Return After Default*)	• **Return After Default** – a patient who stops taking medications for 2 months or more and comes back smear-positive
	• **Treatment after Failure** - patient has previously been treated for TB and has been declared failed at the end of most recent course of treatment	• **Failure** – a patient while on treatment remains smear-positive at 5th month or later or a baseline smear- negative who becomes smear-positive at 2nd month
	• **Previous Treatment Outcome Unknown (PTOU)** –patient has previously been treated for TB but outcome after their most recent course of treatment is unknown or undocumented	• **No mention**
	• **Other** – same definition retained	• **Other** – patients who do not fit in any of the above categories
Management of new cases	• **2HRZE/4HR (Category I)** for pulmonary and extra-pulmonary TB except meninges, bones or joints ***(Strong recommendation, high quality evidence)*** • **2HRZE/10HR (Category Ia)** for extra-pulmonary TB of meninges, bones, joints ***(Strong recommendation, low-high quality evidence)***	• **2HRZE/4HR (Category I)** for all new cases *(Grade A recommendation)*

QUESTION/ISSUE	2016 CPG	2006 CPG
Management of retreatment cases	• Immediate referral for Xpert® MTB/Rif for RIF susceptibility *before* initiating any TB treatment. ***(Strong recommendation, high quality evidence)*** • **2HRZES/1HRZE/5HRE (Category II)** for retreatment of confirmed rifampicin-sensitive pulmonary and extra-PTB *except meninges, bones or joints* (Rifampicin-resistance not detected by Xpert® MTB/Rif) ***(Strong recommendation, moderate quality evidence)*** • **2HRZES/1HRZE/9HRE (Category IIa)** for retreatment of confirmed rifampicin-sensitive extra-PTB of *meninges, bones or joints* (Rifampicin-resistance not detected by Xpert® MTB/Rif)	• **2HRZES/1HRZE/5HRE (Category II)** can be initiated pending DST results among persistently symptomatic patients who received non-supervised self-administered therapy or those who interrupted treatment
Supervision of Treatment	• *Patient-centered* Directly observed treatment (DOT) ***(Strong recommendation, high quality evidence)***	• *Patient-centered* Directly observed treatment (DOT), wheneverpossible *(Grade B recommendation)*
Monitoring new cases for treatment response	• DSSM (1 specimen) at the end of **2nd, 5th**, **6th** month of treatment among *bacteriologically-confirmed PTB;* at the end of **2nd** month for c*linically-diagnosed PTB*	• DSSM (1 specimen) at the end of **2nd, 4th, 6th** month of treatment among *smear+ PTB*; at the end of **2nd** month for *smear- PTB*
	• *Extended* intensive phase NOT recommended for Category I non-converters; continuation phase is started after 2 months; DSSM repeated at the end of **3rd** month • If still smear-positive, refer to DOTS facility with PMDT or Xpert® MTB/Rif services; continue treatment pending results and/or further recommendations	• *Extended* intensive phase for Category I non-converters for 1 month; DSSM is repeated at the end of 3rd month. If still smear+, **DST** is done, treatment continued pending results
	• If smear-positive at the end of **5th** month, classify as *Treatment Failed*; refer to DOTS facility with PMDT and/or Xpert® MTB/Rif services, continue treatment pending results and/or recommendations	• If smear-positive at the end of **5th** month, classify as *Treatment Failed* and refer to DOTS facility with PMDT services, continue treatment pending results and/or recommendations

	2016 CPG	2006 CPG
Monitoring retreatment cases for treatment response	• DSSM (1 specimen) at the end of **3rd, 5th** and **8th** month of treatment for *bacteriologically confirmed* and *clinically diagnosed* cases	• DSSM (1 specimen) repeated at the end of **3rd, 5th** and **8th** of treatment for smear-positive cases
	• If still smear-positive at the end of 3rd month, *refer* immediately to a DOTS facility with PMDT and/or Xpert®MTB/Rif services; start continuation phase while waiting for PMDT recommendations	• If still smear-positive at the end of 3rd month, start *continuation phase* pending baseline DST results
Treatment Outcomes for susceptible TB	• **Cured** – bacteriologically-confirmed TB at the beginning of treatment and and is smear- or culture-negative in the last month of treatment and at least one previous occasion in the continuation phase	• **Cured** – smear-positive patient who has completed treatment and is smear-negative in the last month of treatment and on at least one previous occasion
	• **Treatment Completed** -patient who completes treatment without evidence of failure and either smear or culture was negative, not done or unavailable (includes bacteriologically-confirmed without DSSM follow-up or clinically diagnosed patient who has completed treatment)	• **Treatment Completed –** patient who completes treatment but does not meet criteria for cured or failure
	• **Treatment Failed -** smear- or culture-positive at 5 months or later during treatment OR clinically-diagnosed patient whose sputum cannot be done and no clinical improvement anytime during treatment.	• **Treatment Failed** – patient who is smear-positive at 5 months or later or who has become smear-positive during treatment
	• **Lost to follow-up** -patient whose treatment was interrupted for 2 consecutive months or more (previously known as defaulted)	• **Defaulted** – one whose treatment was interrupted for 2 consecutive months or more
	• **Died** –same definition	• **Died –** a TB patient who dies for any reason
	• **Not evaluated —** a patient for whom no treatment outcome is assigned, including those transferred-out and treatment outcome is unknown	• **No mention**

QUESTION/ISSUE	2016 CPG	2006 CPG
Management of drug-induced hepatotoxicity	• Routine liver function monitoring **NOT** needed among asymptomatic patients. ***(Strong recommendation, moderate quality evidence)*** • Serum ALT (SGPT) should only be requested for: (1) individuals who exhibit symptoms of hepatotoxicity such as jaundice, anorexia, nausea, vomiting, or abdominal pain; (2) monitoring of patients with baseline risk factors for hepatotoxicity or abnormal baseline LFTs (2-4 weeks after the start of anti-TB medications). ***(Strong recommendation, moderate quality evidence)*** • All medications should be stopped immediately and evaluated when serum ALT>3x ULN in the presence of symptoms, or > 5x ULN in the absence of symptoms ***(Strong recommendation, moderate quality evidence)*** • After ALT becomes <2x ULN with symptom resolution, step-wise reintroduction of potentially hepatotoxic anti-TB drugs may be started with Rifampicin (with or without Ethambutol), followed by INH after 3 to 7 days, subsequently rechecking transaminases. • Pyrazinamide should be permanently discontinued in patients with prolonged or severe hepatotoxicity. ***(Strong recommendation, low quality evidence)***	• Should be restarted on a regimen without PZA (HRES) with gradual re-introduction of INH and RIF (Grade B recommendation) • If asymptomatic, therapy should not be altered if AST elevations <5x ULN, with increased frequency of clinical and lab monitoring • If AST >5x ULN without symptoms or >3x ULN with symptoms, all drugs should be stopped immediately and should be evaluated
Management of GI symptoms (not related to hepatotoxicity)	• Reassurance for mild symptoms and anti-TB medications should be continued; antacids may be given if symptoms persist; food intake affects bioavailability of several anti-TB medications and is not recommended as first-line management ***(Strong recommendation, low quality evidence)***	• Medications may be taken with meals or at bedtime which is preferred over splitting dose or taking second-line drugs among patients with persistent GI intolerance *(Grade C recommendation)*

QUESTION/ISSUE	2016 CPG	2006 CPG
Management of cutaneous adverse reactions	• If with generalized erythematous rash, especially if associated with fever and/or mucus membrane involvement, stop all drugs immediately. Referral to a specialist may be necessary. ***(Strong recommendation, low quality evidence)***	• For generalized erythematous rashes associated with fever or mucus membrane involvement, stop all drugs immediately.
	• Recommendations retained; referral to a specialist may be necessary	• For minor rash affecting a limited area or generalized pruritus, antihistamine should be given as symptomatic relief, all TB drugs continued • For petechial rashes, check platelet count to rule out RIF hypersensitivity; discontinue RIF and monitor platelet count until it returns to baseline
	• Recommendations retained • May also restart medications at full dose or reintroduced one by one at intervals of 3-7 days when cutaneous reaction has improved ***(Weak recommendation, low quality evidence)*** • For PLHIV, RIF may be re-introduced last	• When rashes improve, TB medications can be started one by one at 2-3 days interval starting with RIF, then INH, EMB and PZA at gradually increasing dose. If rashes recur, last drug is stopped and not restarted unless rashes are mild and offending drug is considered essential to therapy
Role of micro-nutrient, vitamin supplement	• Only vitamin B complex recommended	• Arginine, vitamin A and zinc are beneficial as adjunct to standard anti-TB therapy in HIV-negative smear+ PTB *(Grade B recommendation)*

Additional Recommendations for Treatment of TB:

- **Pre-treatment clinical evaluation** among patients with TB disease – thorough history and physical examination to identify risk factors for liver, kidney and HIV infection *(Strong recommendation, low quality evidence)*; baseline visual acuity using Snellen and color perception charts when ethambutol is to be used *(Strong recommendation, low quality evidence)*; patient recognition of symptoms of common adverse effects prompting consult when they develop.
- **Treatment for miliary tuberculosis** follow recommendations for new and retreatment cases of PTB (if without dissemination) and extra-PTB (depending on site of dissemination) *(Strong recommendation, low quality evidence)*
- **Additional tests for monitoring treatment response** - Rapid diagnostic tests (such as IGRAs, Xpertt® MTB/Rif, anti-phospholipid antibody tests) are NOT recommended for monitoring treatment response pending further studies. *(Strong recommendation, low quality evidence)*; CXR is NOT a substitute for microbiological monitoring. It may be used in monitoring complications, identifying co-existing conditions. *(Strong recommendation, low quality evidence)*
- **Surgical indications for complications arising from EPTB:**
  - ***CNS:*** Hydrocephalus, tuberculous cerebral abscess, and vertebral TB with paraparesis are indications for neurosurgical referral. Early VP shunting should be considered among those with non-communicating hydrocephalus and among those with communicating hydrocephalus failing medical management. *(Strong recommendation, moderate quality evidence)*
  - ***SPINE:*** Surgery for spinal tuberculosis in addition to the standard chemotherapy is indicated in patients started on (a) ambulant chemotherapy who develop progressive kyphosis; (b) patients with compression of the spinal cord in whom the neurological status deteriorates inspite of chemotherapy. *(Strong recommendation, moderate quality evidence)*
  - ***LYMPH NODE:*** Therapeutic lymph node excision is not recommended for TB lymphadenitis unless unusual circumstances arise (e.g. large fluctuant lymph nodes that are about to spontaneously drain). *(Strong recommendation, moderate quality evidence)*
  - ***PERICARDIUM:*** Open surgical drainage under general anesthesia is an option for patients with TB pericardial effusion *(Weak recommendation, low quality evidence)*
  - ***PLEURA:*** Surgical procedures like pigtail drainage and decortication may be needed in symptomatic patients due to

pleural loculation and thickening. *(Weak recommendation, low quality evidence)*

- ***GASTROINTESTINAL AND PERITONEUM:*** Surgery is reserved for complications such as gut obstruction, fistula formation, and intractable ulceration. *(Strong recommendation, moderate quality evidence)*
- ***LIVER:*** Hepatectomy may be an option for nodular hepatic TB when malignancy is possible. Percutaneous aspiration and drainage may be needed in patients with multiple large hepatic TB abscess. Biliary decompression is done in patients with obstructive jaundice when necessary. *(Weak recommendation, low quality evidence)*
- ***GENITOURINARY:*** Reconstructive surgery is an option for patients who have symptoms caused by sequelae of genitourinary tuberculosis. *(Weak recommendation, low quality evidence)*

- **Other treatment recommendations:**
  - ***FOR MONITORING AND TRACKING:*** Effective ways of tracking patients and monitoring adherence through reminder systems, incentives and enablers, and coordination with support groups *(Strong recommendation, moderate quality evidence)*
  - ***FOR PARADOXICAL RESPONSE,*** non-severe form does not require specific treatment and anti-TB treatment should be continued; severe forms require symptomatic treatment. *(Strong recommendation, low quality evidence)*
- **For the following drug-induced adverse reactions:**
  - ***INH-ASSOCIATED NEUROPATHY:*** risk factors are alcoholism, malnutrition, diabetes, co-infection with HIV, slow acetylator phenotype, pregnancy, breastfeeding and renal failure. *(Strong recommendation, moderate quality evidence);* can be treated with pyridoxine (Vitamin B6) at 50-100mg daily *(Strong recommendation, moderate quality evidence);* co-administering Vitamin B6 at 10mg daily with INH is recommended to prevent INH-induced neuropathy. *(Strong recommendation, low quality evidence)*
  - ***VISUAL IMPAIRMENT:*** testing of visual acuity and color perception should be done for individuals who develop signs and symptoms of ocular toxicity while on anti-TB treatment. *(Strong recommendation, low quality evidence)*; Ethambutol should be discontinued if visual impairment develops. Referral to an ophthalmologist is warranted. *(Strong recommendation, low quality evidence)*
  - ***OTOTOXICITY:*** patients on streptomycin who develop symptoms of ototoxicity (decreased hearing, vertigo, nausea, vomiting,

nystagmus, or ataxia), should be advised to stop streptomycin and referred to an ENT specialist for appropriate management. *(Strong recommendation, low quality evidence)*

- o ***HYPERURICEMIA:*** Patients on PZA should be monitored for symptoms of gouty arthritis. Serum uric acid should ONLY be requested for patients who develop symptoms of gouty arthritis. *(Strong recommendation, low quality evidence);* For patients who develop gouty arthritis, discontinue the PZA, and administer standard treatment for hyperuricemia / gout. PZA may be continued daily or intermittently once symptoms resolve. Referral to a rheumatologist for management may be necessary if symptoms persist. *(Weak recommendation, low quality evidence)*
- o ***CUTANEOUS DRUG REACTIONS:*** examine for cutaneous reactions such as pruritus, maculopapular rashes, wheal formations, angioedema, vesicles, erythema, areas of exfoliation, xerosis, and mucous membrane lesions during patient visits *(Strong recommendation, moderate quality evidence)*
- o ***NEPHROTOXICITY:*** Serum BUN, creatinine and urinalysis should be requested for patients who have signs and symptoms of nephrotoxicity such as oliguria and edema; Among individuals who develop nephrotoxicity from anti-TB drugs, Rifampicin and Streptomycin should be discontinued. Referral to a nephrologist is warranted. *(Strong recommendation, low quality evidence)*

- **When TB patients are considered non-infectious:** At least 14 daily doses of treatment with sputum conversion and clinical improvement for *bacteriologically-confirmed* TB with no risk factors for drug-resistance *(Strong recommendation, high quality evidence);* at least 5 daily doses of treatment with clinical improvement for *clinically diagnosed* TB with no risk factors for drug-resistance *(Strong recommendation, high quality evidence)*

Recommendations retained from 2006 CPG:

1. Use of fixed dose combination (FDC) regimens and indications for single drug formulations *(Strong recommendation, moderate quality evidence)*
2. Daily preferred over intermittent regimen for treatment; 3x weekly intermittent regimens may be offered in special situations where daily regimen is not feasible *(Strong recommendation, moderate quality evidence)*

3. Use of corticosteroids in TB meningitis and pericarditis: In TB meningitis, the recommended regimen is dexamethasone 0.4 mg/kg/24H with a reducing course over 6-8 weeks ***(Strong recommendation, high quality evidence);*** In TB pericarditis, the recommended regimen is prednisolone 60 mg for the first 4 weeks, 30 mg for weeks 5-8, 15 mg for weeks 9-10 and 5 mg for week 11 ***(Strong recommendation, moderate quality evidence)***

C. DRUG-RESISTANT TB:

QUESTION/ISSUE	2016 CPG	2006 CPG
Identifying presumptive Drug-Resistant TB (DR-TB)	*Presumptive* drug-resistant TB are persons at high risk in developing DR-TB which include the following: • **New Cases** – contacts of confirmed DR-TB cases; non-converters of Category I; persons living with HIV (PLHIV) with signs and symptoms of TB ***(Strong recommendation, high quality evidence)*** • **All retreatment cases** – relapse, treatment failure, lost to follow-up (TALF), previous treatment outcome unknown (PTOU), others ***(Strong recommendation, high quality evidence)*** Assessment of likelihood of drug resistance based on history of prior treatment and exposure to a DR-TB case should be undertaken for all patients. ***(Strong recommendation, high quality evidence)*** All presumptive DR-TB *should be referred* to the nearest DOTS facility with Xpert® MTB/Rif facility for screening and testing before initiating any form of TB treatment.	• When a smear-positive patient does not respond to standard WHO re-treatment regimen specially if treatment was given under DOT • When a patient continues to have positive smears after 2 months of SCC under DOT • When a patient has had history of close or long-term exposure to person with documented resistance to anti-TB drugs, or to a person with prior history of treatment whose susceptibility test results are not known

QUESTION/ISSUE	2016 CPG	2006 CPG
Diagnosis of DR-TB	• Conventional (phenotypic) drug susceptibility testing (DST) on culture isolates *preferably* in quality-assured DST centers identified by the NTP • Genotypic DST endorsed by WHO namely Xpert® MTB/Rif and Line Probe Assay (LPA) ***(Strong recommendation, high quality evidence)*** • Xpert® MTB/Rif as initial diagnostic test in adults presumed to have DR-TB ***(Strong recommendation, high quality evidence)***	Sputum TB culture with DST
Management of DR-TB	• All DR-TB patients should be managed under programmatic setting ***(Strong recommendation, high quality evidence)*** • Immediate referral to the nearest DOTS facility with PMDT services (Treatment Center or Satellite Treatment Center) is mandatory ***(Strong recommendation, high quality evidence)***	• Immediate referral to highly specialized centers with a Programmatic MDR-TB Management (PMTM) program is advocated for patients with drug-resistant TB
Treatment Outcomes for DR-TB	• **Cured –** patient with bacteriologically-confirmed RR-TB, MDR-TB, XDR-TB who completed at least 18 months of treatment without evidence of failure AND three or more consecutive negative cultures taken 30 days apart after the intensive phase	• **Cured** – patient who completed treatment and is culture-negative for the last 12 months of treatment
	• **Treatment Completed** – patient who completed at least 18 months of treatment without evidence of failure BUT no record of 3 or more consecutive negative cultures at least 30 days apart after the intensive phase.	• **Treatment Completed** – clinically cured but not meeting the bacteriologic requirement for cure
	• ***Lost to Follow-up*** **-** patient whose treatment was interrupted for 2 consecutive months or more *(previously known as defaulter)*	• **Defaulter** – patients with 2 or more consecutive months of treatment interruption

QUESTION/ISSUE	2016 CPG	2006 CPG
	• **Treatment Failed** – treatment terminated or need for permanent regimen change of at least 2 anti-TB drugs because of lack of conversion by the end of intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs)	• **Failure** – those with more than 1 positive culture during past 12 months of treatment, those with 1 of their last cultures positive, or those remaining persistently culture positive with treatment being stopped by physician
	• **Died** – same definition	• **Died** – those who died from any cause at any point during treatment
	• **Not Evaluated** – patient for whom no treatment outcome is assigned (includes "transferred out" cases to another treatment unit and whose treatment outcome is unknown)	• **No mention**
Role of surgery in DR-TB	• **Indication:** treatment of DR-TB with localized cavitary forms with continuous M. tuberculosis excretion, confirmed by bacterial examination and DST after 4-6 months of supervised anti-TB chemotherapy ***(Strong recommendation, moderate quality evidence)*** • Should be considered as integral component of MDR-TB treatment programs, even in resource-limited countries, as long as adequate surgical expertise and facilities are present ***(Strong recommendation, moderate quality evidence)*** • Multidisciplinary approach involving surgeons, anesthesiologists and specialists should be taken when a patient is being considered for surgery. ***(Strong recommendation, moderate quality evidence)***	• **Indication:** adjuvant resectional surgery may be considered for a patient with pulmonary MDR-TB having reasonable lung function • **Timing of Surgery and TB medications:** to avoid serious and potentially fatal complications, an experienced surgeon must do the procedure when the bacillary population is likely to be at its lowest, preferably after 2 months of intensive chemotherapy which should be continued for 12-24 months after surgery to prevent relapse

D. TB AMONG HIV AND OTHER HIGH RISK CLINICAL GROUPS

QUESTION/ISSUE	2016 CPG	2006 CPG
Screening for TB among PLHIV	• All newly diagnosed PLHIV should be screened for active TB ***(Strong recommendation, high quality evidence)***	• HIV-infected patients should be screened for TB
Diagnosis of TB among persons living with HIV (PLHIV)	• Based on symptomatic screening (i.e. cough of any duration, fever, night sweats and weight loss), CXR, sputum Xpert® MTB/Rif • Xpert® MTB/Rif as initial diagnostic test in adults with presumed HIV-associated TB ***(Strong recommendation, high quality evidence)*** • All presumptive TB-HIV should be referred to the nearest DOTS facility with Programmatic Management of Drug-resistant Tuberculosis (PMDT) services or to an Xpert® MTB/Rif facility for screening and testing before initiating any form of TB treatment ***(Strong recommendation, high quality evidence)*** • If Xpert® MTB/Rif is negative, diagnosis for PTB will be based on a high index of clinical suspicion ***(Strong recommendation, high quality evidence)***	• Both sputum smear examination and TB culture recommended as initial tests to diagnose TB in HIV-infected individuals • As in non-HIV patients, examination of 3 sputum specimens is recommended
Treatment for PTB in PLHIV	• Same recommendation maintained • Co-trimoxazole prophylaxis at a total daily dose of 800 mg sulfamethoxazole + 160 mg trimethoprim should also be given to prevent *Pneumocystis jirovecii* pneumonia among PLHIV regardless of CD4 count ***(Strong recommendation, high quality evidence)***	• Same as general population
Management of TB among pregnant and lactating women	• Same recommendation for treatment regimen • CXR with abdominal shield, if indicated, is considered to be relatively safe during pregnancy. An informed consent is necessary. Pregnancy should neither deter nor delay the diagnosis and management of PTB. ***(Strong recommendation, low quality evidence)***	• 2HRZE/4HR with pyridoxine 25mg/day • Streptomycin is contraindicated
Management of TB among patients with hepatic dysfunction	• Compensated liver cirrhosis - 2HRES/6HR; 2HSE/10HE or 9HRE • In patients with **decompensated** liver cirrhosis, referral to specialized centers is warranted because of the possible use of second line TB drugs. The more advanced the liver disease, the less the number of hepatotoxic drug should be used ***(Strong recommendation, low quality evidence)***	• 2HRES/6HR or 2HRE/6HE • 2HES/10HE for those with more extensive liver damage

QUESTION/ISSUE	2016 CPG	2006 CPG
Management of TB among patients with renal dysfunction	• 2HRZE/4HR initially then adjusted based on subsequent renal function • For patients on hemodialysis on TB treatment, anti-TB medications should be administered immediately *after* hemodialysis session. • For patients on peritoneal dialysis, anti-TB medications may be administered regardless of PD schedule; begin with doses similar to those recommended for patients on hemodialysis. ***(Strong recommendation, low quality evidence)***	• 2HRZ/6HR • Streptomycin and ethambutol to be used with caution, increasing dose intervals instead of decreasing dose

Additional Recommendations for TB in HIV and Other High Risk Clinical Groups:

- For PHLIV with TB: Antiretroviral therapy should be initiated **after the second week** of TB treatment regardless of CD4 count. For patients with TB meningitis, antiretroviral therapy should be initiated **after the intensive phase** of TB treatment. Efavirenz is the preferred NNRTI for HIV patients on TB treatment. Avoid the use of nevirapine because of drug-drug interactions ***(Strong recommendation, high quality evidence)***
- Revised treatment regimens: 2HZE/12-18HE for post-SOT recipients without risk factors for DR-TB ***(Weak recommendation, moderate quality evidence)***; 2RHZE/4-9RH for severe cases of TB ***(Weak recommendation, moderate quality evidence)***; 2HRSE/6HR, 2SHE/10HE or 9HRE for compensated liver cirrhosis
- Immediate referral to PMDT treatment centers: for management of DR-TB among high risk clinical groups similar to general population ***(Strong recommendation, high quality evidence);*** for decompensated liver cirrhosis for possible use of second line TB drugs
- Routine screening recommended for the following high risk groups:
  - PLHIV (when active disease is ruled out, patient is treated for presumed LTBI, no screening needed) ***(Strong recommendation, moderate quality evidence)***
  - Solid organ and hematologic transplant recipients ***(Strong recommendation, low quality evidence)***
  - Rheumatoid arthritis patients on biologicals ***(Strong recommendation, low quality evidence)***
  - Patients on chronic dialysis ***(Strong recommendation, low quality evidence)***
  - Patients with Type 1 diabetics, Type 2 diabetics on insulin therapy with

poor glycemic control, diabetics exposed to active TB or those who are smokers *(Weak recommendation, moderate quality evidence)*

- Pregnant patients with known exposure to active TB, injection drug users, or immunocompromised. *(Strong recommendation, low quality evidence)*

- TST preferred among high risk clinical groups in resource-limited setting like the Philippines *(Strong recommendation, low quality evidence)*; Routine LTBI screening using TST or IGRA for rheumatoid arthritis on biologic therapy *(Strong recommendation, low quality evidence)*
- Recommended treatment for LTBI: INH 300mg for 6 months under DOT *(Strong recommendation, moderate-high quality evidence)*

E. PREVENTION AND CONTROL OF TB:

QUESTION/ISSUE	2016 CPG	2006 CPG
Management of LTBI	• High risk groups for LTBI screening and treatment *(Refer to Chapter 5 on TB-HIV and Other High Risk Clinical Groups)*	• At this time, treatment of patients with LTBI not a priority in the Philippines. While TB remains uncontrolled, resources must be focused on the "source" case. • High risk groups include for LTBI treatment are: diabetics on immunosuppressive treatment, patients on hemodialysis presenting with fibrotic lesions, health care workers who convert from negative to positive, HIV patients

Additional Recommendations on Prevention and Control of TB in the General Population:

- Covering one's mouth when coughing to minimize spread of potentially infectious aerosols, including those laden with MTB. *(Strong recommendation, low quality evidence)*
- Use of surgical face masks among patients presumed or confirmed to have infectious PTB until deemed non-infectious; NOT recommended to wear face-piece respirator masks since these masks are primarily meant to prevent inhalation of the infectious droplets. *(Strong recommendation, low quality evidence)*
- No evidence on use of 2 or more surgical face masks in layers for additional protection. *(Strong recommendation, moderate quality evidence)*
- Use of filtering face-piece respirator masks (i.e., N95 or FFP2) among exposed health care workers when performing procedures with high risk of aerosolization
- Regular fit testing for filtering face-piece respirator masks to ensure proper use *(Strong recommendation, high quality evidence)*

- Household contacts of active TB cases at increased risk of infection and disease should be screened for disease activity according to CPG recommendations on diagnosis, or an CXR at the least, specially if the index case is bacteriologically confirmed, cavitary, with frequent coughs and has yet to receive or in the early stages of the recommended treatment regimen. *(Strong recommendation, high quality evidence)*
- Smokers, alcoholics (i.e., $\geq$ 40 g/day) and underweight individuals (i.e., BMI $\leq$ 20) have slightly increased risk of contracting TB and progressing to disease compared to general population. As modifiable risk factors, clinicians must address these appropriately i.e., identify and advise smokers to quit, and offer dietary or lifestyle modifications.
- The risk of progression to disease is strongly significant among persons with recent TB infection (i.e., < 2 years) and upper lobe fibro-nodular disease on chest x-ray. Periodic monitoring for symptoms suggestive of disease activity and a repeat CXR after 4-6 months to establish radiographic stability is recommended for early detection of disease activity in these individuals. *(Strong recommendation, moderate quality evidence)*
- BCG re-vaccination is NOT recommended. *(Strong recommendation, moderate quality evidence)*
- Isolation is recommended for: (1) bacteriologically confirmed PTB cases who have not started or are in the early stages of anti-TB treatment (including EPTB cases with potential for aerosol generation) and (2) presumptive DR-TB or known MDR/XDR-TB cases
- Documented HIV/AIDS cases or those with strong clinical evidence for HIV/AIDS should be isolated from active TB cases. *(Strong recommendation, moderate quality evidence)*
- Administrative control for all health facilities dealing with presumptive and confirmed TB cases through identification of people with TB symptoms (triage); separation of infectious cases; minimizing time in health care facilities; ensuring prompt and effective full treatment; cough etiquette promotion; surveillance of TB disease among health workers; assessment at all levels of the health system and in congregate settings
- Ensure environmental controls are in place such that health facility design, construction, renovation and use are appropriate – e.g., good ventilation is assured.
- Provide appropriate personal protective equipment for health care workers in areas at high-risk for TB transmission *(Strong recommendation, low quality evidence)*

Chapter 1

Development of the 2016 Philippine Clinical Practice Guidelines for Tuberculosis in Adults

Chapter 1

Development of the 2016 Philippine Clinical Practice Guidelines for Tuberculosis in Adults

This document updates the 2006 Philippine Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis, intended for practicing clinicians and other healthcare professionals involved in the holistic care of adult patients with presumptive or confirmed tuberculosis (TB), and localizes recommendations in the context of the Philippine setting. Its timely release comes after the recent revision of the National Tuberculosis Control Program (NTP) Manual of Procedures (MOP) 5th Edition of the Department of Health (DOH), the 2014 International Standards for Tuberculosis Care (ISTC) and recent TB policies and statements released by the World Health Organization (WHO) since 2006.

The 2016 CPGTB has the following objectives:

1. To update the 2006 CPG on TB in Adults with recent medical evidence (2005-2015) in light of new developments at the global level, further localized in the Philippine setting, in order to assist clinicians and other TB personnel standardize diagnosis and management of TB among adult Filipinos;
2. To harmonize with and complement the NTP Manual of Procedures (MOP) by providing medical evidence to support its policies, with focus on local data where available, in order to facilitate acceptance and compliance among private healthcare providers; and
3. To identify new and relevant TB-related issues and areas for future research in the diagnosis, treatment, prevention and control of all forms of TB (pulmonary or extra-pulmonary, susceptible or drug resistant) among immunocompetent and high risk clinical groups in the Philippine setting.

This document provides the "clinical perspective" beyond the context of the National TB Program processes and procedures, addressing specific clinical questions and issues encountered in various health care settings in the country where resources and expertise may be available, and which cannot be addressed by the NTP Manual of Procedures. This hopes to serve as standard reference for clinicians, training programs for specialty and sub-specialty care, and the academe for the overall management of TB in adults.

This is a joint initiative led by the Philippine Coalition Against Tuberculosis (PhilCAT), Philippine Society of Microbiology and Infectious Diseases (PSMID), and the Philippine College of Chest Physicians (PCCP) in collaboration with other specialty professional societies and the Department of Health (DOH).

Methodology

A Task Force composed of TB experts, clinicians, epidemiologists, academicians and program implementers was created, headed by a Steering Committee for overall technical and administrative direction. An orientation and training workshop on the objectives, context and processes was done to all members of the Task Force using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Clinical questions on diagnosis, treatment, drug-resistance, TB-HIV and other high risk clinical groups, prevention and control were identified, approved in plenary and assigned to Technical Writing Committees (TWCs) who appraised available published or unpublished local and foreign medical evidence from 2005 to 2015. Quality of evidence was assessed to be high, moderate, low, and very low based on the study design and estimate of effect as shown in **Table 1.**

Statements were initially developed through a series of small group discussions (SGDs) in consultation with relevant experts and respective technical advisers at the committee level. Strength of recommendations was assessed by a 27-member Voting Consensus Panel based on the balance between desirable and undesirable effects, quality of evidence, patients values and preferences, cost and access to tests or interventions, largely guided by its potential implications to patients, clinicians and policy makers **(Table 2).**

TABLE 1
Quality of Evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Framework

QUALITY OF EVIDENCE		STUDY DESIGN	LOWER IF:	HIGHER IF:
High	Further research is *very unlikely* to change confidence in the estimate of effect	Randomized controlled studies (RCTs)	***Study quality:*** Poor quality of implementation of RCT ***Inconsistency of results:*** ***Indirectness:*** Different population, intervention, outcomes ***Imprecise results:*** High probability of *reporting bias*	***Stronger association:*** Large magnitude of effect, no plausible confounders ***Very large magnitude of effect,*** no major threats to validity ***Dose response gradient***
Moderate	Further research is *likely* to have impact on the confidence in the estimate of effect	Downgraded RCTs or upgraded observational studies		
Low	Further research is *very likely* to have an important impact on the confidence in the estimate of effect	Observational studies		
Very Low	Any estimate of effect is *very uncertain*	Case series or expert opinion		

Reference: Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336:924-926

Voting was done as follows: A=accept completely; B=accept with some reservations; C=accept with major reservations; D= reject with some reservations; and E= reject completely. Statements reached consensus if 80% voted A or B; rejected if less than 80% was reached or at least one (1) member voted D or E.

The First Draft was presented last February 6-7, 2015 to the Voting Consensus Panel for initial inputs and approval. Statements that reached consensus were presented at the Annual Convention of the Philippine College of Chest Physicians (PCCP) last March 6-7, 2015 for feedback and comments; while those that were not accepted were sent back to the Technical Writing Committees for either revision or further literature review as recommended by the Voting Panel. The Second Draft was finalized in a write shop by the TWCs with their respective technical advisers last June 19-20, 2015, and presented for final voting in the Final Consensus Panel meeting last July 18, 2015. Statements that did not reach consensus but were not rejected

TABLE 2 Implications of Strength of Recommendations (GRADE Approach) to Patients, Clinicians and Policy Makers

STRENGTH OF RECOMMENDATION		IMPLICATIONS OF THE RECOMMENDATIONS		
		TO PATIENTS	*TO CLINICIANS*	*TO POLICY MAKERS*
Strong	The benefits outweighed the harm. There are no cost or access issues for the general population	Most people in the situation would want the recommended course of action and only very few would not; request for discussion if the intervention is not offered	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Weak	Best available evidence is very low to low quality; Magnitude of benefits or risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting; Benefits may not warrant the cost or resource requirements in all settings	Most people in the situation would want the recommended course of action, but many would not	Different choices are appropriate for different patients, and clinician must help patients arrive at a management decision consistent with patient's values and preferences	Policy making will require substantial debate and involvement of any stakeholders

Reference: Guyatt GH et al. Going from evidence to recommendations. BMJ. 2008 May 10; 336(7652):1049-1051.

by the Voting Consensus Panel were reviewed, revised and elevated to the Steering Committee for final approval. The first public dissemination was done at the 22nd PhilCAT Annual Convention last August 13-14, 2015.

An Advisory Committee represented by previous and current heads of participating professional medical societies assisted the Task Force.

Dissemination of this document requires development of standard modules by trained pool of speakers selected among the members of the participating societies for standardized structured dissemination to their members.

FIGURE 1: Status of Tuberculosis in the Philippines 2014

Philippines ■ Population 2014 **99 million**

Estimates of TB burden[a] 2014

	NUMBER (thousands)	RATE (per 100 000 population)
Mortality (excludes HIV+TB)	10 (9–11)	10 (9.1–11)
Mortality (HIV+TB only)	0.08 (0.055–0.11)	0.08 (0.06–0.11)
Prevalence (includes HIV+TB)	410 (360–470)	417 (367–471)
Incidence (includes HIV+TB)	290 (250–320)	288 (254–324)
Incidence (HIV+TB only)	2.5 (2–3.2)	2.6 (2–3.2)
Case detection, all forms (%)	85 (76–97)	

Estimates of MDR-TB burden[a] 2014

	NEW	RETREATMENT
% of TB cases with MDR-TB	2 (1.4–2.7)	21 (16–29)
MDR-TB cases among notified pulmonary TB cases	4 600 (3 300–6 300)	6 500 (4 700–8 700)

TB case notifications 2014

	NEW[a]	RELAPSE
Pulmonary, bacteriologically confirmed	92 991	6 277
Pulmonary, clinically diagnosed	139 950	
Extrapulmonary	4 161	

Total new and relapse	**243 379**
Previously treated, excluding relapses	24 057
Total cases notified	**267 436**

Among 97 578 new and relapse cases:
12 191 (12%) cases aged under 15 years; male:female ratio: 1.8

Reported cases of RR-/MDR-TB 2014

	NEW	RETREATMENT	TOTAL[b]
Cases tested for RR-/MDR-TB	4 415 (5%)	20 196 (67%)	27 287
Laboratory-confirmed RR-/MDR-TB cases			3 000
Patients started on MDR-TB treatment[c]			2 680

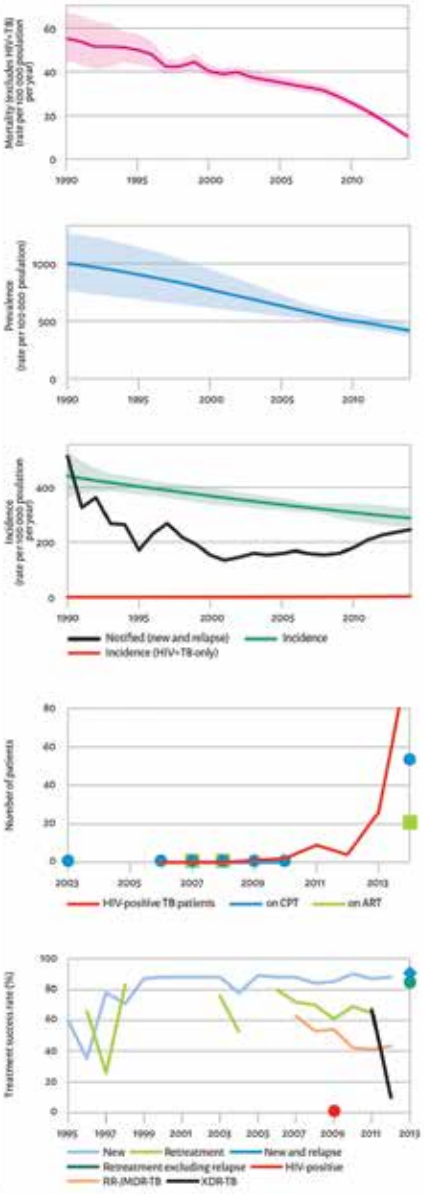
TB/HIV 2014

	NUMBER	(%)
TB patients with known HIV status	53 354	(20)
HIV-positive TB patients	108	(<1)
HIV-positive TB patients on co-trimoxazole preventive therapy (CPT)	20	(19)
HIV-positive TB patients on antiretroviral therapy (ART)	53	(49)
HIV-positive people screened for TB	5 995	
HIV-positive people provided with IPT		

Treatment success rate and cohort size

	(%)	COHORT
New and relapse cases registered in 2013	(90)	216 250
Previously treated cases, excluding relapse, registered in 2013	(86)	2 924
HIV-positive TB cases, all types, registered in 2013		
RR-/MDR-TB cases started on second-line treatment in 2012	(43)	1 798
XDR-TB cases started on second-line treatment in 2012	(10)	10

Data are as reported to WHO. Estimates of TB and MDR-TB burden are produced by WHO in consultation with countries.
[a] Ranges represent uncertainty intervals.
[b] Includes cases with unknown previous TB treatment history.
[c] Includes patients diagnosed before 2014 and patients who were not laboratory-confirmed as having MDR/RR-TB.



Reference: WHO Global TB Report 2015

Chapter 2

Diagnosis of Tuberculosis in Adult Filipinos

Chapter 2
Diagnosis of Tuberculosis in Adult Filipinos

Case finding remains an important tenet in the overall concept of TB control. Certainly, accurately finding possible TB cases early and confirming their diagnosis would translate to better patient outcomes. However, diagnosis of TB remains challenging in various clinical settings where prompt decision-making is crucial for early initiation of appropriate treatment, avoiding over- or under-diagnosis of TB in adults.

In this update, direct sputum smear microscopy (DSSM) still remains the primary diagnostic tool because it is readily available, affordable, and acceptable as long as performed in quality-assured laboratories. However, the demand for rapid tests with shorter turnaround time and higher sensitivity has increased for the past few years which have significant implication in clinical decision-making whether to treat or not to treat an individual as a case of TB. Although radiologic imaging studies like chest radiographs and chest CT scans are usually requested first and are sometimes more available with faster results, their main role remains supportive and bacteriologic confirmation will always be warranted.

The introduction of WHO-recommended rapid diagnostic tools in the overall diagnostic algorithm may be considered a "game changer" in the early diagnosis and management of all forms of TB. Specifically, the Xpert® MTB/Rif, has recently been made available in most national TB programs after the WHO has recognized its pivotal role in TB diagnostic algorithms. It is for this purpose that in 2013, the WHO has revised standard case definitions and reporting framework for TB to emphasize providing more importance in the pursuit towards "bacteriologic" confirmation rather than mere clinical diagnosis of TB, which often mimics a lot of infectious and non-infectious conditions, including malignancy.

Definition of Terms

The following are the WHO revised standard case definitions (WHO 2013) which should be used by all healthcare providers:

Presumptive TB – A patient who presents with symptoms or signs (radiologic findings) suggestive of TB (replaces the term *TB suspect* or *TB symptomatic*).

Bacteriologically confirmed case of TB – A patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic test (such as Xpert® MTB/RIF). All such cases should be notified, regardless of whether TB treatment is started.

Clinically diagnosed case of TB – A patient who does not fulfill the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment (based on imaging studies, suggestive histology and extra-pulmonary cases without laboratory confirmation). Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Case of pulmonary TB – Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of pulmonary TB.

Case of extra-pulmonary TB – Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. abdomen, genitourinary tract, joints and bones, lymph nodes, meninges, pleura, skin.

For purposes of standardized reporting across countries, this document adopts the WHO cut off of **15 years old and above** to refer to adults.

Extensive literature search, retrieval and appraisal were performed to provide evidence-based recommendations in the diagnosis of susceptible TB among immunocompetent adults, harmonized with international standards and policies for easier application for the clinician.

Outline of Issues in the Diagnosis of Tuberculosis:

PULMONARY TUBERCULOSIS

1. In the general population, how is presumptive Pulmonary Tuberculosis (PTB) identified?
2. What examinations should be performed to bacteriologically confirm PTB?

Direct Sputum Smear Microscopy (DSSM)

3. How should sputum be collected for DSSM?
4. How may sputum specimens should be collected? What should be the timing of sputum collection?
5. What is the preferred type of microscopy for DSSM?
6. How are the results of DSSM interpreted?

TB Culture

7. When should TB Culture be requested?

TB Culture with Drug Susceptibility Testing (DST)

8. What are the indications for performing sputum TB culture with drug susceptibility testing (DST)?

Xpert® MTB/Rif

9. When should Xpert® MTB/Rif be requested? How accurate is Xpert® MTB/Rif in confirming PTB?
10. What are the requirements for sputum specimens for Xpert® MTB/Rif? Where should sputum specimens for Xpert® MTB/Rif be submitted?
11. How are results of Xpert® MTB/RIF interpreted?

Work-up for Smear-Negative or Those Without Sputum

12. What should be done for presumptive PTB who cannot expectorate sputum for bacteriologic confirmation?
13. What additional work-up should be performed among patients who are smear-negative?

Chest Radiography

14. What is the role of chest x-ray in the diagnosis of PTB?
15. What is an acceptable chest x-ray film? How should chest x-ray be interpreted?
16. What is the role of digital imaging in the diagnosis of PTB? What are the acceptable specifications for digital imaging?

Chest CT Scan

17. What is the role of chest CT scan in the diagnosis of PTB?

EXTRA-PULMONARY TUBERCULOSIS

18. What are the recommended diagnostic work-up for Extra-Pulmonary Tuberculosis?

OTHER DIAGNOSTIC LABORATORY TESTS

19. What is the role of nucleic acid amplification testing (NAATs) in the diagnosis of TB disease?
20. Can tuberculin skin test (TST) be used in the diagnosis of TB disease?
21. Can Quantiferon-Gold-in-tube (QFT-GIT) be used in the diagnosis of TB disease?
22. Can enzyme-linked immunospot (EliSpot) be used in the diagnosis of TB disease?
23. Can tuberculosis Interferon-gamma release assays (IGRAs) be used in the diagnosis of TB disease?
24. Can Microscopic Observation Drug Susceptibility(MODS) and Lipoarabinomannan (LAM) assays be used in the diagnosis of TB disease?

QUESTION 1 In the general population, how is presumptive PTB identified?

For patients 15 years old and above, a presumptive TB has any of the following:

- Cough of at least 2-weeks duration ***(Strong recommendation, low quality evidence)***
- Unexplained cough of any duration in a close contact of a known active TB case ***(Strong recommendation, low quality evidence)***
- Chest x-ray findings suggestive of PTB, with or without symptoms ***(Strong recommendation, low quality evidence)***
- ANY of the following symptoms: cough of any duration, significant and unintentional weight loss, fever, bloody sputum or hemoptysis, chest pains not referable to any musculoskeletal disorders, easy fatigability or malaise, night sweats, shortness of breath or difficulty of breathing ***(Weak recommendation, low quality evidence)***

Summary of Evidence

In settings where TB prevalence in the general population is 100/100,000 population or higher, systematic screening for active TB should be considered among people who are seeking health care or who are in health care and belong to selected risk groups (WHO, 2013). The estimated epidemiological burden of TB in the Philippines as reported by WHO in 2013 has a prevalence rate of 438 (385–495)/100,000 population (WHO, 2014).

Presumptive TB is prompted largely by the presence of suggestive clinical symptoms (i.e. cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue), suggestive radiographic findings, and by awareness of co-morbidities and epidemiological circumstances that increase the risk of TB in an individual patient. Evaluation for TB is also indicated in vulnerable groups and individuals with increased susceptibility such as persons living with HIV and other co-morbidities, children, and populations at high risk such as prisoners and persons living in high-incidence urban areas even in the absence of typical symptoms. *(Please refer to Chapter 5 on TB in HIV and Other High Risk Clinical Groups).*

Options for initial screening include symptom screening, chest radiography, or in combination, performed either sequentially where chest x-ray is offered among individuals with symptoms, or in parallel where further examinations are offered for those with symptoms and/or chest x-ray abnormalities (Van'tHoog, 2013).

A cough duration of at least 2 weeks serves as indication to initiate evaluation for TB in most national and international guidelines, particularly in areas of moderate to high prevalence (TB CARE I, 2014). The systematic review by Van'tHoog et al (2013) summarized pooled estimates of sensitivity and specificity of symptom and chest x-ray screening tools to detect bacteriologically confirmed PTB (with culture as gold standard). Though this systematic review included studies in general populations with high TB burden, this should still be interpreted with caution due to the small number of studies involved with methodological differences/concerns and heterogeneity. Based on the symptom screens, prolonged cough (defined at least 2 weeks) for PTB had a low pooled sensitivity of 24.7% (95% CI 17.6–31.7) and a high pooled specificity of 96.3% (95% CI 94.7–97.9) in low HIV prevalence population in Asia compared to the pooled sensitivity of 49.2% (95% CI 38.9–59.7) and pooled specificity of 92.3% (95% CI 89.1–95.6) in high HIV prevalence sub-Saharan African regions (Van'tHoog, 2013).

TABLE 3A Summary of Evidence for Prolonged Cough as Diagnostic Criteria for Presumptive PTB in Low HIV Prevalence Population

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		MEASURE OF ACCURACY		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
4	Cross Sectional	High Risk of Bias Very serious	Inconsistent*	Somewhat Indirect	971	182,331	0.247	0.176-0.317	Low	Critical
Specificity										
4							0.963	0.947-0.979		

Inconsistent: there was moderate heterogeneity for sensitivity (based on visual inspection of the confidence intervals); there was little heterogeneity for specificity

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	SPECIFICITY			POSITIVE	NEGATIVE
4	MoH Cambodia, 2005	22160	0.39 (0.33-0.45)	0.94 (.93-.94)	0.0699534	0.991916	6.05587	0.655797
	Hoa, 2012	93758	0.26 (0.21-0.32)	0.96 (0.95-0.96)	0.016905	0.997789	5.976153	0.77007
	MoH Myanmar, 2012	51367	0.20 (0.15-0.25)	0.97 (0.97-0.97)	0.04187	0.995114	7.340294	0.824809
	Datta, 2001	16017	0.14 (0.09-0.22)	0.98 (0.97-0.98)	0.04401	0.99308	5.805992	0.878765

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
MoH Cambodia, 2005	105	1396	167	20492
Hoa, 2012	71	4129	198	89360
MoH Myanmar, 2012	60	1373	244	49690
Datta, 2001	18	391	108	15500
Total	254	7289	717	175042

TABLE 3B Summary of Evidence for Prolonged Cough as Diagnostic Criteria for Presumptive PTB in High HIV Prevalence Population

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		MEASURE OF ACCURACY		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
4	Cross Sectional	Very serious	Inconsistent*	Somewhat Indirect	307	39,793				
Specificity										
4										

Reference: WHO: Systematic screening for active tuberculosis: principles and recommendations: Annex 2 Table 3, 4

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	SPECIFICITY			POSITIVE	NEGATIVE
4	Den boon, 2006	2511	0.54 [0.33, 0.73]	0.87 [0.86, 0.89]	0.042683	0.994503	4.26139	0.528293
	Vant hoog, 2012	20566	0.52 [0.43, 0.61]	0.89 [0.89, 0.90]	0.028269	0.996776	4.83500	0.537521
	Corbett, 2010	8979	0.47 [0.36, 0.58]	0.96 [0.96, 0.97]	0.106017	0.995133	13.3601	0.55096
	Ayles, 2009	8044	0.43 [0.32, 0.55]	0.93 [0.93, 0.94]	0.058219	0.993968	6.23268	0.611871

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
Den boon, 2006	14	314	12	2171
Vant hoog, 2012	64	2200	59	18243
Corbett, 2010	37	312	42	8588
Ayles, 2009	34	550	45	7415
Total	149	3376	158	36417

Household and other close contacts should be systematically screened for active TB. In a systematic review of TB contact investigation in low- and middle-income countries, symptom evaluation of household and close contacts for active TB is recommended as a priority based on their risk to develop active TB. While the quality of evidence is low for the benefit of TB screening in this population, high value is still placed on ensuring early diagnosis of TB, because of the high likelihood of having undetected TB and a high risk of poor health outcomes if not initiated treatment early. Priority contacts for clinical evaluation is based on risk assessment of the index case, the circumstances of the exposure and the contact. All household and close contacts should be evaluated following procedures for presumptive TB (WHO, 2012).

In a systematic review and meta-analysis of 95 studies from low- and middle-income settings, the estimated overall prevalence of active TB (clinically diagnosed and/or bacteriologically confirmed) among contacts was 3.1% (95% CI 2.2–4.4%, I2599.4%), bacteriologically confirmed was 1.2% (95% CI 0.9–1.8%, I2595.9%), and latent TB infection was 51.5% (95% CI 47.1–55.8%, I2598.9%). Incidence was highest in the first year after exposure (Fox, 2013). In a cohort study in India among household contacts of TB, cough had a sensitivity of 71% with a specificity of 100% (Singh J, 2013, *refer to* Table 3A). In a cross sectional TB survey in China among 3,355 household contacts of notified TB cases, symptoms such as cough, hemoptysis and fever had a sensitivity of 50% with specificity of 94% (Jia 2014, *refer to* Table 3B). A comparative meta-analysis of TB contact investigation interventions in 11 lower and middle income countries across Africa, Asia and the Middle East which reviewed the yield of cases among contacts, projects that screened contacts with any TB related symptoms and those that tested all contacts regardless of symptoms showed substantially higher percentage yield of smear (+) cases than the projects using a strict criteria of $\geq$ 2 weeks cough (Blok, L, 2015).

In a study in Hong Kong, index cases with cough or pulmonary cavities and diabetic contacts were independent risk factors of early cases (all $P < 0.05$). Adjusted at risk index characteristics for late TB development included positive sputum smear (2.79, 95%CI 1.31–5.95) and family history of TB (4.26, 95%CI 2.01– 9.03). Contact risk factors included diabetes mellitus (3.44, 95%CI 1.04–11.33) and institutionalization (3.61, 95%CI 1.70–7.65) (Lee, 2008).

In the Philippines, factors that were independently associated with TB disease in household contacts by multivariable models were older age (>50, 36–50 and 18–35 years: odds ratio [OR] 13.4, 95% CI 5.9–30.3; OR

TABLE 4A Summary of Evidence for Cough in a household contact of a known active TB case as Diagnostic Criteria for Presumptive PTB

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		MEASURE OF ACCURACY		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
4	Cohorts	Very serious	Inconsistent*	Indirect	83	1525	0.710843		Low	Critical
Specificity										
4							1			

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	SPECIFICITY			POSITIVE	NEGATIVE
1	Singh J, 2013	432 index cases; 1608 contacts	0.710843	1	1	0.9845	1	0.289157

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)	WITH TB TP + FN	NO TB TN + FP
Singh J, 2013	59	0	24	1525	83	1525

6.7, 95%CI 2.8–16.3; and OR 10.7, 95%CI 4.8–24.2, respectively) and history of TB (OR 8.2, 95%CI 5.1–13.4). For TB infection, age (>50, 36–50 and 18–35 years: OR 2.6, 95%CI 1.3–5.0; OR 2.8,95%CI 1.6–5.0; and OR 2.3, 95%CI 1.5–3.4, respectively), and >10 years of cohabitation (OR 1.9, 95%CI 1.2–3.0) were associated with increased risk (Sia, 2010).

Screening with chest x-ray can be done to identify findings suggestive of TB. Systematic screening for active TB should be considered in people with untreated fibrotic lesions seen on chest x-ray (WHO, 2013). In the systematic review by Van't Hoog, chest x-ray findings compatible with TB (active or inactive) from combined studies of low/high HIV prevalence areas had a sensitivity of 98% (95% CI 95–100) with a specificity of 75 % (95% CI 72–79).

TABLE 4B Summary of Evidence for symptoms such as cough, hemoptysis and fever in a household contact of a known active TB case as Diagnostic Criteria for Presumptive PTB

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		*MEASURE OF ACCURACY*		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
1	Cross sectional	Very serious	Inconsistent	Indirect	92	3263	0.5		Low	Critical
Specificity										
1							0.936255			

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	*SPECIFICITY*			*POSITIVE*	*NEGATIVE*
1	Jia, 2014	1575 index cases; 3355 contacts	0.5	0.936255	0.181102	0.985166	7.84375	0.534043

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)	WITH TB TP + FN	NO TB TN + FP
Jia, 2014	46	208	46	3055	92	3263

Abnormalities suggestive of active TB had a pooled sensitivity of 87% (95% CI 79–95) and pooled specificity of 89% (95% CI 87–92). However, reliance on the chest radiograph as the sole test for the diagnosis of TB will result in both over- and missed diagnosis of TB and other diseases (TB CARE I, 2014).

In the Philippines, the National TB Prevalence Survey (NTPS) showed that the prevalence of those with CXR findings suggestive of TB increased from 4.2% in 1983 to 6.3% in 2007 (DOH, 2013), probably due to the increased survival of TB patients with persisting radiographic changes despite bacteriological cure resulting from increased coverage of DOTS. Further, the same survey showed that the prevalence of sputum smear- negative and culture-positive PTB was 3.8% and 8.4% respectively among 1328 subjects with positive CXR (with or without symptoms), which was considerably greater compared to the 1960 symptomatic subjects (with or without positive CXR) examined (1.7% and 2.6%, respectively) (Tupasi et al, 2009).

Combination of chest x-ray and symptom screening was a more sensitive and accurate screening strategy in identifying TB cases than symptom screening alone (Van'tHoog, 2013). In a Kenya study, sensitivity of 90% [95% CI 81–96] for any CXR abnormality in persons with "TB suggestive symptoms" and 56% [95% CI 54–58] specificity was noted (Van'tHoog, 2013).

A cohort study among Filipino adults done in a university teaching hospital, the Philippine General Hospital, noted TB as a common cause of chronic cough of at least 3-week duration seen in 20.3% of cases; with PTB as the most common etiology at 43.3% among patients with abnormal chest radiograph (Berratio and Wang). A descriptive study in another university teaching hospital, the University of Santo Tomas Hospital (USTH) showed that chronic cough (> 21 days) is still the most common symptom of PTB in 83% of cases among patients without any co-morbid illness, and noted to be even higher among those with co-morbid illness (Solano-Soberano). In another study in the same institution, findings showed that in the absence of other laboratory tests and expert opinion, cough and sputum production, together with presence of ill-defined infiltrates on chest radiographs can help primary physicians in deciding disease activity in smear-negative TB (Kingkay, 2014). Another study at the Manila Doctors Hospital (MDH) showed that most common symptoms of PTB are cough (87.5%), fever (50%) and weight loss (29.2%) (Balcita RG).

TABLE 5A Summary of Evidence for Chest radiography with Any abnormality compatible with TB (active or inactive) as Diagnostic Criteria for Presumptive PTB

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		MEASURE OF ACCURACY		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
3	Cross Sectional	Serious		Indirect	441	71,624				
Specificity										

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	SPECIFICITY			POSITIVE	NEGATIVE
3	Den boon, 2006	2608	0.97 [0.82, 1.00]	0.74 [0.72, 0.76]	0.039886	0.999475	3.6944	0.04668
	Vant hoog, 2012	19216	0.94 [0.88, 0.98]	0.73 [0.72, 0.73]	0.021153	0.999495	3.4389	0.08033
	MOH, Myanmar	50241	0.99 [0.98, 1.00]	0.79 [0.79, 0.80]	0.027263	0.99995	4.7943	0.00863

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
Den boon, 2006	28	674	1	1905
Vant hoog, 2012	113	5229	7	13867
MOH, Myanmar	290	10347	2	39602
Total	431	16250	10	55374

TABLE 5B Summary of Evidence for Chest radiography with Abnormalities suggestive of Active TB as Diagnostic Criteria for Presumptive PTB

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS					
					NUMBER OF PATIENTS		MEASURE OF ACCURACY		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness	With PTB	Without PTB	Estimate	95% CI		
Sensitivity										
5	Cross sectional	Serious		Indirect	974	162,872				
Specificity										

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	SPECIFICITY			POSITIVE	NEGATIVE
5	Den boon, 2006	2608	0.90 [0.73, 0.98]	0.88 [0.87, 0.89]	0.077151	0.998679	7.43474	0.117634
	Hoa, 2012	87642	0.85 [0.80, 0.89]	0.96 [0.96, 0.96]	0.062211	0.999524	21.5471	0.154815
	MOH, Myanmar, 2012	50241	0.91 [0.88, 0.94]	0.92 [0.92, 0.92]	0.063255	0.999457	11.5509	0.092977
	MOH, Cambodia, 2005	22012	0.97 [0.94, 0.99]	0.90 [0.90, 0.91]	0.109726	0.999592	9.85088	0.032626
	Van't Hoog, 2012	1143	0.77 [0.68, 0.84]	0.87 [0.85, 0.89]	0.392694	0.971861	5.95233	0.266525

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
Den Boon, 2006	26	311	3	2268
Hoa, 2012	229	3452	40	83921
MOH, Myanmar, 2012	267	3954	25	45995
MOH, Cambodia, 2005	264	2142	8	19598
Vant hoog, 2012	86	133	26	898
Total	872	9992	102	152680

A descriptive study in a public-private mixed DOTS setting in Iloilo City showed that cough (85.1%), backpain (64.9%), weight loss of >10% (44.6%), easy fatigability (44.6%), and chest pain (43.2%) were the most common symptoms among cases of PTB (Lee R et al, 2011 Abstract).

QUESTION 2 What examinations should be performed to bacteriologically confirm PTB?

A *Bacteriologically Confirmed TB* case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic test (WRD), such as Xpert®MTB/Rif (Refer to **Table 6**)

Summary of Evidence

In 2013, WHO revised its case definitions for TB to include rapid tests used for its bacteriologic confirmation (WHO Definitions and Reporting Framework for TB updated 2014), subsequently adopted by the NTP.

Direct sputum smear microscopy (DSSM) remains as the primary and widely used diagnostic tool mostly available in the country. Presently, this can be done using conventional light microscopy of Ziehl-Neelsen (ZN) stained smears; conventional fluorescence microscopy (FM) or light-emitting diode (LED) microscopy.

TB culture (phenotypic) remains as the gold standard and reference for bacterial confirmation once growth of Mycobacterium tuberculosis is reported.

Xpert® MTB/Rif is a WHO-approved rapid diagnostic test for TB, which employ molecular techniques for the diagnosis of TB. It has been introduced globally and is expected to replace conventional bacteriology for diagnosis in many settings. Unlike DSSM, it does not indicate the level of infectiousness of a TB case.

A case who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient full course of TB treatment based on x-ray or other imaging modalities or suggestive histology is *Clinically Diagnosed TB*. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as *Bacteriologically Confirmed.*

TABLE 6 Bacteriologic Confirmation of PTB Based on Microbiologic Tests

ANATOMIC SITE	BACTERIOLOGIC STATUS	DEFINITION OF TERMS	
Pulmonary (PTB)	**Bacteriologically Confirmed**	Smear positive	A patient with at least one (1) sputum specimen positive for AFB, with or without radiologic 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
	Clinically Diagnosed	A patient with 2 sputum specimens negative for AFB or MTB, smear not done due to specified conditions but with radiographic abnormalities consistent with active TB, and there has been no response to empiric antibiotics and/or symptomatic medications, and who has been decided to have TB disease requiring full course of anti-TB chemotherapy	

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014

QUESTION 3 How should sputum specimens be collected for DSSM?

Sputum for DSSM should be collected through spontaneous expectoration. ***(Strong recommendation, moderate quality evidence)***

Summary of evidence

The overall diagnostic yield of smear positivity among presumptive PTB with spontaneous sputum production was 15.15% that improved to 21.21% with sputum induction. Culture positivity with spontaneous samples was 18.18%, which improved to 27.27% with sputum induction. Although the differences in the results were not statistically significant, sputum induction provides more adequate sputum sample for bacteriological analysis in non-expectorating cases. It can also obviate the need for bronchoscopy (Atiq-ur-Rehman, M., 2009).

TABLE 7 Summary of Evidence for spontaneous sputum expectoration

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS				
					NUMBER OF PATIENTS	*MEASURE OF ACCURACY*		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness		Estimate	95% CI		
Sensitivity									
3	Cross Sectional Case-control	serious	Inconsistent*	Somewhat Indirect	274	0.64	0.33-0.83	Moderate	Critical
Specificity									
3						0.96	0.94-0.99	Moderate	Critical

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	*SPECIFICITY*			*POSITIVE*	*NEGATIVE*
3	Atiq, 2009	146	.83	.96	83	96	23.4	0.17
	Schoch, 2007	101	.64	.99	93	91	52.8	0.37
	Seong, 2014	27	.33	.94	83	60	5.3	0.71

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
Atiq, 2009	20	14	4	108
Schoch, 2007	14	1	8	82
Seong, 2014	5	1	10	15
Total	39	16	22	205

TABLE 8 Summary of Evidence for Sputum Induction

Summary Table

QUALITY ASSESSMENT					SUMMARY OF FINDINGS				
					NUMBER OF PATIENTS	*MEASURE OF ACCURACY*		Quality	Importance
No. of Studies	Design	Limitations	Consistency	Directness		Estimate	95% CI		
Sensitivity									
3	Cross Sectional Case-control	serious	Inconsistent*	Somewhat Indirect	265	0.64	0.50-0.66	Moderate	Critical
Specificity									
3						0.94	0.92-0.99	Moderate	Critical

Summary of Findings

NO. OF STUDIES	STUDY	SAMPLE N	STUDY EVENT RATES (%)		POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	LIKELIHOOD RATIO	
			SENSITIVITY	*SPECIFICITY*			*POSITIVE*	*NEGATIVE*
3	Atiq, 2009	140	.66	.92	75	88	8.7	0.36
	Schoch, 2007	101	.50	.99	88	93	45.5	0.51
	Seong, 2014	24	.64	.94	88	80	10.8	0.39

NAME OF STUDIES	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)
Atiq, 2009	24	8	12	96
Schoch, 2007	7	1	7	90
Seong, 2014	7	1	4	16
Total	38	10	23	202

Induced sputum added no smear-positive cases to those detected by two spontaneous sputum specimens. On-the-spot spontaneous sputum yielded 54% of the smear-positive and 39% of the culture-positive cases. With on-the-spot induced sputum, the yield for smear-positive cases was not increased, but the yield for culture positive cases increased to 46% (Schoch, O.D., et al., 2007).

The NTP MOP requires at least 1 teaspoonful (5-10mL) for DSSM.

QUESTION 4 How many sputum specimens should be collected? What should be the timing of sputum collection?

For the diagnostic evaluation of PTB, two (2) sputum specimens should be obtained for DSSM. ***(Strong recommendation, moderate quality evidence)***

Same day (spot-spot) strategy using 2 consecutive specimens collected 1-hour apart is recommended for direct Ziehl-Neelsen microscopy ***(Strong recommendation, moderate quality evidence)***

Please refer to **Appendix A** for the procedure for collection for DSSM.

Summary of evidence

Overall, the value of the third specimen is low, regardless of study design, study population and microscopy method. A systematic review of 37 studies showed that the overall weighted average percentage of cases detected with the first sputum specimen was 85.8%. An additional 11.9% is attained with the second specimen and the average incremental yield from the third sputum specimen was 2.3% (Mase, S. et al., 2007). Reider et al., likewise, reported that examination of more than two specimens adds minimally to the number of positive specimen obtained, with an incremental yield of 0.7-7.2% from a third serial smear (Rieder, H.L., et al, 2015).

The microscopic analysis of two sputum samples will improve case findings through enhanced quality of service, decreased time for diagnosis and initiation of treatment and decreased number of patients dropping out of the diagnostic pathway (WHO Proposed reduction of number of smears for the diagnosis of pulmonary TB: background document).

Sputum specimen should be submitted for DSSM to a well-functioning external quality-assured laboratory (Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care [ISTC], 2014).

A systemic review conducted by the WHO in 2009 assessing the evidences for a diagnostic approach for tuberculosis showed that, using

two specimens and direct Ziehl-Neelsen microscopy, same day diagnosis with two consecutive specimens ('spot-spot') was only on average 2.8% less sensitive than the conventional approach ('spot-morning') (95% CI, -5.2% - +0.3%). The specificity of the two approaches (with culture as the reference standard) was identical (98%; 95% CI, 97-99%). There was sufficient generalizable evidence that same-day diagnosis (microscopy two consecutive spot-spot sputum specimens) is equivalent, in terms of diagnostic accuracy, to conventional case-finding strategies by microscopy (WHO Policy Statement, 2011).

A retrospective study of 546 cases showed that examination of third sample, especially second spot sample, does not add significantly to the diagnostic yield. Examination of one spot and early morning samples were able to correctly diagnose 98% of cases (Rao, S. 2009).

QUESTION 5 What is the preferred type of microscopy for DSSM?

If available, light-emitting diode (LED) microscopy is the preferred diagnostic microscopy method for DSSM replacing conventional ZN microscopy ***(Strong recommendation, moderate quality evidence)***

Summary of evidence

The systemic review and meta-analysis done by the WHO revealed that LED microscopy is statistically significantly more sensitive by 6% (95% CI, 0.1-13%), with no appreciable loss in specificity, when compared with direct ZN microscopy. LED microscopy is 5% (95% CI, 0-11%) more sensitive and 1% (95% CI, -0.7% - 3%) more specific than conventional FM (WHO Policy Statement. Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis., 2011).

A cross-sectional study reported that LED microscopy, FM and ZN microscopy have sensitivities of 72.8%, 52.5% and 28.5%, respectively (Trusov A, Bumargarner R, Valijev R, et al, 2009).

QUESTION 6 How are the results of DSSM interpreted?

A case of PTB is already considered bacteriologically confirmed if at least one (1) sputum smear is positive for acid-fast bacilli ***(Strong recommendation, moderate quality evidence).***

Refer to Table 9 for the quantitative interpretation of DSSM using light or fluorescence microscopy which signifies bacterial load of the disease and correlates with patient's level of infectiousness.

Summary of Evidence

The revised NTP Manual of Procedures defines bacteriologically confirmed TB as at least one (1) sputum smear that is positive for acid-fast bacilli if using sputum microscopy. This is based on the quantitative reporting for conventional light and fluorescence microscopy detailed in the Laboratory Diagnosis of TB by Sputum Microscopy Handbook Global Edition (Lumb R, Van Deun A, Bastian I, Fitz-Gerald M, 2013) and adopted by the National TB Reference Laboratory for use in all TB microscopy laboratories in the country (see **Table 9**). It is sufficient for one (1) sputum smear as basis for bacteriologic confirmation in TB microscopy laboratories where External Quality Assessment (EQA) is well established.

Positivity of sputum smears correlate with the patient's baseline infectiousness which is 10x more among smear-positive TB cases compared to those who are smear-negative.

TABLE 9 Interpretation of DSSM results using Light and Fluorescence Microscopy

WHAT TO REPORT	CONVENTIONAL LIGHT MICROSCOPY	FLUORESCENCE MICROSCOPY (FM)	
		200X MAGNIFICATION 1 LENGTH = 30 FIELDS	*400X MAGNIFICATION 1 LENGTH = 40 FIELDS*
0	No AFB seen in 300 OIF	No AFB observed/ one length	No AFB observed/ one length
Confirmation required*		1-4 AFB/1 length	1-2 AFB/1 length
+n	1-9 AFB seen in 100 OIF	5-49 AFB/1 length	3-24 AFB/1 length
1+	10 – 99 AFB seen in 100 OIF	3-24 AFB/1 field	1-6 AFB/1 field
2+	1-10AFB/OIF, at least 50 fields	25-250/1 field	7-60/1 field
3+	>10 AFB/OIF, at least 20 fields	>250/1 field	>60/1 field

Reference: Laboratory Diagnosis of Tuberculosis by Sputum Microscopy: The Handbook, Global Edition (a publication of the Global Laboratory Initiative, a Working Group of the Stop TB Partnership) as adopted by the NTP Manual of Procedures 5th edition.

OIF- oil immersion field

**Requires confirmation by another technician, or another smear is prepared, stained and read.*

QUESTION 7 When should TB culture be requested? How are the results of DSSM interpreted?

TB culture remains the gold standard for TB diagnosis. If available, sputum TB culture can be requested in the diagnostic work-up of TB, specifically in ruling out NTM. The long turnaround time of results, limited access and cost of test, limits its routine use.

TB culture should be performed preferably in quality assured culture centers recommended by the National TB Program (see **Appendix B**)

If culture-positive for *Mycobacterium tuberculosis* (MTB), case is bacteriologically-confirmed PTB.

Care of patients with TB commences with a quality-assured diagnosis obtained by identifying M. tuberculosis from clinical specimens, conventionally performed using TB culture which remains as the gold standard and reference for TB diagnosis. It is important that all mycobacterial isolates be speciated at least to the level of M. tuberculosis complex versus NTM. A patient with positive culture for M. tuberculosis is considered a Bacteriologically Confirmed case of TB.

Although recognized as gold standard for the diagnosis of TB, it remains cumbersome, requires biosafety compliance and has long turnaround time. In the country, there are only 23 TB culture centers under the NTP Laboratory Network to date, which provide limited access to the general population (see **Appendix B**).

QUESTION 8 What are the indications for performing sputum TB culture with drug susceptibility testing (DST)?

Sputum TB culture with DST should be performed for the following:

- Retreatment cases ***(Strong recommendation, high quality evidence)***
- Treatment failure ***(Strong recommendation, high quality evidence***
- Contacts of known drug-resistant TB cases ***(Strong recommendation, moderate quality evidence)***

DST should not be routinely performed among new cases of PTB. ***(Strong recommendation, high quality evidence)***

Summary of evidence

Previous treatment with anti TB medications is a known determinant of drug resistance. The 2012 national Drug Resistance Survey (DRS) revealed that 44% of re-treatment cases had drug resistant TB of which 21% had MDR TB (Macalalad, 2012).

A cross sectional study conducted in a Programmatic Management of Drug-Resistant TB (PMDT) clinic showed that among 2438 patients with history of prior TB treatment, 85% were drug resistant and of which 76% were MDR TB (Gler, 2011).

Treatment failure to first-line anti TB drugs is associated with MDR TB. The 2004 national Drug Resistance Surveillance determined that 89% of identified patients who failed TB treatment were found to have MDR TB (Mori, 2004). Gler (2011) showed very high rates (83% to 97%) of MDR TB among patients who failed first-line anti TB treatment.

The prevalence of MDR TB among new cases included in the 2012 national DRS was low at 2% (95%CI 1.4-2.7) (Macalalad, abstract). The 2012 rate is lower compared to the 3.8% (95% CI 2.6-5.5) MDR TB prevalence rate in 2004 (Philippine Nationwide Tuberculosis Drug Resistance Survey Team, 2009).

QUESTION 9 When should Xpert® MTB/Rif be requested? How accurate is Xpert® MTB/Rif in confirming PTB?

If available, sputum Xpert® MTB/Rif can be requested in the following clinical situations:

- As initial diagnostic test in adults with presumptive TB ***(Weak recommendation, high quality evidence)*** with a pooled sensitivity of 89%, specificity 99%. ***(Strong recommendation, high quality evidence)***
- As follow-on test to smear-negative patients with chest x-ray findings suggestive of active PTB ***(Weak recommendation, high quality evidence***) with a pooled sensitivity of 67%, specificity of 99%. ***(Strong recommendation, high quality evidence)***
- As initial diagnostic test for presumptive drug-resistant TB ***(Strong recommendation, high quality evidence)***, with a pooled sensitivity of 95% and specificity of 99% for rifampicin resistance detection. ***(Strong recommendation, high quality evidence)***

In comparison with smear microscopy, Xpert® MTB/Rif increased TB detection among culture-confirmed cases by 23% ***(Strong recommendation, high quality evidence).***

For smear-positive, culture-positive TB, Xpert® MTB/Rif pooled sensitivity was 98% and specificity was not reported (all smear positive considered TB positive). ***(Strong recommendation, high quality evidence).***

Summary of evidence

Recognizing that Xpert® MTB/Rif increases case finding by about 30% as an initial or add-on test to microscopy, the evidence for use as a replacement test for the general population of presumptive TB, or as add-on test for smear-negative patients with chest x-ray findings suggestive of PTB without risk for MDR-TB or HIV-associated TB is good.

However, major resource implications have to be considered. There is substantially greater cost of using Xpert® MTB/Rif compared to microscopy, although the cost of culture and DST is comparable. Even at a higher cost, the use of Xpert® MTB/Rif in these situations remains cost effective, but may be out of reach for a significant number of national programs in resource-poor settings (WHO 2011; WHO 2013).

QUESTION 10 What are the requirements for sputum specimens for Xpert® MTB/Rif? Which health care facilities accept sputum specimens for Xpert® MTB/Rif

Sputum, including pellets from decontaminated specimens can be used for Xpert® MTB/Rif. At least 1 mL of sputum specimens or 2mL of fresh sputum for test and retest is needed for Xpert® MTB/Rif. If available, bronchial washings may be alternate specimens for sputum.

The DOH National TB Program (NTP) has designated DOTS centers nationwide ***(Appendix C)*** with capacity to process specimens for free Xpert® MTB/Rif testing for the following priority cases: presumptive DR-TB, presumptive HIV-associated TB, follow-on test for smear negative with CXR-positive new presumptive TB.

Summary of Evidence

Please refer to **Table 10** for the prescribed volume requirements for sputum specimens recommended for Xpert® MTB/Rif.

TABLE 10 Required Specimen Volume for Xpert® MTB/Rif

SPECIMEN TYPE	MINIMUM VOLUME FOR ONE TEST	MINIMUM TOTAL VOLUME FOR TEST AND RETEST
Sputum Sediment	0.5 mL	1 mL
Fresh Sputum	1 mL	2 mL

Reference: Cepheid, Xpert® MTB/Rif Product Insert (2012)

Based on the NTP Laboratory Network Strategic Plan, availability of Xpert® MTB/Rif in the country will be scaled up targeting one Xpert facility per 500,000 population by 2016 (DOH, 2013). Please refer to **Appendix A** for the procedures for sputum collection, and **Appendix C** for the current list of facilities with free Xpert® MTB/Rif testing as of December 2015.

If for transport, specimens are placed in a properly labelled sputum specimen container tightly closed in a small plastic bag and sealed at the end of the bag, put in a styropor box or any sturdy container with ice together with NTP Request Form properly accomplished by the providing/ referring TB DOTS hospital or DOTS facility.

Xpert® MTB/Rif services are also commercially available in some tertiary private health care facilities and laboratories in the country.

QUESTION 11 How are results of Xpert® MTB/Rif interpreted?

Xpert® MTB/Rif assay should be interpreted along with clinical, radiographic, and/or other laboratory findings ***(Strong recommendation, high quality evidence).***
If sputum Xpert® MTB/Rif is positive for Mycobacterium tuberculosis, case is considered bacteriologically-confirmed PTB

Summary of evidence

Table 11 outlines the readouts and interpretations of the test as outlined by the manufacturer of Xpert® MTB/Rif (APHL, 2013).

TABLE 11. Readout, interpretation and suggested minimal language of Xpert test

XPERT® MTB/RIF READOUT	INTERPRETATION	REPORT* (SUGGESTED MINIMAL LANGUAGE)
MTB DETECTED; RIF Resistance DETECTED	MTB target is detected within sample. A mutation in the *rpoB* gene has been detected. A full first and second line drug panel should be conducted.	MTBC detected. rpoB mutation detected; likely rifampin resistance; Confirmatory testing in progress OR isolate has been forwarded to a reference laboratory for confirmatory testing.
MTB DETECTED; RIF Resistance NOT DETECTED	MTB target is detected within sample. A mutation in the *rpoB* gene has not been detected.	MTBC detected. No *rpoB* mutation detected; likely rifampin susceptible.
MTB DETECTED; RIF Resistance INDETERMINTE	MTB target is detected within sample. A mutation in the *rpoB* gene could not be determined due to insufficient signal detection.	MTBC detected. Insufficient MTB in the sample to allow determination of *rpoB* mutation result.
MTB Not Detected	MTB target is not detected within the sample.	MTBC not detected

Reference: Product insert of Xpert® MTB/Rif

QUESTION 12 What should be done for presumptive PTB who cannot expectorate sputum for bacteriologic confirmation?

Sputum induction (15-20 minutes of nebulization with 15mL 2.5-5% hypertonic saline) should be done for individuals who are unable to expectorate, provided it is done by trained staff in well-equipped facilities, with special caution for patients with history of asthma. ***(Strong recommendation, low quality evidence)***

The Revised NTP Manual of Procedures 5th Edition recognizes the following conditions where patients are classified as "Sputum Not Done"when unable to follow instructions on proper sputum expectoration, or "Unable to Produce Sputum (UPS)" when conditions are present where sputum collection is not feasible:

- Mentally incapacitated as decided by a specialist or medical institution
- Debilitated or bedridden
- Patients unable to produce sputum despite sputum induction

QUESTION 13 What additional work up should be performed among patients who are smear-negative?

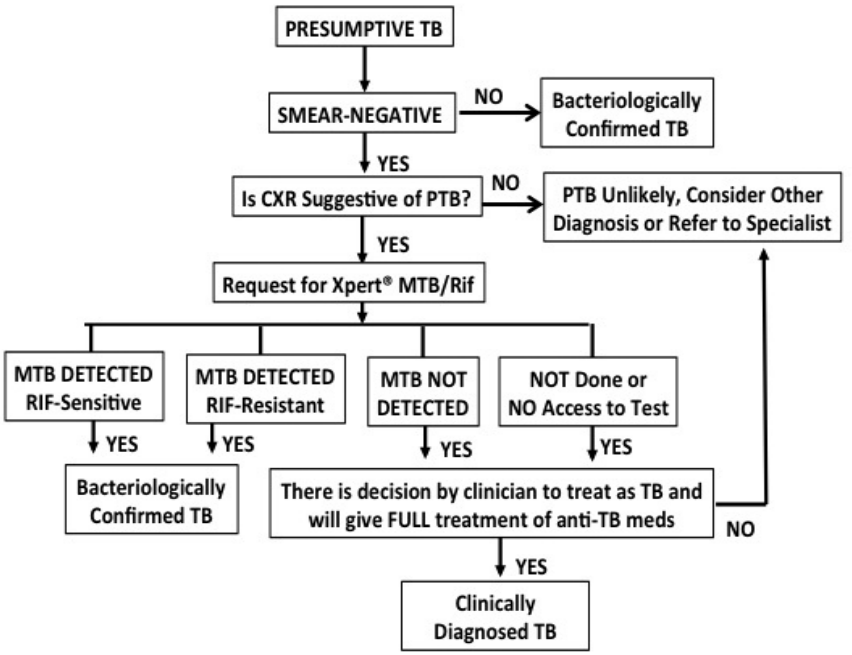
If not yet done, chest x-ray should be performed for all smear-negative presumptive PTB. ***(Strong recommendation, moderate quality evidence)***

If available, Xpert® MTB/Rif should be requested among smear-negative presumptive TB cases with radiologic findings suggestive of PTB with no risk for drug-resistant TB or HIV-associated TB. ***(Strong recommendation, high quality evidence)***

Summary of Evidence:

Based on the diagnostic algorithm using laboratory results detailed in the revised NTP MOP (DOH, 2013), the chest radiograph needs to be assessed among smear negative presumptive TB. If with radiologic findings suggestive of PTB, Xpert® MTB/Rif may be used as follow-on test for the negative DSSM with a pooled sensitivity of 67% and specificity of 99%. **(Figure 2).** However, access to this test is presently limited in the country pending efficient roll-out of more Xpert facilities under the NTP in the next few years.

FIGURE 2: Decision Making for TB Diagnosis Among Smear-Negative Presumptive TB Adults Based on Laboratory Results



Modified from: NTP Revised Manual of Procedures 5th Edition, Department of Health, 2014

QUESTION 14 What is the role of chest x-ray in the diagnosis of PTB?

Although chest x-ray is a good screening test to identify presumptive PTB, a single film cannot accurately confirm active PTB by this modality alone ***(Strong recommendation, high quality evidence)***

There are no radiographic findings considered specific for active TB. Clinical correlation, together with bacteriologic confirmation, is required to assess activity BEFORE initiation of full course of appropriate treatment ***(Strong recommendation, high quality evidence)***

Together with a good clinical history, a good quality chest x-ray film is needed to initially guide the clinician in the identification of presumptive PTB for further bacteriologic confirmation ***(Strong recommendation, moderate quality evidence)***

Chest x-ray examinations should follow the standards set by the ACR-PCR Practice Guidelines. Interpretation and reporting of CXRs should follow standardized radiographic terms which remain unchanged since CPG TB 2006.

Summary of evidence

Recent reviews strengthened the observations from previous investigations that there are no consistent radiographic findings specific for PTB. It is now recognized that radiologic features depend primarily on host immunity. Variable features on plain CXR films were associated with smear or culture positive cases. In a series by Woodring, culture positive cases were even found among those whose radiograph were read as normal or even among those whose main finding was "fibrosis" or "scarring" or just lymphadenopathy.[3] Radiologic interpretations are mainly terms that describe the structural or anatomic extent of the disease and do not imply disease activity.

A good clinical history with adequate radiologic correlation may be critical as an initial approach to pursue the diagnosis of PTB. Data should include any previous intake of anti-TB drugs, past medical advice on laboratory examinations and possible treatment and their outcomes. These may dictate the subsequent steps which should include bacteriologic confirmation for TB if warranted.

Assessment of disease activity cannot be made accurately on the basis of a single radiograph alone. Previous imaging studies will likewise be essential. However, comparison with a previous film may establish the stability of a lesion. The stability of radiologic lesions can only be ascertained if comparison can be made among films taken four or ideally, six months apart.

QUESTION 15 What is an acceptable chest x-ray film? How should chest x-ray be interpreted?

The quality of the chest x-ray film cannot be overemphasized. A standard chest examination should be an erect PA and left lateral projection performed during full inspiration, and should include both lung apices and costophrenic sulci.

Radiographic interpretation remains unchanged since 2006 recommendations.

The radiographic descriptions recommended in the 2006 CPG remains the same. Consistent use of standardized radiographic terms and need to indicate "for microbiologic confirmation and clinical correlation" is advocated in order to regulate interpretation and reporting of chest x-rays to facilitate better communication among readers and users of this diagnostic modality.

QUESTION 16 What is the role of digital imaging in the diagnosis of PTB? What are the acceptable specifications for digital imaging?

If available, digital imaging can be used in the diagnostic work-up of PTB similar to a chest film if the appropriate standards are followed. ***(Strong recommendation, moderate quality evidence)***

For digitized radiographic films, the recommended minimum specifications are 2.5 lp/mm spatial resolution with an 8-bit pixel depth.

Summary of evidence

The utilization of digital imaging, improvements in data storage and availability of high speed internet have all paved the way for tele-radiography practice in the Philippines. Tele-radiography is defined as the transmission of imaging studies electronically or through a digital storage media from one location to another for the purposes of interpretation and/or consultation. Its main goal is to link the expertise of on- and off-site radiologists to ensure access to imaging interpretative services by health care facilities in the country and abroad to help achieve delivery of optimum patient care. Images can be adjusted electronically to optimize evaluation of the chest x-ray, achieve rapid processing with fewer repeat examinations, and lesser radiation exposure. Likewise, images can be efficiently stored, archived and can easily be retrieved for comparison and monitoring of patients undergoing or who have already finished treatment.

For digitized radiographic films, the recommended minimum specifications are 2.5 lp/mm spatial resolution with an 8-bit pixel depth. The display stations must be able to accurately reproduce the original study with capabilities in window and level adjustments, zoom (magnification) and pan functions, rotating or flipping images, and perform linear measurements. Digital studies, however, will not improve poorly acquired images.

It is emphasized that facilities must be duly licensed by the Department of Health (DOH) and comply with specific technical standards of Digital Imaging and Communications in Medicine (DICOM) and the Philippine College of Radiology (PCR) for the acquisition of new and upgrading of equipment, image capture and data management including storage of records.

QUESTION 17 What is the role of chest CT scan in the diagnosis of PTB?

The routine use of chest CT scan in the diagnosis of active pulmonary tuberculosis cannot be recommended, unless other co-existing disease conditions are highly considered to explain the patient's presentation, or to evaluate possible complications or sequelae of PTB. Clinical correlation and bacteriologic confirmation should still be done. ***(Strong recommendation, moderate quality evidence)***

Summary of evidence

In general, chest CT scan has a 91% sensitivity and 76% specificity rate in diagnosing pulmonary tuberculosis compared to the sensitivity rate of 49% for a plain chest radiograph. There are certain advantages of this modality with its ability to detect subtle changes which may be due to

TB. High Resolution CT (HRCT), in particular, is able to detect small cavitations within areas of consolidation or dense scarring in a number of cases. Other findings which have been documented to be associated with bacteriologically confirmed cases include peculiar patterns of parenchymal abnormalities, presence of cavitations or evidence of endobronchial spread (i.e. presence of centriblobular nodules or tree-in-bud pattern). CT scan may be also useful in evaluating the pleural structure for possible complications or TB sequelae such as presence of effusion, empyema or broncho-pleural fistula.

The routine use of this modality to diagnose active TB cannot be recommended at the moment. Its potential added cost and increased radiation exposure may further limit its utility as an initial screening tool. However, chest CT can possibly complement other diagnostic tests because of its ability to present parenchymal structures in greater detail. This aspect was supported in a study by Lee and colleagues where cases of PTB were established when HRCT was utilized as a complementary imaging modality.

QUESTION 18 What are the recommended diagnostic work-up for Extra-Pulmonary Tuberculosis (EPTB)?

Similar to PTB, diagnostic bacteriologic confirmation of EPTB includes direct microscopy, TB culture and Xpert® MTB/Rif.

Xpert® MTB/Rif should be preferred over conventional microscopy and culture as initial diagnostic test for CSF specimens from presumptive TB meningitis. ***(Strong recommendation due to urgency for rapid diagnosis, very low quality evidence)***

Xpert® MTB/Rif may replace usual practice (conventional microscopy, culture or histopathology) for testing lymph node and other selected tissues from presumptive extra-pulmonary TB. ***(Weak recommendation, very low quality evidence)***

A patient with histological and/or clinical radiologic evidence consistent with active EPTB without laboratory confirmation by direct microscopy, culture or Xpert® MTB/Rif, and decided to be treated by a physician with full course of anti-TB drugs is *Clinically Diagnosed* EPTB.

The revised definitions and reporting framework for TB (WHO, 2013) classifies EPTB whether bacteriologically confirmed or clinically diagnosed based on results of DSSM, culture or Xpert® MTB/Rif.

Meta-analysis of Xpert® MTB/Rif in diagnosing EPTB as detailed in Table 12 shows consistently high specificity using various non-pulmonary specimens, with variable sensitivity highest with lymph node tissue and aspirate, gastric

TABLE 12 Meta-analysis of the sensitivity and specificity of Xpert® MTB/Rif in diagnosing extra-pulmonary TB by type of extra-pulmonary specimen. (WHO, 2013)

SPECIMEN TYPE	COMPARISON (NO. OF STUDIES, NO. OF SAMPLES)	MEDIAN (%) POOLED SENSITIVITY (POOLED 95% CrL)	MEDIAN (%) POOLED SPECIFICITY (POOLED 95% CrL)
Lymph node tissue and aspirate	Xpert® MTB/Rif compared against culture (14 studies, 849 samples)	84.9 (72-92)	92.5 (80-97)
	Xpert® MTB/Rif compared against a composite reference standard (5 studies, 1 unpublished)	83.7 (74-90)	99.2 (88-100)
CSF	Xpert® MTB/Rif compared against culture (16 studies, 709 samples)	79.5 (62-90)	98.6 (96-100)
	Xpert® MTB/Rif compared against a composite reference standard (6 studies, 512 samples)	55.5 (51-81)	98.8 (95-100)
Pleural fluid	Xpert® MTB/Rif compaed against culture (17 studies, 1385 samples)	43.7 (25-65)	98.1 (95-99)
	Xpert® MTB/Rif compared against a composite reference standard (7 studies, 698 samples)	17 (8-34)	99.9 (94-100)
Gastric lavage, aspirate	Xpert® MTB/Rif compared against culture (12 studies, 1258 samples)	83.8 (66-93)	98.1 (92-100)
Other tissue samples	Xpert® MTB/Rif compared against culture (12 studies, 699 samples)	81.2 (68-90)	98.1 (87-100)

Crl, credible interval; the Crl is the Bayesian equivalent of the confidence interval

Reference: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert® MTB/Rif assay for the diagnosis of pulmonary and extra-pulmonary TB in adults and children: Policy Update. Geneva, WHO 2013

lavage and other tissue samples. Because of very high mortality associated with TB meningitis, use of Xpert® MTB/Rif is strongly recommended for testing of CSF. Pleural fluid remains a suboptimal sample for bacterial confirmation; pleural biopsy is a preferred sample. There is still very limited data on samples using ascitic and pericardial fluid, stool, urine or blood.

Patients with very high clinical suspicion for EPTB should be treated even if Xpert® MTB/Rif result is negative, specially after adequate further diagnostic testing.

QUESTION 19 What is the role of nucleic acid amplification testing (NAATs) in the diagnosis of PTB?

NAAT (other than Xpert® MTB/Rif) is not recommended as a stand-alone test for the diagnosis of tuberculosis ***(Strong recommendation, high quality evidence).***

If available, NAATs (other than Xpert® MTB/Rif) can be a more sensitive and specific adjunct to diagnose PTB which requires clinical and radiographic correlation ***(Weak recommendation, moderate quality evidence).***

Commercial NAATs are preferred over in-house (home brew) assays since they are more sensitive and specific ***(Strong recommendation, high quality evidence).***

Summary of evidence

A meta-analysis and meta-regression of 125 studies evaluating NAATs in the diagnosis of TB (Ling et al, 2008) showed a pooled sensitivity of 85% (CI 36%, 100%), specificity of 97% (CI 54%, 100%), positive likelihood ratio of 32.7 (CI 26, 41.2) and negative likelihood ratio of 0.14 (CI 0.12, 016). However, the sensitivity and specificity of commercial nucleic acid tests in respiratory specimens in the included studies were highly variable, and were dependent on the tests and cutoffs used. Therefore, the summary measures of diagnostic accuracy were not clinically meaningful. Based on these findings, commercial NAATs alone cannot be recommended to replace conventional tests for diagnosing pulmonary TB. Improvements in diagnostic accuracy, particularly sensitivity, need to be made in order for this expensive technology to be worthwhile and beneficial in low-resource countries.

Due to standardization of reagents and larger validation studies, commercial NAATs have higher specificity and positive predictive value compared to in-house assays. However, they still have relatively lower (and highly variable) sensitivity and negative predictive value for all forms of TB, especially in smear-negative and extra-pulmonary disease compared to culture (TB CARE I, 2014).

QUESTION 20 Can tuberculin skin test (TST) be used in diagnosing active pulmonary tuberculosis (PTB)?

TST cannot be used to diagnose active PTB ***(Strong recommendation, high quality evidence).***

Summary of Evidence

A meta-analysis of cross sectional studies in 2010 (Diel et al, 2010) and two cohort cross-sectional studies in 2014 (Wlodarczyk et al, 2014, Park et al, 2014) showed poor sensitivity and specificity of TST in diagnosing active PTB. These studies showed a median sensitivity of 0.58 (CI 0.56, 0.72), specificity of 0.68 (CI 0.63, 0.71), PPV 0.67 (CI 0.65, 0.69) and NPV 0.58 (0.52, 0.63) in 2658 participants. These results are consistent for all three studies. However, these studies are indirect given that the samples were heterogenous and non-Filipinos.

QUESTION 21 Can Quantiferon-Gold-in-tube (QFT-GIT) be used in diagnosing active pulmonary tuberculosis (PTB)?

QFT-GIT cannot be used to diagnose active PTB ***(Strong recommendation, low quality evidence).***

Summary of evidence

A meta-analysis of cross-sectional studies (Metcalfe et al, 2011) and 2 cohort cross sectional studies (Wlodarczyk et al, 2014, Park et al, 2014), with a total of 1054 participants, showed a median sensitivity of 0.819 (CI 0.65, 0.91), specificity 0.75 (0.62, 0.87), positive predictive value of 0.72 (CI 0.61, 0.82) and negative predictive value of 0.78 (CI 0.73, 0.83). The studies done were heterogenous and showed a wide range of values. Samples included non-Filipino patients and included mostly hospitalized patients, compromising directness of the studies. Most of the studies included came from low TB prevalence countries. This test is also not readily available in the Philippines, and the examination is expensive.

QUESTION 22 Can enzyme-linked immunospot (EliSpot) be used in diagnosing active pulmonary tuberculosis (PTB)?

EliSpot cannot be used to diagnose active PTB ***(Strong recommendation, low quality evidence)***

Summary of Evidence

A total of 870 patients, a meta-analysis (Metcalfe et al, 2011), and 2 cross sectional studies (Wang et al 2007, Feng, 2012) showed a median sensitivity of 0.88 (CI 0.81, 0.96), specificity of 0.79 (CI 0.69, 0.88), positive predictive

value of 0.88 (CI 0.84, 0.92) and negative predictive value of 0.86 (CI 0.82, 0.9). Despite these acceptable values, the studies were heterogenous and done among non-Filipino patients. Most of the included samples were also among hospitalized patients, which is not the usual case in the Philippines where majority of TB diagnosis is done among outpatients. Most of the studies came from low TB prevalence countries. This test is not readily available in most hospitals and very expensive.

QUESTION 23 Can tuberculosis Interferon-gamma release assays (IGRAs) be used as a diagnostic modality for TB in the Philippines?

IGRA is not recommended for the diagnosis of active pulmonary or extra-pulmonary TB regardless of HIV status ***(Strong recommendation, high quality evidence)***

Summary of evidence

There is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden. IGRAs and the TST cannot accurately predict the risk of infected individuals developing active TB disease. Neither IGRAs nor the TST should be used for the diagnosis of active TB disease. IGRAs are costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended. This recommendation places a high value on avoiding the consequences of unnecessary treatment (high false-positives) given the low specificity of IGRAs (and the TST) in these settings (WHO, 2011).

QUESTION 24 Can Microscopic Observation Drug Susceptibility (MODS) and Lipoarabinomannan (LAM) assays be used in the diagnosis of TB disease?

MODS and LAM are not recommended to diagnose TB disease. These tests are not readily available in the country. In areas where they are available, they are mainly used for research purposes

Research Recommendations

- To assess local estimates of sensitivity and specificity of one or more symptoms, chest radiography, and combinations of symptoms and chest radiography as screening tools among immunocompetent presumptive TB and their contacts
- Assessment of utilization of Xpert® MTB/Rif services under the National TB Program Laboratory Network
- Utility of Xpert® MTB/Rif in the diagnosis of extra-pulmonary TB

Chapter 3

Treatment of Pulmonary and Extra-Pulmonary Tuberculosis in Adults

Chapter 3
Treatment of Pulmonary and Extra-Pulmonary Tuberculosis in Adults

It is crucial to understand that once treatment is initiated for TB, whether bacteriologically confirmed or clinically diagnosed, clinicians assume a public health responsibility both to the individual patient and to the community at large. Evaluation of TB patients before and during treatment should not only be clinical, it should also involve assessment of risk factors leading to disruption of treatment.

A TB patient, who is cured or has completed treatment with appropriate standardized treatment regimen, no longer becomes infectious thus preventing further disease transmission and emergence of drug-resistance. For clinicians who likely cannot monitor the adherence of their individual patients to TB treatment, they need to consider referring to healthcare providers (public or private facilities) offering support for supervised treatment services.

This chapter covers recommendations for pulmonary and extra-pulmonary TB that have been harmonized with the recently revised NTP policies and procedures before, during and after treatment of confirmed TB cases with no known co-morbidities. Treatment of patients who are immunocompromised or who have pre-existing medical conditions will be discussed in *Chapter 5.*

Definition of Terms

The following WHO revised standard case definitions (WHO 2013) based on history of previous TB treatment (patient registration group), independent of bacteriologic confirmation or site of disease, are adopted in this document to facilitate standardized reporting.

New Case – patient who has never been treated for TB or has taken anti-TB drugs for less than 1 month.

Retreatment Case – patient who has received 1 month or more of anti-TB drugs in the past (excluding prophylaxis or treatment for latent TB infection), further classified by the outcome of most recent course of treatment, as follows:

- **Relapse** – patient has previously been treated for TB, declared cured or treatment completed at the end of most recent course of treatment, and is now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection
- **Treatment after failure** – patient has previously been treated for TB and declared treatment failed at the end of most recent course of treatment
- **Treatment after lost to follow-up (TALF)** – patient has previously been treated for TB, declared lost to follow-up at the end of most recent course of treatment (previously known as *Return After Default)*
- **Previous Treatment Outcome Unknown (PTOU)** – patient has previously been treated for TB but outcome after their most recent course of treatment is unknown or undocumented
- **Other** - patients who do not fit into any of the categories listed above.

Outline of Issues on Treatment of TB

PRE-TREATMENT EVALUATION

1. What pre-treatment clinical evaluation should be done to patients with TB disease?
2. What baseline laboratory examinations should be routinely requested before starting anti-TB treatment?

TREATMENT OF PULMONARY AND EXTRAPULMONARY TB

3. What is the effective treatment regimen for new PTB cases?
4. How should RETREATMENT cases be managed?
5. How should PTB patients who have interrupted treatment be managed?
6. What is the effective treatment regimen for miliary TB and miliary TB with dissemination?
7. What are the effective treatment regimens for EPTB?

8. How effective are corticosteroids for the treatment of EPTB?
9. What is the role of surgery in the management of EPTB?

ORGANIZATION AND SUPERVISION OF TREATMENT

10. How should anti-TB medications be administered?
11. What are the effective ways of tracking patients and monitoring adherence to treatment?
12. How effective are fixed-dose combination drugs compared to single-drug formulations?
13. How effective is daily vs. intermittent regimen for the treatment of TB?

MONITORING OF OUTCOMES AND TREATMENT RESPONSE

14. How should we monitor treatment response?
15. How should we classify treatment outcomes?
16. When is a patient on TB treatment considered non-infectious?
17. What is paradoxical treatment response and how should it be managed?

MONITORING FOR AND MANAGEMENT OF ADVERSE REACTIONS

18. What are the common adverse reactions to anti-TB drugs?
19. How should the most common adverse reactions due to anti-TB drugs (HRZES) be monitored and managed?
20. How should drug-induced hepatotoxicity be monitored and managed?
21. How should gastrointestinal reactions be monitored and managed?
22. How should peripheral neuropathy be monitored and managed?
23. How should visual impairment be monitored and managed?
24. How should patients presenting with symptoms of ototoxicity be managed?
25. How should patients with hyperuricemia be monitored and managed?
26. How should cutaneous reactions be monitored and managed?
27. How should nephrotoxicity be monitored and managed?

ADJUNCTIVE THERAPY FOR TB

28. Should immunomodulators be given as an adjunct in the management of TB?
29. Should vitamin and micronutrient supplementation be routinely given?

QUESTION 1 What pre-treatment clinical evaluation should be done to patients with TB disease?

Thorough history and physical examination should be done on all patients with TB disease. History should include past medical history (*previous TB treatment, risk factors for hepatic, renal and ocular toxicity*), sexual history, personal and social history, and occupation. ***(Strong recommendation, moderate quality evidence)***

The liver risk factors that should be identified include chronic alcohol consumption, viral hepatitis, pre-existing liver diseases, exposure to hepatotoxic agents, previous abnormal results of ALT/AST/bilirubin and HIV infection. ***(Strong recommendation, moderate quality evidence)***

Baseline testing of visual acuity using Snellen and color perception charts are advised when ethambutol is to be used. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

Clinical monitoring of all TB patients for adverse effects is important during treatment even though only a small percentage of patients develop adverse effects (WHO, 2010). A comprehensive clinical history, thorough physical examination and eliciting risk factors for liver, kidney and eye disease is recommended to promptly identify patients who will need close monitoring for adverse effects of TB drugs and to guide the choice of treatment regimen.

The risk factors for drug induced liver injury include chronic alcohol consumption, viral hepatitis, pre-existing liver diseases, pregnancy or three months post-partum, intake of hepatotoxic medications, previous abnormal results of ALT/AST/bilirubins and HIV infection (Saukkonen, Cohn, Jasmer, Schenker, & Jereb, 2006).

In a systematic review of the incidence of Ethambutol-related visual impairment during treatment of active TB, the pooled cumulative incidence of any visual impairment in all patients was 22.5/1000 persons treated with EMB, and permanent impairment was 4.3/1000. When stratified according to EMB dose, at a dose of 17.6-22.5 mg/kg/day, any visual impairment occurred in 15.4/1,000 persons and permanent impairment occurred in 4.2/1,000 persons. The review consisted of 19 cohort studies mostly from developed countries (Ezer, Benedetti, Darvish-Zargar, & Menzies, 2013).

The incidence of EMB-related Toxic Optic Neuropathy (ETON) in Filipinos taking anti-TB drugs is unknown (Neuro-Ophthalmology Club of the Philippines, 2015). The only local case series ever published to date showed that even at the standard dose of 15mg/kg, ocular toxicity occurred in 26 of 34 patients at the Philippine General Hospital, with best-corrected visual acuity (BCVA) of 20/200 or worse at 1 year. Only three patients recovered their full vision by 1 year, four patients by the second year. The results of this case series is consistent with previous studies, which showed that ocular toxicity may occur even at the usual dosing regimen and may manifest as early as 2 months of treatment. Withdrawal of EMB once ocular toxicity develops did not ensure reversal of effects. Hence, the authors emphasized the importance of careful monitoring of patients taking EMB for early detection and prevention of visual loss (Inocencio & Castillo, 1999).

In a Taiwan nationwide study of 231 newly diagnosed patients with ETON and 924 controls, the risk factors associated with ETON were older age, hypertension (adjusted OR=1.62, 95% CI 1.16 to 2.26) and renal diseases without end-stage renal disease (ESRD) (adjusted OR=2.11, 95% CI 1.02 to 4.35); with ESRD (adjusted OR=3.73, 95% CI 1.79 to 7.74).[Chen 2012]

The ATS/CDC/IDSA guidelines also recommend that testing of visual acuity and red-green color discrimination should be done when EMB is to be used (ATS/CDC/IDSA, 2003).

QUESTION 2 What baseline laboratory examinations should routinely be requested before starting anti-TB treatment?

- Baseline testing for serum alanine aminotransferase (ALT) and serum creatinine are recommended before starting anti-TB treatment.
- In resource-limited settings, baseline ALT and serum creatinine, at the least, should be requested for patients older than 60 years old, and those with risk factors for liver or kidney disease before starting TB treatment. ***(Strong recommendation, moderate quality evidence)***
- All patients should be taught how to recognize symptoms of common adverse effects and to consult if they develop such symptoms.
- All patients with TB with history of high-risk behavior for HIV and coming from areas with high prevalence of HIV (see **Table 13**) should be offered provider initiated counseling and testing (PICT) for HIV. ***(Strong recommendation, moderate quality evidence)***

- Screening for diabetes mellitus using Fasting Blood Sugar (FBS), Random Blood Sugar (RBS), or 75g Oral Glucose Tolerance Test (OGTT) is recommended for all patients with TB. At present, HbA1c is not routinely recommended in the Philippines to screen for DM due to problems with standardization; if available, however, should be confirmed by FBS, RBS or 75-grams OGTT. Proper management of glucose levels is essential to treatment of TB. *(Strong recommendation, high quality evidence)*
- Serum uric acid testing is NOT recommended before starting anti-TB treatment. The finding of asymptomatic hyperuricemia is not an indication to avoid pyrazinamide. *(Strong recommendation, moderate quality evidence)*

Summary of Evidence

Baseline laboratory testing

Regardless of whether baseline laboratory examinations are done, the patients should be taught how to recognize the symptoms associated with drug toxicity and to report them promptly.

Drug-induced hepatitis is the most serious and common adverse effect. Among the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage. In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis. In a retrospective cohort of 421 PTB patients treated at the PGH Out-patient Department, significant risk factors associated with adverse effects on bivariate analysis were age > 60 years old (OR 1.8; 95% CI 1.1, 2.9), history of hepatitis (OR 21.6; 95% CI 1.2, 398.3) and use of fixed-dose combination preparations (OR 3.0; 95% CI 1.7, 5.4). However, adjustment for confounders was not done in this study. The most common adverse effects were pruritus and exanthem (54.4%), nausea and/or vomiting (24.1%), hepatitis (9.7%) and headache (8.3%) (Pamittan, Araune, Lagunzad, & Fernandez, 2003). In another retrospective cohort of 114 patients from January 2007 to December 2012 from PGH who developed adverse reactions to anti-TB drugs, the most common systemic manifestation was transaminitis (10.5%), 9.6% had jaundice and 14% experienced nausea, vomiting and other abdominal symptoms (Toledo & Aleta, 2013).

Acute kidney injury (AKI) is a rare and severe complication that can interrupt treatment and cause permanent kidney damage. In a retrospective cohort of 1,394 patients on TB treatment in Taiwan, 99 patients (7.1%) had AKI; median age was 68 years with male predominance. AKI developed within two months of anti-TB treatment in 60 (61%) patients, including 11 (11%) with a prior history of rifampicin exposure. Thirty (30%) had co-morbid chronic kidney disease or end-stage renal disease. However, risk factors of AKI during TB treatment were not identified (Chang, Chen., Wu, Shu, & Lee, 2014).

HIV testing

TB and HIV/AIDS display a lethal bidirectional interaction, with major epidemic overlap (Trinh, Nguyen, VN, Nguyen, & Sintchenko, 2015). There were 360,000 TB-related deaths reported in people living with HIV during 2013. The first key intervention for reducing the burden of HIV-associated TB is HIV testing for TB patients. In 2013, 48% of TB patients globally had a documented HIV test result, but progress in increasing coverage has slowed (World Health Organization, 2014).

Gupta, et al. (2014) reviewed 62 guidelines from the 23 high-burden countries representing 76% of the global HIV burden and 89% of HIV-associated TB. Guidelines from 15 (65%) countries with 79% of the world's HIV-TB burden recommended HIV testing and counseling for TB patients.

Irrespective of epidemic setting, WHO recommends HIV testing for patients of all ages who present with presumptive or confirmed TB. In addition, the HIV status of TB patients alters their TB treatment (World Health Organization, 2010; TB CARE I, 2014).

The Philippines is one of the 22 high TB burden countries, with incidence of 290/100,000 in 2013 (World Health Organization, 2014). In a cross-sectional study of 101 TB patients in PGH in 2012, 3 patients (3%) tested positive for HIV. This is much higher than the 0.1% cutoff recommended for universal screening of a population at risk, and very much higher than the general population prevalence of 0.01%. This study provides data to support universal HIV screening for TB patients in the Philippines (Roa, Depayso, Bajandi, Alejandria, Lim, & Salvana, 2013).

Cohort analysis of 547 HIV patients at the Philippine General Hospital from 1993 to 2011 showed that TB is the most common opportunistic infection. (Leyritana, et al, 2013)

TABLE 13 Comparison of 2012 and 2015 Updated Priority Areas (Category A) for HIV Intervention in the Philippines

2012 CATEGORY A AREAS	UPDATED 2015 CATEGORY A AREAS	
Metro Manila:	***Greater Metro Manila:***	***Metro Cebu:***
Caloocan City	Caloocan City	Cebu City
Las Piñas City	Las Piñas City	Danao City
Makati City	Makati City	Lapu-Lapu City
Malabon City	Malabon City	Manadaue City
Mandaluyong City	Mandaluyong City	Naga City
Manila City	Manila City	Talisay City
Marikina City	Marikina City	
Muntinlupa City	Muntinlupa City	***Other High Prevalence Areas:***
Navotas City	Navotas City	Angeles City
Parañaque City	Parañaque City	Bacolod City
Pasay City	Pasay City	Cagayan De Oro City
Pasig City	Pasig City	Davao City
Pateros	Pateros	Iloilo City
Quezon City	Quezon City	Zamboanga City
San Juan City	San Juan City	
Taguig City	Taguig City	
Valenzuela City	Valenzuela City	
	San Jose Del Monte City, Bulacan	
Other High Prevalence Areas:	Antipolo City, Rizal	
Angeles City	Cainta, Rizal	
Davao City	Bacoor City, Cavite	
Cebu City	Imus City, Cavite	
Mandaue City	Dasmarinas City, Cavite	
Davao City	Sta. Rosa City, Laguna	

Source: Department of Health Epidemiology Bureau, April 17, 2015

Screening for Diabetes Mellitus (DM)

In the Philippines, DM and TB are highly prevalent conditions especially in the >40-year old age group where DM and TB coincide. A systematic review showed that treatment outcomes differ between TB patients with DM as compared to non-diabetics with greater relapse, treatment failure and death among patients with both DM and TB (Baker, Harries, Jeon, Hart, & Kapur, 2011). Another study showed that patients with both DM and TB have higher mycobacterial load compared to TB patients without DM (Alisjahbana, Sahiratmadja, Nelwan, Purwa, & Ahmad, 2007).

DM increases the risk of TB three-fold and poor glycemic control increases the risk of poorer outcomes among those with TB. In a study in Indonesia, after 2 months of TB treatment, the results of sputum microscopic examination were more often positive in diabetic patients (18.1% vs. 10.0%). After 6 months, 22.2% of cultured sputum specimens from diabetic patients were positive for Mycobacterium TB (adjusted OR, 7.65). Compared to non-diabetic individuals, those with DM and TB also had higher risk for

relapse (RR=3.89, 95% CI 2.43 to 6.23), death (RR=1.89, 95% CI 1.52 to 2.36) and treatment failure and death combined (RR=1.69, 95% CI 1.36 to 2.12). There appears to be no strong evidence though for increased risk of recurrence of drug resistant strains and delayed sputum conversion (Baker, Harries, Jeon, Hart, & Kapur, 2011).

In 2011, WHO recommended that all patients with TB should be screened for DM. A systematic review showed that screening for DM among patients with TB yielded a prevalence of 1.9 to 35%, depending on the prevalence of these two diseases in a given country (Jeon, Harries, Baker, Hart, & Kapur, 2010). This systematic review included countries in North America, Africa and Asia with comparable prevalence of DM as the Philippines. Studies done in India, Malaysia, Indonesia and Thailand showed that prevalence of DM among TB patients are 35.5%, 17.7%, 14.8% and 16.3% respectively (Jali, et al., 2013; Ismail, 2004; Duangrithi, et al., 2013). A small study done at Quezon Institute Philippine Tuberculosis Society, Inc. (PTSI) TB DOTS Center yielded a prevalence of 18.4% (Pablo-Villamor, Benedicto, Benedicto, & Perez, 2014).

FBS remains a useful tool for the diagnosis of DM due to its wide availability, lower cost and reproducibility (Expert Committee on Diagnosis & Classification of DM, 1997; Engelgaue etal, 1995). It has a sensitivity ranging from 45 to 60% and a specificity of >90% and a positive predictive value of 26 to 30 (Engelgau etal, 2000). Subjects with IFG (FBS of 100-125) need a confirmatory 75-gram OGTT since it would lead to greater detection of patients with diabetes at a sensitivity of 90 to 93% and specificity of 100% with a positive predictive value of 47 to 48 across populations with low and relatively higher prevalence of diabetes. FBS might not detect some patients who are positive with the OGTT OGTT (Engelgaue etal 2000; Gabir etal 2000, DECODE Study Group, 2003; Harris etal, 1998; Qiao etal 2003).

HBA1c using a method approved by the National Glycohemoglobin Standardization Program (NGSP) is recommended for diagnosis and risk assessment. In almost all parts of the Philippines, it cannot be confirmed whether the HBA1c assay used is NGSP certified, hence, the result cannot be used for diagnosis.

Hyperuricemia

It is well known that anti-TB therapy with PZA may affect uric acid levels. In a non-blinded clinical trial to evaluate the efficacy and toxicity of PTB and EPTB treatment, PZA caused uric acid elevation in 64% of 160 patients (Cohn, Catlin, Peterson, Judson & Sbarbaro, 1990). In another non-blinded, randomized, multicenter clinical trial in the United States with 1451 TB patients, 52.2% of patients had hyperuricemia. Both studies concluded that hyperuricemia is not a significant side effect of PZA and uric acid levels always return to normal after PZA is withdrawn (Combs, O'Brien, & Geiter, 1990).

Hyperuricemia is common among patients on PZA and no intervention is required unless frank gout has developed. Serum uric acid determination becomes unnecessary, costly and may improve patient compliance (Koumbaniou, Nicopoulos, & Vassiliou, 1998).

TABLE 14 Average price of laboratory tests in private hospitals and government hospitals

LABORATORY TEST	PRIVATE HOSPITALS (PRICE IN PHP)	GOVERNMENT HOSPITALS (PRICE IN PHP)
CBC with platelet	275	140
Creatinine	190	80
ALT	260	100
AST	260	100
Alkaline phosphatase	220	80
DBIB	270	200
Uric acid	200	70
HIV antibody test	540	410
Anti HCV	880	470
HBsAg	420	270

**Price as of June 2015*

QUESTION 3 What is the effective treatment regimen for new PTB cases?

The effective treatment regimen for new PTB cases (without risk factors for drug resistance) is 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (2HRZE) as intensive phase followed by 4 months of isoniazid and rifampicin (4HR) as continuation phase or Category I (2HRZE/4HR) regardless of bacteriologic status. *(Strong recommendation, high quality evidence)*

Summary of Evidence

The treatment regimen 2HRZE/4HR (Category I) is recommended for all new cases of pulmonary TB. Various treatment guidelines concur that a rifampicin-containing regimen is the backbone of anti-TB chemotherapy (WHO 2010; ATS/CDC/IDSA 2003; Ait-Khaled et al. 2010; TB CARE I 2014). Minimum of six months therapy is required as regimens of less than six months have unacceptably high rates of relapse (Gelband, 2000).

For the six-month treatment duration to be maximally effective, the regimen must include PZA during the two-month intensive phase and RIF must be included throughout the six months. A systematic review of the outcome of treatment in the presence of single or poly-drug resistance (not multidrug resistance) demonstrated that failure, relapse, and acquisition of additional resistance were associated with shorter duration of rifampicin therapy (Lew, Pai, Oxlade, Martin, & Menzies, 2008).

Evidence is inadequate to prove that EMB has value in the continuation phase (World Health Organization, 2010). Currently, there is an urgent need to define the level of INH resistance that will warrant the addition of EMB to the continuation phase of the standard treatment regimen for PTB.

TABLE 15 Mechanisms of Action and Resistance of First-Line Anti-TB Drugs

DRUG	TARGET	MECHANISM OF ACTION	MECHANISM OF RESISTANCE
Isoniazid (H)	Cell wall	Inhibits mycolic acid synthesis	Mutations in KAtG gene producing catalase peroxidase enzyme needed for its activation Mutation in inhA gene that binds with activated INH to inhibit mycolic acid
Rifampicin (R)	Nucleic acid	Inhibits transcription by interfering with DNA-dependent RNA polymerase	Mutation in rpoB gene preventing its interaction with Rifampicin
Pyrazinamide (Z)	Intracellular	Targets essential membrane transport, in fatty acid synthesis	Mutations in pncA gene
Ethambutol (E)	Cell wall	Affects lipid and cell wall metabolism Inhibits RNA synthesis	Mutation of embCAB operon
Streptomycin (S)	Ribosome	Inhibits translation during protein synthesis	Mutations of ribosome target binding sites

Reference: The Enhanced Curriculum on TB Control for Philippine Medical Schools, Instructor's Manual, 2011

TABLE 16 Treatment Category I (2HRZE/4HR) for Fixed Dose Combination (FDCs)

BODY WEIGHT (KG)	INTENSIVE PHASE 2 MONTHS OF (HRZE) DAILY	CONTINUATION PHASE 4 MONTHS OF (HR) DAILY
30-37	2 tablets/day	2 tablets/day
38-54	3 tablets/day	3 tablets/day
55-70	4 tablets/day	4 tablets/day
>70	5 tablets/day	5 tablets/day

Reference: NTP Revised Manual of Procedures 5th Ed., Department of Health, 2014

TABLE 17 Drug dosage per kilogram body weight for Single Dose Formulations (SDFs)

DRUG	ADULTS	
	DOSE (MG/KG)	*MAXIMUM DOSE*
Isoniazid (H)	5 (4-6)	400 mg daily
Rifampicin (R)	10 (8-12)	600 mg daily
Pyrazinamide (Z)	25 (20-30)	2g daily
Ethambutol (E)	15 (15-20)	1.2 g daily
Streptomycin (S)	15 (12-18)	1g daily

Reference: NTP Revised Manual of Procedures 5th Ed., Department of Health, 2014

QUESTION 4 How should retreatment cases be managed?

All retreatment cases should immediately be referred to the nearest Xpert® MTB/Rif facility for rifampicin susceptibility testing. ***(Strong recommendation, high quality evidence)***

Category II regimen (2HRZES/1HRZE/5HRE) should only be given among confirmed Rifampicin-sensitive retreatment cases or in circumstances where Xpert® MTB/Rif services cannot be performed (i.e. no access or no sputum specimen). ***(Strong recommendation, moderate quality evidence)***

Rifampicin-resistant cases should immediately be referred to a PMDT facility for further management (refer to Chapter 4 on drug-resistant TB)

Summary of Evidence

In a systematic review of 27 studies, Xpert® MTB/Rif had a pooled sensitivity of 95% (95% CI 90-97%) in 17 studies with 555 rifampicin resistant cases and pooled specificity of 98% (95% CI 97%- 99%) in 24 studies with 2411 rifampicin sensitive cases. Based on this review, the authors concluded that Xpert® MTB/Rif provides accurate results allowing rapid initiation of treatment for MDR-TB while waiting for the results of the conventional culture and drug sensitivity (Steingart, Schiller, Horne, Pai, & Boehme, 2014).

If rapid DST is not available, standard conventional DST should be done. While waiting for the results or if this is not available, patient may be empirically retreated with Category II regimen (World Health Organization, 2010).

In a study by Saravia, et al. (2005), treatment based on DST was three times more likely to cure patient than the Category II regimen in retreatment patients (79% vs 38%, RR=2.9, 95% CI 1.7-5.1). Dooley, et al. (2011) also concluded that retreatment with Category II are suboptimal and vary by subgroup which may relate to different rates of drug resistance.

In another prospective cohort study of 288 smear- and culture-positive retreatment TB patients, 70%–80% of patients had successful treatment outcome at the conclusion of anti-TB therapy. However, the retreatment regimen has unacceptably low treatment response rates in certain subgroups of patients and is associated with poor long-term outcomes, particularly in MDR-TB and in HIV-infected patients (Jones-Lopez, Ayakaka, Levin, Reilly, & Mumbowa, 2011). **Table 18** is a summary of retrospective studies done in India, Malawi, and Ethiopia. The success/cure rate for relapse cases ranged from 68-81%; for return after default 56-73%; lowest with treatment failure at 49-67%.

TABLE 18 Summary of retrospective cohorts on outcome of retreatment of TB with Category II regimen

AUTHORS	DESIGN	N	SUCCESS/CURE RATE % (N)			
			RELAPSE	*TREATMENT FAILURE*	*RAD*	*OTHERS*
Srinath etal	Cross-sectional	5,365	78% (1625)	59% (59)	73% (1127)	83% (1029)
Sarpal etal	Longitudinal cohort	545	81% (213)	54% (21)	67% (50)	96% (160)
Tweya etal	Retrospective cohort	662	73% (149)	57% (12)	57% (17)	63% (257)
Hamusse, etal	Retrospective cohort	984	68% (593)	67% (34)	58% (38)	-
Mehra etal	Retrospective cohort	632	76% (338)	49% (93)	-	-
Mukherjee etal		234	76% (113)	54% (28)	56% (19)	-

QUESTION 5 How should PTB patients who have interrupted treatment be managed?

Patients who fail to follow-up as scheduled should be immediately traced through: telephone call, text message or home/workplace visit.

Assess the cause of interruption and agree on solutions and treatment plans based on length of interruption and duration of treatment prior to interruption as outlined in **Table 19.**

TABLE 19 Management of Cases Who Interrupted Treatment

LENGTH OF INTERRUPTION	DO DSSM IF >1 MONTH INTERRUPTION	HOW LONG HAS PATIENT BEEN TREATED?	DISPOSITION
Less than 1 month	Continue treatment and prolong to compensate		
More than 1 month but less than 2 months	Negative DSSM	Continue treatment and prolong to compensate	
	Positive DSSM	Less than 5 months	Continue treatment and prolong to compensate
		More than 5 months	Classify as "Treatment failed"
More than 2 months	Classify as "Lost to follow up", repeat DSSM		

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014

QUESTION 6 What is the effective treatment regimen for miliary TB and miliary TB with dissemination?

In the absence of meningitis or bone and joint involvement, the effective treatment regimen for new miliary TB cases is Category I (2HRZE/4HR).

Dissemination to other organs such as the CNS, joints/bones, lungs, heart, gastrointestinal tract, and genitourinary tracts are to be treated according to the recommendations for treatment of EPTB. (See **Table 20**) ***(Strong recommendation, low quality evidence).***

Summary of Evidence

Miliary TB is a pathological term that describes millet seed-sized (1–2 mm) granulomas in various organs of the body affected by tubercle bacilli. It results from massive lympho-hematogenous dissemination from *Mycobacterium tuberculosis*-rich focus (Sahn & Neff, 1974).

The ATS/CDC/IDSA (2003) and National Institute for Health and Clinical Excellence (NICE) TB guidelines concur with the WHO guidelines that 6 months of standard treatment (2HRZE/4HR) should be adequate in miliary TB. The NICE TB guidelines also suggest that all patients with miliary and disseminated TB be tested for CNS involvement by CT or MRI of the

brain and/or lumbar puncture for those without CNS symptoms and signs (National Institute for Health and Clinical Excellence, 2011).

These recommendations highlight the fact that each patient with miliary TB should be assessed individually both clinically and radiologically in terms of extent of dissemination. While the standard six-month treatment may be sufficient for most of miliary TB patients, it may be suboptimal for those who have undiagnosed TB meningitis, and/or bone and joint involvement.

QUESTION 7 What are the effective treatment regimens and duration of treatment for EPTB?

The effective treatment regimen for majority of new EPTB cases is Category I (2HRZE/4HR). CNS, bones/joints are to be treated with Category Ia (2HRZE/10HR). **Table 20** and **Table 21** list the treatment regimens for different EPTB. ***(Strong recommendation, low-high quality evidence)***

Referral to relevant specialties is warranted in managing EPTB for optimal treatment.

TABLE 20 Summary of Evidence for Treatment Regimens for Extra-Pulmonary TB (EPTB)

SITE	REGIMEN	RECOMMENDATION/ LEVEL OF EVIDENCE
CNS	2HRZE/10HR	***Strong recommendation, high quality evidence***
Bone and Joints	2HRZE/10HR	***Strong recommendation, moderate quality evidence***
Lymph node	2HRZE/4 HR	***Strong recommendation, moderate quality evidence***
Pericardium	2HRZE/4 HR	***Strong recommendation, low quality evidence***
Pleura	2HRZE/4 HR	***Strong recommendation, moderate quality evidence***
Liver	2HRZE/4 HR	***Strong recommendation, moderate quality evidence***
GI, Peritoneum	2HRZE/4 HR	***Strong recommendation, moderate quality evidence***
Kidney, Genitourinary	2HRZE/4 HR	***Strong recommendation, low quality evidence***

TABLE 21 Summary of Treatment Regimens for Pulmonary and Extra-Pulmonary TB

TREATMENT CATEGORY	INDICATION	REGIMEN
Category I	New Pulmonary TB New Miliary TB New EPTB (except CNS/ bones or joints)	2HRZE/4HR
Category Ia	CNS TB, TB of Bones or joints	2HRZE/10HR
Category II	Retreatment of Rif susceptible PTB and EPTB (except CNS/ bones or joints)	2HRZES/1HRZE/5HRE
Category IIa	Retreatment of Rif susceptible CNS, bones or joints	2HRZES/1HRZE/9HRE

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014

Summary of Evidence:

CNS

Thwaites et al. (2009) recommended 2HRZE followed by 10HR for treatment of all forms of CNS tuberculosis. This treatment regimen was further supported by the 2010 WHO recommendation and the 2014 National Tuberculosis Program Manual of Procedure.

An open label, phase 2 trial of 60 patients showed that treatment with a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with TB meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease. However, since this is a phase 2 trial only and due to issues of emergence of resistance, it is not recommended to use this regimen at this time (Ruslami, Ganiem, Dian, Apriani, & Achmad, 2013).

Bone and Joints

Management of bone tuberculosis (TB), including spinal TB, varies and conflicting guidelines exist. The recommendations range from six to 12 months of treatment. In a study by Ramachandran, et al. (2005), 38 patients (34 with spinal TB and four with TB of other bones) were reviewed. Relapse rates were statistically significantly higher in the group treated for 6 months compared to those treated for more than 6 months ($P<0.05$). Of eight patients who received 6 months of therapy, five relapsed. Of 30 patients who received treatment for 9 months or longer, none relapsed. Thus the

study concluded that six months of treatment may be inadequate for bone TB, including spinal TB and suggest that a minimum course of 9 months should be strongly considered.

Lymph Node

A randomized clinical trial done in South India, comparing 6-month twice-weekly directly observed regimen of rifampicin, isoniazid and pyrazinamide and a daily self-administered two drug (isoniazid and rifampicin) regimen showed no significant difference in favorable clinical response. Two-hundred sixty-eight (268) patients, 63 children and 171 adults, with biopsy confirmed superficial lymph node tuberculosis were randomly allocated to each group. At the end of treatment, 114 of 134 patients (87%; 95% CI 81–93%) in each group had favorable clinical response measured by disappearance or regression of lymph nodes to less than 10mm, and healing of sinuses and abscesses. At 36 months after completing treatment, 126 of 134 (94%; 95% CI 90–98%) patients treated daily and 129 of 134 (96%; 95% CI 94–98%) patients given twice-weekly regimen had a successful outcome. Relapse was noted in 5 patients, 2 (2%; 95% CI 1–3%) in the daily group and 3 (2%; 95% CI 1–3%) in the twice-weekly regimen group (Jawahar, Rajaram, Sivasubramanian, Paramasivan, & Chandrasekar, 2005).

A retrospective study done in India also from January 2006 to December 2008 evaluated the 6-month regimen 2HRZE/4HR given 3 times a week. Ethambutol was added in complicated cases. 240 patients were on CAT-III regimen and 55 were on CAT-I because of complicated lymphadenopathy. Treatment response was based on improvement of clinical parameters and reduction in the size of the nodes. Of the 295 patients, 212 (71.86%) responded to treatment, 54 (18.30%) responded to re-treatment, while 29 (9.83%) patients were found to be drug resistant. Relapse was seen in 11 cases (5.18%) (Jain, Bajpai, & Jain, 2010).

Pericardium

The task force did not find any randomized controlled trials directly comparing treatment regimens and duration for TB pericarditis, including effects on pericardiectomy, hence the panel still recommends six months of treatment. Clinical trials that evaluated other modalities of treatment for TB pericarditis used 6-9 months of treatment, and one study that evaluated a diagnostic test for TB pericarditis gave anti-TB drugs for 12 months (Koh, et al., 1999; Strang, et al., 2004; Sagrista-Salueda, et al., 1988).

Pleura

A six-month duration of therapy consisting of a 2HRZE followed by 4HR is considered adequate for uncomplicated cases of pleural TB (ATS/CDC/IDSA, 2003; World Health Organization, 2010).

Liver

A systematic review on the epidemiology, diagnosis and treatment of hepatic tuberculosis involving 618 patients showed that 6 to 12-month treatment duration appears to be effective. Of the 14 case series included, nine (n=323) reported on treatment regimens and outcomes. One of the 9 case series involved HIV patients (n=20). Anti-TB drugs were given for at least 6 months (2HRZE + 4HR; 2 studies), 9 months (HRZE; 1 study), and 12 months (2HRZE + 10HR; 2 studies). Treatment duration was not mentioned in the remaining 4 cases series. Improvement was reported on 223 patients. Positive clinical response reported were improved appetite, reduced hepatomegaly, weight gain, resolution of fever and decreased jaundice. In a cohort of 96 patients with hepatic TB receiving either < 2 drugs (n=10), > 2 drugs but no HR (n=29), HR + others (16), and no treatment (37), mortality rate was 42% and mostly among those without treatment and receiving monotherapy (Hickey, Gounder, Moosa, & Drain, 2015).

Gastrointestinal and Peritoneum

A randomized, open trial (n=90, 18-75 years) comparing a 6-month (2/HRZE/4HR) vs 9-month regimen (2HRZE/7HR) in abdominal TB demonstrated no significant difference in complete response to treatment defined as endoscopic healing of active lesions (6-month group, 93.3% vs 9-month group, 91.1%; p= 1.00) or recurrence rate (2.4% vs 0.0%, p=1.00). Diagnosis of intestinal TB was based on any one of the following criteria: demonstration of caseating granuloma on endoscopic biopsy; identification of acid-fast bacilli (AFB) in a histological specimen; positive culture of M. TB from a biopsy specimen; colonoscopic findings strongly suggestive of intestinal TB with associated active pulmonary TB, regardless of sputum AFB smear or TB culture result. Patients with EPTB other than GI, anti-TB treatment within the last 5 years, immunosuppressed, pregnant were excluded (Park, Yang, Yang, Kim, Yoon, & Choe, 2009).

A retrospective study of 17 patients with abdominal TB done in England also showed that at least 6 months of therapy resulted in favorable results. Of the 17 patients, six completed 6 months treatment. Those who received extended duration had pyrazinamide intolerance (1), isoniazid intolerance (2), co-existing tuberculoma in the occipital region of the brain (1), vertebral

involvement (2). The infected sites in this study were peritoneum (5), ileo-cecal valve (5), small intestine (4), retroperitoneum (3), colon (2), and liver (2) (Mamo, Brij, & Enoch, 2013).

Another retrospective study in England, between 1985 and 2004, included 86 patients, ages 6-93, with abdominal TB. Sites of involvement were peritoneum (41), ileo-cecal (14), ileum (12), colon (4), liver (4) gallbladder (3) and anal margin (2). Twenty-eight patients had TB in multiple sites. Sixty-one of 82 patients who completed treatment received 6-month therapy of either 2HRZE/4HR (37) or 2HRZ/4HR (23) and one received 2HRZ+ciprofloxacin/4HR due to advanced renal disease. Nine patients were given modified and extended regimens because of pyrazinamide or isoniazid intolerance. There were four deaths – 2 elderly with concomitant extensive pulmonary TB, 1 with severe congestive heart failure and 1 with associated gastric carcinoma. One patient with isoniazid resistance relapsed. No relapse was reported among those given 6 months treatment (Ramesh, Banait, & Ormerod, 2008).

Of 14 adults with abdominal TB in Taiwan reported between January 2000 to December 2006, 11 patients completed at least 6 months of anti-TB drugs. Three patients died from causes unrelated to TB (Lu, Lee, Kuo, Huang, Tai, & Chang, 2009).

Kidney and Genitourinary tract

There are no randomized controlled trials on the duration of treatment of genitourinary TB. Some case reports showed clinical improvement with 6 months of TB treatment with adjunctive surgical intervention. A case report of a 43- year old man with genitourinary TB treated for 6 months and underwent reconstructive surgery did well after 6 months (Dogra, et al., 2014). The authors suggest at least 3-6 weeks of anti-TB therapy before doing any reconstructive surgery to allow the inflammatory process to settle, the disease to stabilize and to better assess the procedure to be done.

In another case report by Gascon et al., an 18-year old woman presented with hypogastric discomfort and repeated urinary symptoms complicated with pelvic inflammatory disease after a hysterosalpingography, underwent laparotomy and revealed large pelvic abscesses. Drainage, adhesiolysis and bilateral salpingectomy were performed. Histopathological specimens and cultures were positive for MTB. She was treated for 6 months and after 8 years, she presented with normal menstruation (Gascon et al, 2014).

QUESTION 8 How effective are corticosteroids for the treatment of EPTB?

- The use of corticosteroids as adjunctive therapy is recommended **ONLY** for patients with TB meningitis and/or TB pericarditis.
- In TB meningitis, the recommended regimen is dexamethasone 0.4 mg/kg/24H with a reducing course over 6-8 weeks ***(Strong recommendation, high quality evidence)***
- In TB pericarditis, the recommended regimen is prednisolone 60 mg for the first 4 weeks, 30 mg for weeks 5-8, 15 mg for weeks 9-10 and 5 mg for week 11 ***(Strong recommendation, moderate quality evidence)***

Summary of Evidence

Corticosteroid use in TB meningitis and pericarditis have sufficient evidence for recommendation. Other forms of EPTB do not have sufficient evidence.

TB Meningitis

A Cochrane systematic review of 7 trials (n= 1140 participants, 411 deaths) comparing corticosteroid plus anti-TB treatment with anti-TB treatment alone in patients with clinically diagnosed TB meningitis showed that corticosteroids reduced the risk of death (RR 0.78, 95% CI 0.67 to 0.91) of patients with TB meningitis (Prasad & Singh, 2008).

In an RCT done in Vietnam, 545 patients were randomized to either dexamethasone or placebo. Two-year survival probability was higher in the dexamethasone arm (relative risk, 0.69; 95% CI 0.52-0.92) but 5-year survival rates were similar in both groups. Thus this study concluded that adjunctive dexamethasone appears to improve the probability of survival in patients with TBM until at least two years follow up (Török, Bang, Chau, Yen, & Thwaites, 2011).

The British Infection Society recommended giving adjunctive corticosteroids (either dexamethasone or prednisolone) to all patients with TB meningitis, regardless of disease severity (Thwaites, Fisher, Hemingway, Scott, Solomon, & Innes, 2009).

TB Pericarditis

An updated Cochrane systematic review (Mayosi 2009) found no new evidence on the effectiveness of corticosteroids for TB pericarditis. One

small RCT that followed up patients with TB pericardial effusion and constrictive pericarditis after 10 years found no significant difference in the overall adverse events (RR 0.70, 95% CI 0.44-1.14), death rates (RR 0.26, 95% CI 0.057-1.185) and incidence of pericardiectomy (RR 0.85, 95% CI 0.50-1.44) among patients with TB constrictive pericarditis, on steroids and placebo (Strang, Nunn, Johnson, Casbard, Gibson, & Girling, 2004).

For TB pericardial effusion, there was no significant difference in all outcomes studied in patients who had open drainage and received steroids compared to patients who did not receive steroids. Among patients with effusion who did not undergo open surgical drainage, steroids significantly reduced the number of death from pericarditis (10.2% vs 2.3%, p = 0.03, RR 0.22, 95% CI 0.05-0.99) and the need for repeat pericardiocentesis (23% vs 10.2%, p= 0.025, RR 0.45, 95% CI 0.21-0.93) (Strang, Nunn, Johnson, Casbard, Gibson, & Girling, 2004).

QUESTION 9 What is the role of surgery in the management of EPTB?

Complications arising from EPTB may warrant surgical referral.

CNS

Hydrocephalus, tuberculous cerebral abscess, and vertebral TB with paraparesis are indications for neurosurgical referral. Early VP shunting should be considered among those with non-communicating hydrocephalus and among those with communicating hydrocephalus failing medical management. ***(Strong recommendation, moderate quality evidence)***

Spine

Surgery for spinal tuberculosis in addition to the standard chemotherapy is indicated in patients started on (a) ambulant chemotherapy who develop progressive kyphosis; (b) patients with compression of the spinal cord in whom the neurological status deteriorates in spite of chemotherapy. ***(Strong recommendation, moderate quality evidence)***

Lymph Node

Therapeutic lymph node excision is not recommended for TB lymphadenitis unless unusual circumstances arise (e.g. large fluctuant lymph nodes that are about to spontaneously drain). ***(Strong recommendation, moderate quality evidence)***

Pericardium

Open surgical drainage under general anesthesia is an option for patients with TB pericardial effusion. ***(Weak recommendation, low quality evidence)***

Pleura
Surgical procedures like pigtail drainage and decortication may be needed in symptomatic patients due to pleural loculation and thickening. *(Weak recommendation, low quality evidence)*

Gastrointestinal and Peritoneum
Surgery is reserved for complications such as gut obstruction, fistula formation, and intractable ulceration. *(Strong recommendation, moderate quality evidence)*

Liver
Hepatectomy may be an option for nodular hepatic TB when malignancy is possible. Percutaneous aspiration and drainage may be needed in patients with multiple large hepatic TB abscess. Biliary decompression is done in patients with obstructive jaundice when necessary. *(Weak recommendation, low quality evidence)*

Genitourinary
*R*econstructive surgery is an option for patients who have symptoms caused by sequelae of genitourinary tuberculosis. *(Weak recommendation, low quality evidence)*

Summary of Evidence

CNS

Hydrocephalus is the most common reason for referral to neurosurgery in patients with TB meningitis. Early ventriculo-peritoneal shunting is suggested in all patients with non-communicating hydrocephalus by some although response to the drainage has failed to predict those who benefit from early shunting (Mathew, et al., 1998). Although rare, tuberculomas can lead to cerebral abscess which may necessitate surgical intervention such as aspiration, burr hole, stereotactic aspiration and total excision (Mohanty, et al., 1999).

Spine

Surgery in spinal TB is performed only if the outcome will be more beneficial than treatment with chemotherapy alone. A systematic review found no statistically significant benefit with routine surgery, and surgery had no effect on kyphosis angle. The review revealed no between- group difference in healing. However, results showed that deterioration of more than 10 degrees was noted when baseline kyphosis is more than 30 degrees (Zhang, Ji, & Liu, 2013).

An RCT by Parthasarathy, et al., (1999) recommended surgery (in addition to chemotherapy) for the following patient population:

1. Age <25 years, in whom the initial angle of kyphosis is more than 30 degrees
2. Those started on ambulant chemotherapy who develop progressive kyphosis
3. Children less than 10 years old with destruction of vertebral bodies who have partial or no fusion even during the adolescent growth spurt
4. Those with compression of the spinal cord in whom the neurological status deteriorates despite chemotherapy.

Patients with vertebral body TB associated with paraparesis whose MRI shows extradural compression, but with little fluid component compressing or constricting the cord, probably need early surgical decompression (Turgut, 2001)

Lymph Node

TB lymphadenitis can increase in size during treatment and this phenomenon is called paradoxical response to treatment. Treatment can be continued under close observation. Surgery is reserved when lymph nodes are about to spontaneously drain.

Surgical excision of lymph nodes has been recommended for patients experiencing worsening of symptoms during treatment, or treatment failure caused by drug-resistant organisms and for patients who have discomfort from tense, fluctuant lymph nodes (Fontanilla, Barnes, & von Reyn, 2011). In a study by Hawkey, et al. (2005), aspiration of pus from the node, incision and drainage, or excision performed during the paradoxical reaction were associated with a shorter duration of paradoxical response (median duration, 46 vs. 92 days; p=0.10).

Pericardium

In an RCT of TB pericardial effusion, open surgical drainage did not significantly decrease the mortality of patients (8.7% vs 9%, RR 0.96; 95% CI 0.30-3.15), and the need for pericardiectomy (3.5% vs 9%, RR 0.39; 95% CI 0.08 to 1.91), compared to those who receive the standard of care. No trials were found evaluating the benefit of percutaneous drainage of the pericardium under local anesthesia (Strang, Kakaza, Gibson, Allen, & Mitchison, 1988).

In a case series of 82 patients in Turkey diagnosed with chronic constrictive TB pericarditis, perioperative mortality was 8.6%, and the predictors for this outcome were presence of ascites (OR 10.79, 95% CI 1.02-113.45, p=value 0.047) and longer duration of symptoms before pericardiectomy (OR

11.11, 95% CI 1.01-1.22, p-value 0.036) (Cinar, Goksel, Cimen, Ketenci, & Teskin, 2006). However, no RCT studied the timing of pericardiectomy in TB constrictive pericarditis, hence this is still controversial. A systematic review recommended that pericardiectomy be done if the patient has not improved or has deteriorated after 4 to 8 weeks of anti-TB therapy. Early surgical intervention can be done if there is evidence of pericardial calcification (Burgess & Doubell, 2005).

Pleura

An RCT by Chung, et al. (2008), showed that early drainage in addition to anti-TB treatment may hasten clearance of pleural effusion and pulmonary function recovery, and reduce residual pleural thickening. In the study, 64 patients with TB pleurisy were treated with anti-TB medications and pigtail drainage. They were divided into 3 groups: free-flowing effusions irrigated with saline, loculated effusions irrigated with streptokinase, and loculated effusions irrigated with saline. The free-flowing and streptokinase groups had significant improvement in radiological scores, forced vital capacity and had lower occurrence of residual pleural thickening.

In another RCT of 30 patients who received pigtail drainage combined with anti-TB drugs compared to 31 patients who received anti-TB drugs only, no significant difference was found in terms of symptom scores, forced vital capacity, and incidence of residual pleural thickening (Lai, Chao, Wang, & Lin, 2003).

However, surgical procedures like decortication may be needed in some patients because of dyspnea resulting from pleural loculations and thickening despite anti-TB treatment. In a comparative study, 48 patients were randomly assigned into 3 groups (control: repeated thoracentesis; catheter group: small bored catheterization; and urokinase group: catheterization with intrapleural urokinase instillation). Better results were seen in the urokinase group in terms of the frequency of catheterization, frequency of obstruction, and the duration of catheterization (Lee, Lee, Lee, Park, Suh, & Cho, 1996)

Gastrointestinal and Peritoneum

In a descriptive study by Arif, et al. (2008) of 50 patients with intestinal tuberculosis, 23 patients presented with subacute intestinal obstruction, 13 had acute intestinal obstruction, and 12 had signs of peritonitis. Forty-eight underwent surgery plus anti-TB therapy. Two were given medications alone.

After follow up for 3 to 12 months, 2 patients were readmitted for subacute obstruction and one for ileostomy prolapse. No death was reported.

In another study by Marjanovic, et al. (2008), 11 patients with abdominal TB underwent surgery due to acute abdomen and peritonitis (6), subocclusion (2), and ileus (3). Three patients who presented with acute abdomen died. All patients were on anti-TB drugs.

Liver

In a case series, three patients underwent surgical procedure while the other two received medical treatment alone. Among those who had surgery, one had liver mass and concomitant calculous cholecystitis; the second case was misdiagnosed with cholangiocarcinoma with intrahepatic masses and was accompanied by biliary obstruction. The third patient had multiple liver masses accompanied by hilar mass which was misdiagnosed as hilar cholangiocarcinoma. Four of the five patients recovered without complications and recurrence after a 3-year median follow-up (Zheng, Wang, Zhu, Cheng, & Dong, 2013).

A retrospective study by Xing, et al. (2005), eight patients with hepatic TB pseudotumor underwent segmentectomy or hepatectomy. Preoperative diagnoses were hepatic TB pseudotumor (3), liver cancer (3), hepatic adenoma (1), incidentaloma (1). No recurrence of hepatic TB in 7 patients after a 4-year follow up was reported. Aspiration of liver abscess plus anti-TB drugs have been done in several case studies resulting in favorable outcome (Purohit & Verma, 1982; Chen, et al., 2003).

Genitourinary

Reconstructive surgery for genitourinary TB has an important role in cases with grossly distorted and dysfunctional anatomy that are unlikely to regress with chemotherapy alone.

Augmentation cystoplasty includes the goals of increasing bladder capacity, while retaining as much of bladder as possible. Orthotopic neobladder reconstruction is a feasible option, suitable in cases of tubercular thimble bladder with a markedly reduced capacity (as little as 15 ml), where an augmentation alone may be associated with anastomotic narrowing or poor relief of symptoms. Surgical complications including bladder perforation, anastomosis leaks and stenosis should be taken into consideration (Gupta, et al., 2014; Dogra, et al., 2014; Gascón & Acién, 2014).

In a study by Huang, et al. (2013), of 239 cases of GUTB in China from 2000 to 2010, only 21 cases were treated with anti-TB medications alone. The rest underwent surgical procedures.

QUESTION 10 How should anti-TB medications be administered?

Patient-centered, directly observed therapy (DOT) should be offered to all patients who will undergo treatment for TB in health facilities with accredited DOTS programs

In patient-centered DOT, a patient is given the opportunity to choose where they want to be treated, and who will supervise them, either a healthcare worker, community health worker or family member, depending on clinical, social, cultural circumstances.

Outcomes are better with patient-centered DOT in terms of completion of treatment, smear conversion and default rates compared to daily health facility based treatment and is less expensive in a programmatic setting.

(Strong recommendation, high quality evidence)

Summary of Evidence

Directly observed treatment, short-course (DOTS) is a framework developed by WHO for controlling TB. Under DOTS, patients take their medications under supervision by a treatment partner to improve compliance. It is important to combine this with patient-centered treatment (PCT). The patient can choose to be treated at home or in a health facility. The treatment partners can be a trained health worker or family member (WHO, 2008).

There was no significant difference between DOT and self-administered treatment (SAT) in the completion of treatment (RR 1.06, 95% CI 0.98-1.15) and cure (RR1.02, 95% CI 0.86-1.21) (Garner, 2007). The location of DOT also did not matter whether at home or in a health facility. However, Pasipanodya & Tawanda (2013) showed that DOT was significantly associated with lower default rates compared to SAT (RR 0.48, 95% CI 0.43-0.54), but there was no significant difference in microbiological failure, adverse events and or relapse.

In a systematic review of 31 RCTs, community-based interventions (such as community mobilization and support, patient treatment literacy

training, adherence support from trained community health worker and family members, involvement of NGO, formation of community groups, and engagement of successfully treated patients) contribute to treatment success rate (RR 1.10, 95% CI 1.08-1.12) and decrease relapse (RR 0.26 95% CI 0.18-0.39) (Arshad, Salam, Zohra, Das, Naqvi, & Zulfiqar, 2014).

The 2014 ISTC has recognized the limitations of the use of health facility-based DOT and is currently moving away from the strict traditional provider to a more dynamic, flexible approach that involves the patient in decision-making and responsibility. A systematic review by Munro (2007) of 44 studies enumerated four factors that contribute to adherence to TB medication: structural factors including poverty, financial burden and gender discrimination; personal factors including knowledge, attitudes and beliefs towards treatment, and the interpretation of illness; social factors including family, peer, community and stigma; and health service factors including organization of care and education about side effects. Thus, it is important to recognize that often the reasons for non-adherence are outside the direct control of the patient.

There are multiple factors related to adherence to therapy. **Table 22** enumerates the factors likely to improve adherence. Thus, current ISTC recommends PCT where patients are given an opportunity to choose where they want to be treated and who will supervise them (TB CARE I, 2014).

TABLE 22 Factors likely to improve adherence to TB medication

- Increase the visibility of TB programs in the community, which may increase knowledge and improve attitudes towards TB.
- Educate patients and communities about the disease and treatment.
- Increase support from family, peers and social networks.
- Minimize costs and unpleasantness related to clinic visits and increase flexibility and patient autonomy.
- Increase flexibility in terms of patient choice of treatment plan and type of support.
- Increase the patient centeredness of interactions between providers and clients.
- Address "structural" and "personal" factors, such as cash incentives, food assistance, travel reimbursements and other empowerment initiatives and prevent loss of employment through addressing employment policies.
- Education on side effects of medication to reduce the risks of patients becoming non-adherent when experiencing treatment adverse reactions.

Modified from Munro SA, et al. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med.4: 2007; e238.

In a cohort study of PCT approach done inTanzania, more patients completed treatment in the PCT arm (79%) than in the control group (71.6%) (RR 1.10, 95% CI 1.05-1.15) and more deaths were observed in the control arm (17.6% vs 13.9%, RR 0.79, 95% CI 0.66-0.95). However, there was no significant difference in the default rates in the two groups (RR 0.77 95% CI 0.52-1.14). Smear conversion rate was higher in the PCT arm (80.2% vs 74.6%, RR 1.07, 95% CI 1.01-1.26). Thus, PCT approach was more likely to cure patients than those directly observed in the health facility (Egwaga, Mkopi, Range, Haag-Arbenz, & Baraka, 2008).

A cross-sectional study in Tanzania identified the factors associated with the success of PCT: female gender (OR 1.94, 95% CI 1.24-3.02), ages between 35-44 (OR 0.77, 95% CI 0.59-0.99) and a more proximate guardian with residence of supporter >15-minute walk (OR 0.08 95% CI 0.02-0.25) (Mkopi, Range, Lwilla, Egwaga, & Schulze, 2012).

QUESTION 11 What are the effective ways of tracking patients and monitoring adherence to treatment?

The healthcare provider should educate the patient and treatment partner along with the following strategies to track and monitor adherence to treatment:

- Remind patients of their appointments, by pre-appointment phone calls and SMS
- Default reminder letter or home visits for those who miss appointments
- Use of SMS as reminders
- Give incentives and enablers such as nutritious, culturally appropriate daily meals and food packages
- Coordinate with DOTS centers and support groups

(Strong recommendation, moderate quality evidence)

Summary of Evidence

A healthcare worker should develop a good relationship with the patient in order to discuss issues about TB treatment. Education is a significant component in improving adherence. A study by Lee (2013) showed that educating patients on TB and anti-TB medications resulted to better adherence compared to the control group (80% vs 70%, p-value 0.03).

Remind patients of their appointments

A Cochrane systematic review of 5 trials showed that TB treatment completion rate was significantly increased with pre-appointment phone calls, and

letters or home visits for those who missed appointments (RR 1.17, 95% CI 1.11, 1.23) (Lu, 2014). One trial showed that default reminder letter can also increase the attendance of patients who missed an appointment (RR 5.04, 95% CI 1.61, 15.78) (Paramasivan, et al., 1993). An RCT by Irribarren et al. (2013) examined the use of SMS in increasing adherence. Patients were instructed to text-in after medication administration as well as encouraged to text-in questions or concerns with regards to their treatment. However, both arms had similar treatment success rates.

Give incentives and enablers

A meta-analysis evaluated the effect of material incentives and enablers in adherence to treatment for active TB, INH prophylaxis and return for TST reading (Lutge et al, 2012). One trial showed no difference in completion of treatment for active TB between those given nutritious, culturally appropriate daily meals and food packages and those who were given nutritional advice only (RR 0.98, 95% CI 0.86,1.12) (Martins, et al., 2009). Evidence is insufficient to prove that material incentives work in increasing adherence to anti-TB medications.

Coordinate with support groups

In a systematic review of community-based trials, formation of support groups, such as non-governmental organization and community groups, can contribute to the knowledge about TB and treatment adherence. Patients who were successfully treated can also be tapped to assist in stigma reduction and discrimination in the community (Arshad, Salam, Zohra, Das, Naqvi, & Zulfiqar, 2014).

QUESTION 12 How effective are fixed-dose combination drugs compared to single-drug formulations?

Fixed-dose combination (FDC) drugs are convenient in terms of acceptability, side effects and adherence and are preferred especially in a programmatic setting. They are similar to single-drug formulations (SDF) in preventing treatment failure or disease relapse when given under DOT. ***(Strong recommendation, moderate quality evidence)***

Single-drug formulations are useful for the following situations:

- Those who experience adverse reactions or at risk for adverse reactions (elderly, liver disease)
- With co-morbid conditions requiring dose adjustments (liver or kidney disease) or expected to have significant drug interactions (HIV, DM)

Summary of Evidence

In a review of 15 studies comparing FDC vs SDF drugs (Mondero 2011), almost all studies were unblinded and involved smear-positive and new, probably susceptible cases. Three studies were conducted under program conditions, without complete DOT or self-supervision.

Information on treatment modality was not available for studies, while the remaining studies were performed under DOT and controlled study conditions. Acceptability, side effects and adherence were measured in 9 studies and all reported similar or better results with FDCs. Only one study reported lower levels of acquired DR (0.47% vs. 1%) in patients taking self-administered FDCs or mostly FDCs. This study however, reproduces the real circumstances of a well performed NTP, without using DOT. Although all studies reported similar efficacy regardless of drug formulation, studies that included DOT obtained outstanding cure rates (between 93% and 100%).

In a more recent meta-analysis by Albanna, et al. (2013), 15 RCTs (5,630 patients), one comparative cohort and three non-comparative studies were reviewed. Compared to SDFs, FDCs resulted in a non-significant trend towards a higher risk of treatment failure or disease relapse (RR 1.28, 95% CI 0.99 to 1.7; 13 RCTs). There were no significant differences between treatment groups for acquired drug resistance (4 RCTs) or adverse drug reaction (10 RCTs). Subgroup analyses reported a significantly higher risk of treatment failure or drug relapse with FDCs for patients with baseline drug-sensitive TB (RR 1.48, 95% CI 1.04 to 2.09; six RCTs) and for patients receiving self-administered therapy (RR 1.94, 95% CI 1.05 to 3.57).

QUESTION 13 How effective is daily vs. intermittent regimen for the treatment of TB?

- Daily regimen is recommended for the treatment of TB particularly if FDC is used.
- Intermittent regimens less than 3x/week are not preferred because of the greater impact of missed doses on success rates.
- Thrice weekly intermittent regimens may be offered in special situations where daily regimen is not feasible

(Strong recommendation, moderate quality evidence)

Summary of Evidence

A Cochrane systematic review (Mwandumba & Squire 2001) yielded one RCT (399 participants) that compared three times weekly versus daily chemotherapy for six months in people with newly diagnosed PTB. No significant differences in bacteriological cure rates or relapse rates between the two regimens were found one month after treatment was completed. Bacteriological cure rate was 99.9% with 3 times weekly vs 100% with daily; relapse rate was 5/186 (2.7%) with 3 times weekly vs. 1/192 (0.5%) with daily regimen (RR 4.0; 95% CI 0.7, 24.1). The authors concluded that there is not enough evidence to assess the equivalence between fully intermittent, rifampicin-containing short course chemotherapy and a similar daily therapy in patients with PTB.

An RCT in Singapore which compared 4-month daily treatment (2HRZ/2HR) with combined daily treatment during the intensive phase and thrice weekly during the continuation phase (2HRZ/2H3R3) in smear-negative TB cases found no difference in relapse rates after five years in the two groups (Teo, 2002).

A local study by Auer, et al. (2002) that compared daily versus thrice-weekly treatment in 20 public health centers in Taguig, Metro Manila likewise found no difference in treatment outcomes for daily and intermittent therapy. While the thrice-weekly regimen was popular among patients and health providers, it was also associated with more gastrointestinal side effects and a lower sputum conversion rate.

Several studies also noted similar success rates between intermittent and daily treatment regimen. However, intermittent treatment is still not recommended because of the greater impact of missed doses with intermittent regimens (Balanag, et al., n.d.; Mandal, et al., 2013).

QUESTION 14 How should we monitor treatment response?

- Clinically diagnosed and bacteriologically-confirmed cases treated with first-line drugs: DO at least one sputum smear microscopy at the end of the intensive phase of treatment (end of 2 months for new cases and end of 3 months for retreatment cases)
- New patients - if the specimen obtained at the end of 2 months is smear-positive, repeat DSSM at the end of the third month.

- New and Retreatment patients - if the specimen obtained at the end of third month is still smear-positive, do Xpert®MTB/Rif, sputum culture and DST.
- Clinically diagnosed cases whose sputum smears are negative at end of intensive phase need no further sputum monitoring.
- Sputum specimen at end of 5 and 6 months should be obtained for all new smear positive TB patients. If results are positive, do culture and DST
- Patients found to be harboring a drug-resistant strain at any point during treatment should be referred to a PMDT center.
- All PTB and EPTB patients should also be monitored clinically. Body weight is a useful progress indicator that should be monitored and medication doses adjusted according to weight

(Strong recommendation, low quality evidence)

Rapid diagnostic tests (such as Interferon Gamma Release Assay, Xpert® MTB/Rif, Antiphopholipid Antibody tests) are **NOT** recommended for monitoring treatment response pending further studies. *(Strong recommendation, low quality evidence)*

CXR is NOT a substitute for microbiological monitoring. It may be used in monitoring complications, identifying co-existing conditions. *(Strong recommendation, low quality evidence)*

Summary of evidence

Sputum smear microscopy

Recent available evidence showed that smear status at the end of the intensive phase is a poor predictor of relapse, failure and pretreatment Isoniazid resistance. In a systematic review by Horne et al in 2010, sputum smear and culture at 2 months of treatment had low sensitivity (smear: 24%, 95% CI 12-42; culture: 40%, 95% CI 25-26) and modest specificity (smear: 83%, 95% CI 72-90; culture: 85%, 95% CI 77-91) in predicting relapse. In the same review, sputum smear at 2 months of treatment had a sensitivity of 57% (95% CI 41-73) and specificity of 81% (95% CI 72-87) in predicting treatment failure (Horne, et al., 2010).

Nonetheless, WHO recommends performing smear microscopy at the end of intensive phase because a positive smear should trigger an assessment of the patient. It is also important to check sputum smear status at the end

of intensive phase for clinically diagnosed cases to assess possible disease progression or an error at the time of initial diagnosis (i.e. a true smear-positive patient misdiagnosed as smear negative). Smear conversion at the end of intensive phase is also an indicator of TB program performance (World Health Organization, 2010).

Only one sputum examination is recommended during monitoring of treatment as the yield of positivity in the second on-the spot sputum specimen has no added benefit to the assessment of treatment outcome. In a large retrospective study done in India, the yield of the second on-the-spot sputum is negligible, provided that the first smear is from an overnight specimen (Shivakumar, Prabbhakarareddy, Rajaprasannakumar, Vijayakumaran, & Krishnamurthy, 2006).

TABLE 23 Possible reasons for sputum smear positivity at the end of intensive phase

- The initial phase of therapy was poorly supervised and patient adherence was poor
- Poor quality of anti-TB drugs
- Doses of anti-TB drugs are below the recommended range
- Slow resolution because the patient had extensive cavitation, bilateral lung involvement
- Heavy initial bacillary load or high sputum grade
- Co-morbid conditions (eg HIV, DM) that interfere either with adherence or with response
- The patient may have drug-resistant TB that is not responding to first line treatment
- Non-viable bacteria remain visible by microscopy
- Smoking
- Absence of hemoptysis

Reference: Shivakumar, et al., 2006; Horne, et al., 2010; Lee, et al., 2012; Ozsahin, et al., 2011; Horita, et al., 2012; Kayigamba, et al., 2013; Pefura-Yone, et al., 2014; Stoffel, et al., 2014

Extending intensive phase beyond two months for patients with positive AFB smears did not reduce treatment failure rates. In a prospective, operational study done in Bangladesh in 2012 involving 16,708 patients, extension of the intensive phase reduced relapse but not treatment failure. The relative risk (RR) of relapse of smear positive patients at 2 months vs. smear negative patients was reduced from 2.2 (95% CI 1.6-3.0) to 0.7 (95%CI 0.4-1.2), while the RR for failure remained high, at 7.3 (95% CI 4.7-11.5) with extension and 4.2 (95%CI 2.5-7.2) without extension (Aung, et al., 2012).

Weight gain

Few studies have investigated the utility of weight in monitoring outcomes and predicting treatment response. In a retrospective study done in Peru, body weight gain <5% at end of treatment predicted 2x risk (RR 1.8) of unsuccessful treatment outcome (i.e., early relapse) as this correlates with high bacterial load and lack of sputum conversion. Weight monitoring is particularly useful in localities without microscopy. Suggested weight gain cut-offs as predictors of poor outcome were 2.2% at month 1, 4.5% at month 2 and 7% at end of treatment (Krapp, Veliz, Cornejo, & Seas, 2008).

Rapid diagnostic tests

Rapid diagnostic tests have been evaluated in several studies as to their utility in monitoring treatment response in TB. One systematic review done in 2012 showed that Interferon Gamma Release Assay had low conversion rates. With T-SPOT, TB test conversion was 5-13% in patients treated for active TB (3 out of 6 studies) while QuantiFERON Gold TB showed 50-71% reduction and QuantiFERON Gold TB In tube had 28-39% conversion rate (3 out of 9 studies) (Chippiani, Fossi, Bonsignori, Sollai, Galli, & de Martino, 2012). A prospective cohort done in Canada, showed that the test did not offer much value for treatment monitoring as it has substantial within subject variability, with only 13% of patients (95% CI 8-20%) reverting to negative at end of treatment. Sensitivity was 83%, specificity 17%, PPV 10.4%, and NPV 90% (Denkinger, Pai, Patel, & Menzies, 2013).

The Xpert@ MTB/RIF has poor specificity as an early sputum biomarker for monitoring TB treatment. There is less rapid fall in mycobacterial load with Xpert@ MTB/Rif compared to sputum smear. Moreover, the test does not differentiate between viable, dormant, and nonviable intact MTB. In the prospective cohort study of Friedrich et al, sensitivity was 97%, specificity 48.6%, PPV 73.9% and NPV 91.4% (Friedrich, Rachow, Saathoff, Singh, & Mangu, 2013).

Another potential biomarker for monitoring treatment response is the antiphospholipid antibody (APA) which was investigated in a small prospective cohort study by Goodridge et al. It was postulated that APA IgM may be useful in monitoring response in noncavitary TB. Sensitivity was 83% with IgM to 1 lipid antibody tested and 93.3% with IgM to at least 2 lipid antibodies tested. The IgM level may be reflective of bacterial burden and it was suggested that combination of CXR and antilipid IgM response could be an inexpensive approach to monitor TB treatment. However, larger studies are needed to validate the sensitivity of this test (Goodridge, Cueva, Mahiff, Muzanye, & Johnson, 2012).

Chest Radiography

The WHO does not recommend chest x-ray in monitoring treatment response. CXR had poor correlation with disease activity, symptom duration and culture conversion (Ozsahin, Arslan, Epozturk, El, & Dogan, 2011). However, a small retrospective study done in Malaysia suggested that chest x-ray may correlate with underlying disease as majority of patients have improved chest x-rays after treatment (How, Kuan, Ng,, Razali, & Fauzi, 2014)

QUESTION 15 How should we classify treatment outcomes?

This document adopts treatment outcomes definitions described in the NTP MOP 5th Ed (see **Table 24**), as recommended by the WHO for drug-susceptible TB, which is clearly differentiated from the treatment outcomes for drug-resistant TB (see **Table 27**)

TABLE 24 Treatment Outcomes for Drug Susceptible TB

OUTCOME	DEFINITION
Cured	A patient with bacteriologically-confirmed TB at the beginning of treatment and who is smear- or culture-negative in the last month of treatment and on at least one previous occasion in the continuation phase.
Treatment Completed	A patient who completes treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because tests are not done or because results are unavailable. This group includes: • A bacteriologically-confirmed patient who has completed treatment but without DSSM follow-up in the last month of treatment and on at least one previous occasion. • A clinically diagnosed patient who has completed treatment.
Treatment Failed	A patient whose sputum smear or culture is positive at five (5) months or later during treatment. OR A clinically-diagnosed patient for whom sputum examination cannot be done and who does not show clinical improvement anytime during treatment.
Died	A patient who dies for any reason during the course of treatment.
Lost to Follow-up	A patient whose treatment is interrupted for two (2) consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. This includes cases transferred to another DOTS facility and whose treatment outcome is unknown.

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014

QUESTION 16 When is a patient on TB treatment considered non-infectious?

Patients who are bacteriologically-confirmed and do not have risk factors for drug-resistance are considered non-infectious when they have received at least 14 daily doses of treatment with sputum conversion and clinical improvement. ***(Strong recommendation, high quality evidence)***

Patients who are clinically diagnosed and do not have risk factors for drug-resistance are considered non-infectious when they have received at least 5 daily doses of treatment with clinical improvement. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

Bacteriologically confirmed PTB patients on treatment with the standard WHO Regimen (2HRZE/4HR) are considered non-infectious when they have received treatment for at least 2-5 weeks (Horne, et al., 2010; Telzack, 1997). The California TB Controllers Association conducted a randomized controlled trial and documented that most PTB patients without risk factors for MDR-TB are rendered non-infectious when they have received at least 14 daily doses of treatment for TB, preferably by directly observed therapy (DOT), taken and tolerated and with noted clinical improvement (CDPH/CTCA, 2009). One prospective study demonstrated 93% smear conversion by the 5th week (35 days) and culture conversion by 6.5 weeks (45 days). Delayed non-conversion was associated with cavitary disease, high smear grade, and past history of PTB (Parikh, Nataraj, Kanade, Khatri, & Mehta, 2012). Another prospective study (Fortun et al 2007) noted sputum culture conversion by 34 +/- 26 days and sputum smear conversion by 38 +/- 32 days.

The CTCA also documented that most PTB patients who are negative on DSSM and with no risk factor for MDR-TB are rendered non-infectious when they have received at least 5 daily doses of treatment for TB. PTB patients with low smear grades (1–9 AFB per 100 hpf and 1–9 AFB per 10 hpf in sputum specimens before treatment) should receive treatment in respiratory isolation for 7 days, provided the risk of drug resistance is low (Ritchie, Harrison, Vaughan, Calder, & Morris, 2007).

QUESTION 17 What is paradoxical treatment response and how should it be managed?

Paradoxical Response (PR) is the unusual expansion or new formation of a tuberculous lesion (pulmonary or extra-pulmonary) during TB treatment in the absence of evidence of disease relapse or presence of another diagnosis. In some cases, despite adequate treatment, paradoxical deterioration may occur, most commonly in patients with extra-pulmonary and disseminated TB.

Non-severe form does not require specific treatment and anti-TB treatment should be continued. Severe forms require symptomatic treatment. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

In a study by Jung et al (2011) PR was present in 23% of 139 patients after a mean of 51.1 days following initiation of treatment. Risk factors for PR are younger age, high serum albumin level, low proportion of lymphocyte and high proportion of PMN in pleural fluid. Patients with extrapulmonary and disseminated TB, like miliary TB and TB meningitis are at high risk for PR. The median time to development of a paradoxical response is 60 days, ranging from 14 to 270 days in HIV-negative patients (Cheng, 2006). Severe forms of PR usually require only symptomatic treatment. Corticosteroid treatment appears to be safe (Lee, 2009; Breen & Smith, 2004).

QUESTION 18 What are the common adverse reactions to anti-TB drugs?

Common adverse reactions to anti-TB drugs may be divided into minor and major reactions:

Minor adverse reactions

- Gastrointestinal intolerance
- Mild or localized skin reactions
- Orange/red-colored urine
- Pain at the injection site
- Burning sensation in the feet due to peripheral neuropathy
- Arthralgia due to hyperuricemia
- Flu-like symptoms (fever, muscle pains, inflammation of the respiratory tract)

Major adverse reactions

- Severe skin rash due to hypersensitivity
- Jaundice due to hepatitis
- Impairment of visual acuity and color vision due to optic neuritis
- Hearing impairment, ringing of the ears, dizziness due to damage of the eighth cranial nerve
- Oliguria or albuminuria due to renal disorder
- Psychosis and convulsion
- Thrombocytopenia, anemia, shock

QUESTION 19 How should the most common adverse reactions due to anti-TB drugs (HRZES) be monitored and managed?

General principles in the management of adverse reactions due to anti-TB drugs are as follows:

- Minor adverse reactions can be managed with symptomatic therapy. First-line drugs should not be stopped without adequate justification.
- For major adverse reactions, all drugs must be discontinued. Switching to single drug formulations may be needed. Referral to a specialist is warranted

QUESTION 20 How should drug-induced hepatotoxicity be monitored and managed?

Routine liver function monitoring is **NOT** needed among asymptomatic patients. ***(Strong recommendation, moderate quality evidence)***

Serum ALT (SGPT) should only be requested for: (1) individuals who exhibit symptoms of hepatotoxicity such as jaundice, anorexia, nausea, vomiting, or abdominal pain; (2) monitoring of patients with baseline risk factors for hepatotoxicity or abnormal baseline LFTs (2-4 weeks after the start of anti-TB medications). ***(Strong recommendation, moderate quality evidence)***

Hepatotoxicty is defined as serum ALT level greater than 3x the upper limit of normal in the presence of symptoms, or more than 5x the upper limit of normal in the absence of symptoms.

ALL medications should be stopped immediately and the patient evaluated promptly if serum ALT levels are: (1) more than 5x the upper limit of normal (ULN); or more than 3x the ULN and symptomatic. *(Strong recommendation, moderate quality evidence)*

After normalization of ALT to less than twice the ULN and resolution of clinical symptoms, step-wise reintroduction of potentially hepatotoxic anti-TB drugs may be started with Rifampicin (with or without Ethambutol), followed by INH after 3 to 7 days, subsequently rechecking transaminases.

Pyrazinamide should be permanently discontinued in patients who have experienced prolonged or severe hepatotoxicity. *(Strong recommendation, low quality evidence)*

Summary of Evidence

Monitoring of liver function tests

The 2006 ATS guidelines recommended that liver function testing be done every 2 to 4 weeks for individuals with risk factors for developing hepatotoxicity. For individuals with symptoms i.e., nausea, anorexia and vomiting, ALT measurement is recommended for monitoring liver injury; measurements of AST, bilirubin, and alkaline phosphatase are adjunctive for monitoring chronic liver disease, cholestasis, or severe hepatocellular injury (Saukkonen, Cohn, Jasmer, Schenker, & Jereb, 2006).

On the other hand, WHO, NTP and ISTC do not recommend routine laboratory monitoring among patients receiving anti-TB treatment. Clinical monitoring for adverse reactions of individuals receiving anti-TB therapy is recommended in these three guidelines (World Health Organization, 2010; Philippine Department of Health, 2014; TB CARE I, 2014).

In a prospective cohort of 4,488 TB patients in China, 273 developed hepatotoxicity. Of the 273 patients, 111 were diagnosed through scheduled AST and ALT testing done within two months of starting treatment, while the rest were diagnosed after they developed signs and symptoms of hepatotoxicity. More hospitalizations occurred among patients in whom liver injury was identified through passive detection (scheduled 1.8% vs. passive 11%, p=0.004). More changes in anti-TB regimen were also needed in the passive group (scheduled 35% vs. passive 56%, p=0.0006). No differences between the two groups were seen in terms of incidence of severe liver dysfunction and the duration of treatment (Wu, et al., 2012).

Singanayagam, et al. (2012) also disputed the risk factors-based approach to determining who will develop early drug induced hepatitis. Their study revealed that the risk factors defined by ATS have poor sensitivity (66.7%) and specificity (65.6%) in predicting development of hepatotoxicity.

Management of hepatotoxicity and alternative regimens

The WHO (2010) recommends that alternative regimen of 2HES/10HE is given if rifampicin is implicated. If isoniazid cannot be used, the regimen can be shifted to 6 to 9 months of RZE. If pyrazinamide is discontinued before completion of intensive phase, extend HR for 9 months total duration. If there are no SDFs, replace pyrazinamide with streptomycin during the intensive phase; during continuation phase, restart HR to complete 4 months

The official ATS statements on interventions for hepatotoxicity are:

- The first-line anti-TB drugs, especially RIF, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-TB treatment.
- If serum transaminase concentrations are more than five times the ULN (with or without symptoms) or more than three times the ULN with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly.
- Serologic tests for hepatitis A, B, and C viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol, and other hepatotoxic drugs.
- Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy.
- If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity.

The ATS statement also recommended re-introduction of anti-TB drugs after ALT returns to less than two times the ULN, starting with RIF, with or without EMB. After 3 to 7 days, INH may be reintroduced, subsequently rechecking ALT. If symptoms recur or ALT increases, the last drug added should be stopped. PZA can be reintroduced in some milder cases of hepatotoxicity.

For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with RIF and INH, re-challenge with PZA may be

hazardous. In this circumstance, PZA may be permanently discontinued, with treatment extended to 9 months. The benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from PZA re-challenge (Saukkonen, Cohn, Jasmer, Schenker, & Jereb, 2006)

Surendra, et al. (2010) compared three reintroduction regimens after hepatotoxicity (see **Table 25**). The recurrence rate of hepatotoxicity was not significantly different among the three groups. They concluded that all three potentially hepatotoxic drugs (INH, RIF, and PZA) can be safely reintroduced simultaneously at full dosage from day 1, especially for patients with bilateral extensive pulmonary TB, to halt disease transmission or to treat patients with life-threatening TB.

TABLE 25 Reintroduction regimens after development of hepatotoxicity

	REGIMEN
Arm I	H, R, and Z at maximum dosages from day 1
Arm II	R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15 (ATS)
Arm III	H at dosage of 100mg/day from day 1, maximum dosage from day 4; R at dosage of 150mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500mg/day from day 15, maximum dosage from day 18 (BTS)

Note: Maximum dosage was determined according to body weight, as follows, H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg

While the evidence presented in this study is of moderate quality, further studies may be necessary to support the simultaneous reintroduction of anti-TB medications. Many experts contend that once elevations of transaminases have been observed with the use of PZA, reintroducing it is likely to cause recurrence of hepatotoxicity.

QUESTION 21 How should gastrointestinal reactions be monitored and managed?

Mild gastrointestinal symptoms are frequent in the initial weeks of treatment. Patients must be reassured and anti-TB medications should be continued. ***(Strong recommendation, low quality evidence)***

Antacids may be given to patients who develop persistent gastrointestinal adverse drug reactions. ***(Strong recommendation, moderate quality evidence)***

Food intake affects the bioavailability of several anti-TB medications and is not recommended as first-line management of gastrointestinal reactions. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

A systematic review of 15 studies with 157 patients (Lin, et al. 2011) compared the effects of food and antacids on the bioavailability of first-line anti-TB drugs. The overall results showed that:

- Food significantly reduced the Cmax mean difference (Cmax MD −1.42, 95%CI, -1.56-1.28, P <0.00001) and AUC (Cmax MD −3.33, 95%CI −4.05–2.62, P < 0.00001) of INH but antacids did not.
- Food also significantly reduced the Cmax MD (Cmax MD −2.47, 95%CI −3.30–1.64, P < 0.00001) but not the AUC of Rifampicin. Antacids had no effect on the Cmax MD or AUC of Rifampicin.
- The Cmax and AUC of PZA were unaffected by both food and antacids.
- Both food and antacids reduced the Cmax but not the AUC of Ethambutol.

The authors concluded that, from a pharmacokinetic point of view, the better option for patients with gastrointestinal upsets during chemotherapy would be to add antacids rather than dosing with meals, as the reduction of Cmax and the AUC may result in treatment failure. The authors, however, acknowledged that this metaanalysis had several limitations; primarily not all of the studies included were RCTs. However, the results of most of the studies reviewed were consistent.

QUESTION 22 How should peripheral neuropathy be monitored and managed?

- All individuals receiving INH should be monitored for signs and symptoms of peripheral neuropathy i.e., burning, numbness or tingling sensation in the hands and feet. No laboratory tests are recommended for monitoring of peripheral neuropathy or pyridoxine deficiency.
- Risk factors for INH-associated neuropathy are alcoholism, malnutrition, diabetes, co-infection with HIV, slow acetylator phenotype, pregnancy, breastfeeding and renal failure. ***(Strong recommendation, moderate quality evidence)***
- INH-induced neuropathy can be treated with pyridoxine (Vitamin B6) at 50-100mg daily. ***(Strong recommendation, moderate quality evidence)***

- Co-administering Vitamin B6 at 10mg daily with INH is recommended to prevent INH-induced neuropathy. *(Strong recommendation, low quality evidence)*

Summary of Evidence

INH is the main drug responsible for polyneuropathy in individuals on anti-TB treatment, owing to its various effects on vitamin B6 metabolism that result in a deficiency in biologically active vitamin B6. **Risk factors for INH-associated neuropathy are alcoholism, malnutrition, diabetes, co-infection with HIV, slow acetylator phenotype, pregnancy, breastfeeding and renal failure** (van der Watt 2011, WHO 2010). The prevalence of polyneuropathy is 2-12% among HIV-negative individuals receiving INH at 3-5 mg/kg/day.

A systematic review by Van der Watt, et al. (2011) concluded that guidelines for the prevention and treatment of peripheral neuropathy differ between industrialized and developing countries. Further research is needed to define the optimum dosing of pyridoxine supplementation in populations where there is a significant burden of TB and HIV. Without further evidence, it appears prudent to support the co-administration of pyridoxine with INH in the chemotherapy of TB.

The MOP recommends giving pyridoxine (Vitamin B6) at 50-100mg daily for treatment of the symptoms of neuropathy, and 10mg daily for prevention (Philippine Department of Health, 2014).

QUESTION 23 How should visual impairment be monitored and managed?

- Manifestations of ocular toxicity include bilateral progressive painless blurring of vision, decreased color perception, loss of central vision and optic atrophy.
- Testing of visual acuity and color perception should be done for individuals who develop signs and symptoms of ocular toxicity while on anti-TB treatment. *(Strong recommendation, low quality evidence)*
- Ethambutol should be discontinued if visual impairment develops. Referral to an ophthalmologist is warranted. *(Strong recommendation, low quality evidence)*

Summary of Evidence

(see also related summary of evidence under Question 1)
Impairment of visual acuity and color perception because of optic neuritis may be associated with Ethambutol intake. Routine ophthalmologic monitoring is not recommended by the WHO. Referral to an ophthalmologist is recommended by the NTP for all individuals who experience ophthalmologic adverse reactions while on anti-TB treatment.

In a Taiwan nationwide study of 231 newly diagnosed patients with ETON and 924 controls, the risk factors associated with ETON were older age, hypertension (adjusted OR=1.62, 95% CI 1.16 to 2.26) and renal diseases without end-stage renal disease (ESRD) (adjusted OR=2.11, 95% CI 1.02 to 4.35); with ESRD (adjusted OR=3.73, 95% CI 1.79 to 7.74).[Chen 2012]

In a narrative review by Kwok (2006), the clinical course of ETON can be acute or chronic and typically progressive. Manifestations of ocular toxicity include bilateral progressive painless blurring of vision, decreased color perception, loss of central vision and optic atrophy. Although some abnormalities are detected only by vision tests and patients may remain asymptomatic; they should be advised to stop the drug immediately and seek consult, in case visual symptoms arise. During follow up consultations, patients should be assessed for symptoms of visual disturbance.

QUESTION 24 How should patients presenting with symptoms of ototoxicity be managed?

Patients on streptomycin who develop symptoms of ototoxicity (decreased hearing, vertigo, nausea, vomiting, nystagmus, or ataxia), should be advised to stop streptomycin and referred to an ENT specialist for appropriate management. ***(Strong recommendation, low quality evidence)***

A major adverse effect of aminoglycoside therapy targets the vestibular and auditory organs. Ototoxicity induced by aminoglycosides manifests as irreversible bilateral sensorineural hearing loss beginning at high frequencies (cochleotoxicity) or as a combination of vertigo, nausea, vomiting, nystagmus, and ataxia (vestibulotoxicity). The potential severity of auditory and vestibular deficits depends on the particular aminoglycoside used; streptomycin is more likely to target the vestibular sensory epithelium. The incidence of ototoxicity in TB patients on aminoglycoside treatment depends on the duration and dose. It may be as low as 3.2% during initial phase of therapy but prolonged treatment will eventually lead to hearing loss in all patients (Xie, Talaska, & Schacht, 2011).

Aminoglycoside-induced generation of reactive oxygen species is presumed to be the principal mechanism underlying sensory cell death. In animal models, antioxidants were effective in preventing ototoxicty due to various aminoglycosides. There were no studies found on interventions to prevent ototoxicity in patients receiving streptomycin.

QUESTION 25 How should patients with hyperuricemia be monitored and managed?

Patients on PZA should be monitored for symptoms of gouty arthritis. Serum uric acid should ONLY be requested for patients who develop symptoms of gouty arthritis. ***(Strong recommendation, low quality evidence)***

For patients who develop gouty arthritis, discontinue the PZA, and administer standard treatment for hyperuricemia / gout. PZA may be continued daily or intermittently once symptoms resolved. Referral to a rheumatologist for management may be necessary if symptoms persist. ***(Weak recommendation, low quality evidence)***

Summary of Evidence

A prospective study in Greece showed that 19 of 20 patients taking PZA had hyperuricemia. Among them, only one developed arthritis. Uric acid levels returned to normal after PZA was stopped (Koumbaniou C. , Nicopoulos, Vassiliou, Manda-Stachouli, & Sakellariou, 1998). Thus, in asymptomatic individuals who may be found to have hyperuricemia, anti-TB medications should not be stopped, but the hyperuricemia should be addressed accordingly.

Another prospective study in India followed up 189 patients who had received PZA for a duration of more than one month. Hyperuricemia was seen in 82 patients (43.38%) using doses of 1.5gm/day. Of these cases, 26 presented with arthralgia (31.7%). Patients with hyperuricemia and/or arthralgia were randomly allocated to 3 treatment groups: aspirin group (A), placebo group (P), discontinuation of PZA (D). Serum uric acid levels were rechecked after 15 days. The study showed that uric acid levels returned to normal in all patients in the aspirin group and with discontinuation of PZA. Relief of joint symptoms was seen in all patients in group D and in 94% of patients in group A. The results of the study suggested that aspirin had a beneficial effect on signs and symptoms of arthralgia and withdrawal of PZA was not necessary (Sharma, 1981). Unfortunately, the sample sizes in this study were small.

QUESTION 26 How should cutaneous reactions be monitored and managed?

During patient visits, examine for cutaneous reactions such as pruritus, maculopapular rashes, wheal formations, angioedema, vesicles, erythema, areas of exfoliation, xerosis, and mucous membrane lesions. *(Strong recommendation, moderate quality evidence)*

For minor rashes affecting a limited area or predominantly manifesting as pruritus, antihistamines may be given for symptomatic relief. All drugs may be continued.

If with generalized erythematous rash, especially if associated with fever and/or mucus membrane involvement, stop all drugs immediately. Referral to a specialist may be necessary. *(Strong recommendation, low quality evidence)*

Petechial rash may suggest thrombocytopenia in patients taking RIF. Check platelet count; if low, consider RIF hypersensitivity as the cause. Discontinue RIF and monitor platelet count until it returns to baseline.

When the cutaneous reaction has improved, medications can be restarted at full dose or reintroduced one by one at intervals of 3-7 days. *(Weak recommendation, low quality evidence)*

- Rechallenge with the drug least likely to be responsible for the reaction (INH followed by RIF and then PZA or EMB), with gradually increasing doses over 3 days. If there is no reaction after the 3rd day, add the second drug at a small challenge dose. This procedure is repeated adding in one drug at a time
- If the rash recurs, the last drug added should be stopped. If no rash appears after the first three drugs have been restarted, the fourth drug should not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.
- For HIV infected individuals, RIF may be re-introduced last.

Summary of Evidence

Two local studies have shown that cutaneous reactions are the most common type of adverse reactions to anti-TB drugs. A retrospective cohort of 421 patients showed that 79 individuals (18%, 95% CI 15.2-22.7%) developed pruritus and exanthema (Pamittan, Araune, Lagunzad, & Fernandez, 2003). Another retrospective study showed that 67% of patients had a cutaneous adverse drug reaction to anti-TB treatment, with pruritus as the most common manifestation (89 of 114 patients). Other skin manifestations of adverse reactions to anti-TB drugs included maculopapular rash, wheals, angioedema, vesicles, exfoliation, erythema, and xerosis (Toledo & Aleta, 2013).

A small retrospective study conducted in South Africa that compared reintroduction of anti-TB medications with incremental dosing and full dosing reported no significant difference between the two regimens. This may be due to the small number of patients given full dose reintroduction. In this study, RIF was the offending drug in 13/23 (57%), INH in 5/23 (22%), PZA in 3/23 (13%), and EMB, streptomycin and ofloxacin each in 1/23 (4%) cases. In a high HIV prevalent setting, RIF was more frequently implicated. Older studies though have implicated PZA as the most common offending drug (Lehloenya, Todd, Badri, & Dheda, 2011).

A small local clinical trial (unpublished) investigated the response to rechallenging by shifting to a different brand of anti-TB medication. The success rate was 14/42 (33%). In this study, the most common drugs associated with cutaneous reactions were EMB and PZA (Aleta, 2007).

In general, there is lack of robust data that could suggest relatively safe and effective strategies for the reintroduction of anti-TB drugs, considering the dose of the drug and the schedule of administration (Rezacovic, Pastar, & Kostovic, 2014).

TABLE 26 Likelihood of anti-TB drugs causing a reaction and challenge doses for each drug

DRUG	LIKELIHOOD OF CAUSING A REACTION	CHALLENGE DOSES		
		DAY 1	*DAY 2*	*DAY 3*
Isoniazid	Least likely	50mg	300mg	full dose
Rifampicin	↓	75mg	300mg	full dose
Pyrazinamide		250mg	1000mg	full dose
Ethambutol	Most likely	100mg	500mg	full dose
Streptomycin		125mg	500mg	full dose

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014

QUESTION 27 How should nephrotoxicity be monitored and managed?

- Routine monitoring of renal function is not needed among asymptomatic patients and among those without risk factors for nephrotoxicity.
- Serum BUN and creatinine, and urinalysis should be requested for patients who have signs and symptoms of nephrotoxicity such as oliguria and edema.

- Among individuals who develop nephrotoxicity from anti-TB drugs, Rifampicin and Streptomycin should be discontinued. Referral to a nephrologist is warranted. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

A number of case reports have described nephrotoxicity resulting from anti-TB drugs. INH, RIF, EMB and streptomycin have been reported to result in renal toxicity among individuals taking these drugs for the treatment of TB (Rosati, 2013; Collier, 1976; Park, 2015). Renal toxicity may manifest as edema or oliguria. Laboratory testing among individuals with nephrotoxicity from anti-TB drugs will show rising serum BUN and creatinine levels. Urinalysis may reveal proteinuria, glucosuria and casts. Renal biopsies will help show evidence of kidney damage.

It is not recommended to do routine monitoring of kidney function among individuals receiving anti-TB treatment. Among individuals who develop nephrotoxicity from anti-TB drugs, the drugs that are most likely to be responsible are RIF and streptomycin. These drugs must be promptly discontinued and the patient expeditiously referred to the appropriate specialist (Philippine Department of Health, 2014; WHO 2010).

QUESTION 28 Should immunomodulators be given as an adjunct in the management of TB?

Immunomodulators are **NOT** recommended as adjunctive therapy for TB. The value of these immunomodulatory agents remain unclear and well-conducted RCTs are needed to establish benefit for routine use. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

Standard anti-TB therapy combined with immunotherapeutic modalities could be a promising new approach for the treatment of TB. Potential immunotherapeutic agents that have been tested in clinical trials are the following:

Mycobacterium vaccae

A randomized placebo controlled Phase II-b trial of V5 (Oral TB vaccine) did not demonstrate a difference in mycobacterial clearance between immunotherapy and placebo groups (Butov, Pashkov, Stepaneko,

Choporova, & Butova, 2011). Follow-up Phase II trials on oral Mycobacterium (V7) vaccae showed enhanced mycobacterial clearance after 30 days among the immunotherapy group (RR 3.5 [CI 1.56-7.81]). These preliminary findings need to be explored further in a larger population and followed up for longer periods. (Butov, et al., 2013; Efremenko, et al., 2013)

Interferon gamma

In two RCTs, the use of interferon gamma aerosol did not show a statistically significant difference in sputum conversion and radiographic improvement rates between the treatment and placebo groups (Gao, et al., 2011; Dawson, et al., 2009).

Immunoxel (Dzherelo)

An open label 60-day trial in 75 newly diagnosed TB patients in Ukraine showed that immunoxel was safe and was observed to have enhanced bacillary clearance compared to standard anti-TB treatment alone (Zaietziva, et al., 2009). However, large RCTs with longer follow up are needed to evaluate bacteriologic relapse and clinical improvement.

QUESTION 29 Should vitamin and micronutrient supplementation be routinely given?

Vitamin and micronutrient supplementation should **NOT** be routinely given as adjunctive therapy for TB (except for vitamin B6 or if the patient has pre-existing nutritional deficiency). No significant difference in mortality, treatment completion, bacterial eradication, or mean body mass index was shown in RCTs. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

TB and micronutrient deficiency affect each other. On one hand, TB can cause micronutrient deficiency because of increased nutritional requirements, altered metabolic processes, decreased appetite and reduced food intake (Macallan, 1999). On the other hand, low body mass index and some micronutrient deficiencies can depress cell-mediated immunity, which is the key host defense against TB (Chandra 1996; Zachariah 2002; Cegielski 2004). Among the most important micronutrients affecting TB cited in literature are the following:

Vitamin A - involved in both T- and B-lymphocyte function, macrophage activity and the generation of antibody responses (Semba 1998; Stephenson 2001).

Vitamin D - involved in the function of macrophages, a key component of the immune response to TB (Wintergerst 2007).

Vitamin E - has anti-oxidant properties and may protect against T-lymphocyte failure due to oxidative stress (Wintergerst 2007).

Zinc - necessary for adequate functioning of many aspects of human immunity (Shankar 1998).

Selenium - essential for both cell-mediated and humoral immunity (Arthur 2003).

Arginine - L-arginine is the sole biological precursor of nitric oxide (NO), a molecule with key immunological functions. L-arginine is converted to NO in macrophages by nitric oxide synthase 2 (NOS2). NO is capable of killing TB bacilli in vitro with a molar potency exceeding that of antibiotics (Long 1999).

Vitamin A

A randomized controlled trial of Vitamin A supplementation of 5000 IU (1500 retinol equivalents) daily in the treatment of newly-diagnosed smear positive PTB did not show a statistically significant difference in mortality, treatment completion and bacteriologic persistence (sputum smear/culture positive at 2 months). The mean body mass index (BMI) at 6 months was also not significantly different between those given Vitamin A supplementation vs. placebo (18.1 vs. 18.4), with a mean difference of -0.30 (95% CI -1.15-0.55) (Pakasi 2010).

Vitamin D

Supplementation with oral or parenteral vitamin D did not show a statistically significant difference in mortality, bacteriologic persistence at 6, 8, 12 weeks of treatment nor at end of treatment. (Nursyam 2006, Ralph 2013, Salahuddin 2013, Wejse 2008).

Among newly-diagnosed PTB with uncontrolled DM (HbA1C > 7%) and serum vitamin 25(OH) D levels < 20 ng/ml given oral cholecalciferol (60,000 units/week) + CaCO3 (1g/day) versus placebo, Kota et al (2011) reported no significant difference in the time to sputum conversion (6 weeks in the treatment group vs 8 weeks in the placebo group, p = 0.067).

Martineau et al. (2011) reported that with vitamin D supplementation (four oral doses of Vitamin D 2.5 mg on or before Day 7, Day 14, Day 28 and Day 42 after the start of TB treatment), the median time to sputum culture

conversion did not differ between the intervention group (36 days 95% CI 31·8–40·2) and control group (43.5 days 95% CI 36·5–50·5) (unadjusted p=0·41, log-rank test).

In a randomized, double-blind, placebo-controlled factorial trial of adults with smear-positive PTB in Indonesia comparing oral adjunctive vitamin D (cholecalciferol) 50,000 IU at baseline and at Day 28 versus placebo, no difference in the median time to smear negativity was found in the vitamin D group (5 weeks, range 2-8) and placebo group (4 weeks, range 2-8) (p=0.45) (Ralph 2013).

Three RCTs evaluated the effect of vitamin D supplementation on clinical improvement using the 8-week TB clinical score. A high TB score correlates well with mortality and low TB scores correlate with favorable outcomes, cure, and completed treatment. Wejse et al (2008) reported that changes in TB score and time to clinical improvement (progression to low-severity class) were similar in the treatment and control groups. Using the same TB score system, Salahuddin et al (2013) reported no significant differences observed in TB scores at weeks 4 (p 0.18), 8 (p 0.89) and 12 (p 0.16) between the 2 study arms.

Martineau et al (2011) and Nursyam (2006) reported mean body mass index at 6-8 weeks, which was not significantly different between treatment and control groups. The pooled mean difference in BMI was -0.35 (95% CI -1.05, 0.35).

Zinc

Three RCTs (Lawson 2010, Pakasi 2010, Range 2005) reported no statistically significant difference in mortality and bacteriologic persistence (sputum smear/culture positive) at 8 weeks with zinc supplementation. Pakasi et al. further reported that zinc supplementation did not affect rate of treatment completion at 6 months and the mean BMI at 6 months of those given zinc supplementation vs. placebo (18.5 vs. 18.4).

Vitamin A + Zinc

Four RCTs (Armijjos, 2010; Lawson, 2010; Pakasi, 2010; Visser 2011) assessed the effect of vitamin A + zinc supplementation on mortality. There was no statistically significant difference in mortality rates and bacteriologic persistence (sputum smear/culture positive) at 2 and 6 months between the two groups. Pakasi et al. (2010) also reported no difference in rate of treatment completion at 6 months. Lawson et al. reported that the overall median sputum conversion time was 6.5 weeks. The mean difference in BMI at 6 months between those given vitamin A + zinc supplementation

and placebo were not significantly different -0.24 (95% CI -0.91, 0.43) (Karyadi, 2002; Pakasi, 2010).

Arginine

Arginine supplementation of 1g daily for 4 weeks (Schön, 2003) or L-arginine 6.0g daily for 8 weeks (Ralph, 2013) did not result in any significant difference in mortality compared to placebo. Schön et al. (2011) reported no significant difference in cure rates with or without arginine. These three RCTs likewise detected no significant difference in bacteriologic persistence (sputum smear/culture positive) at 2 months.

In a randomized, double-blind, placebo-controlled factorial trial in adults with smear-positive pulmonary TB in Indonesia comparing L-arginine 6.0 g daily versus placebo, the median time to smear negativity did not differ significantly between the arginine group (4 weeks, range 2-8 weeks) and placebo group (5 weeks, range 2-8 weeks) (p=0.85) (Ralph, 2013).

Arginine + vitamin D

In a randomized, double-blind, placebo-controlled factorial trial in adults with smear-positive pulmonary TB in Timika, Indonesia comparing L-arginine 6.0 g daily + vitamin D (cholecalciferol) 50,000 IU at baseline and at Day 28 versus placebo, Ralph et al. (2013) reported no significant difference in rates of bacteriologic persistence (culture positive) at week 4.

Vitamin E + Selenium

Daily supplements containing vitamin E (140 mg) and selenium (200 ug) given for 4 months did not result in any significant difference in bacteriologic persistence (sputum smear positive) at 60 days compared to placebo (Seyedrezazadeh, 2006).

Multivitamins + Minerals

Three RCTs (Range, 2005; Semba, 2007; Villamor, 2008) reported no difference in mortality with or without multivitamins + minerals supplementation. There was also no difference in bacteriologic persistence (sputum smear positive) at 1 month (Range, 2005; Villamor, 2008) or 2 months (Range, 2005).

In summary, there is insufficient evidence to recommend micronutrient and vitamin supplementation (except vitamin B6) as adjunctive treatment for TB. No statistically significant differences in mortality, treatment completion, bacterial eradication, nor mean body mass index were detected.

Research Recommendations:

- Systematic review or cohort analysis to better estimate the incidence or prevalence of adverse effects and risk factors associated with development of adverse effects - ethambutol related toxicity, drug-induced hepatitis, acute kidney injury, PZA-induced arthritis/arthralgia, hepatotoxicity and nephrotoxicity in TB-HIV, cutaneous reactions
- Optimal testing strategy for biochemical monitoring of adverse reactions – hepatotoxicity, nephrotoxicity, hyperuricemia
- Systematic review or Cohort analysis of EPTB, various sites – prevalence, outcomes, monitoring strategies
- Optimal and cost-effective monitoring strategy for treatment response and predicting development of resistance
- Prediction of treatment outcomes of patients who remain smear positive at 2 months, 3 months, and so forth in a high burden country
- How well can sputum monitoring predict MDRTB?
- Utility of CXR in predicting outcomes among previously-treated patients
- Cost-effective strategies to monitor and improve adherence to treatment
- Clinical trials on micronutrient supplementation to determine optimal dosages, using weight gain and sputum conversion as surrogate markers of effectiveness
- What level of INH resistance will warrant the addition of EMB to the continuation phase of the standard treatment regimen for PTB?
- Can kinetics of serum ALT concentration distinguish between impending drug-induced liver injury and inconsequential hepatic adaptation? Should monitoring for hepatotoxicity be risk factor-based or routine?
- Studies regarding specific visual test and testing intervals appropriate for monitoring asymptomatic patients during treatment
- Local studies on the impact of anti-TB treatment in terms of outcome and liver function in patients with Hepatitis B or C infection.
- Monitoring and management strategies for hepatotoxicity and hyperuricemia
- Systematic review or cohort analysis to describe the clinical spectrum and outcome of ethambutol-related toxicity
- Systematic review or cohort analysis to describe the clinical spectrum, outcome and management strategies for cutaneous hypersensitivity reactions to anti-TB drugs
- Prevalence of diabetes mellitus among patients with pulmonary and extra-pulmonary tuberculosis

Chapter 4

Diagnosis and Treatment of Drug-Resistant Tuberculosis in Adult Filipinos

Chapter 4

Diagnosis and Treatment of Drug-Resistant Tuberculosis in Adult Filipinos

Definition of Terms

Drug-resistant tuberculosis (DR-TB) – resistance of the TB bacilli to one or more anti-TB drugs based on drug susceptibility test (DST) results.

- **Mono-resistant TB -** resistance to one first-line anti-TB drug only
- **Polydrug-resistant TB** - resistance to more than one first-line anti-TB drug, other than both Isoniazid and Rifampicin
- **Multidrug-resistant TB (MDR-TB)** - resistance to at least both Isoniazid and Rifampicin
- **Extensively drug-resistant TB (XDR-TB)** - multidrug-resistant TB plus resistance to any fluoroquinolone and at least one of three second-line injectable drugs (Capreomycin, Kanamycin and Amikacin)
- **Rifampicin-resistant TB (RR-TB)** - resistance to Rifampicin detected using Xpert® MTB/Rif test or conventional DST, with or without resistance to other anti-TB drugs. It includes any resistance to Rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance

There are two principal pathways leading to the development of active drug-resistant - primary or acquired (secondary) resistance, both of which are interconnected and have many contributing factors (**Figure 3**):

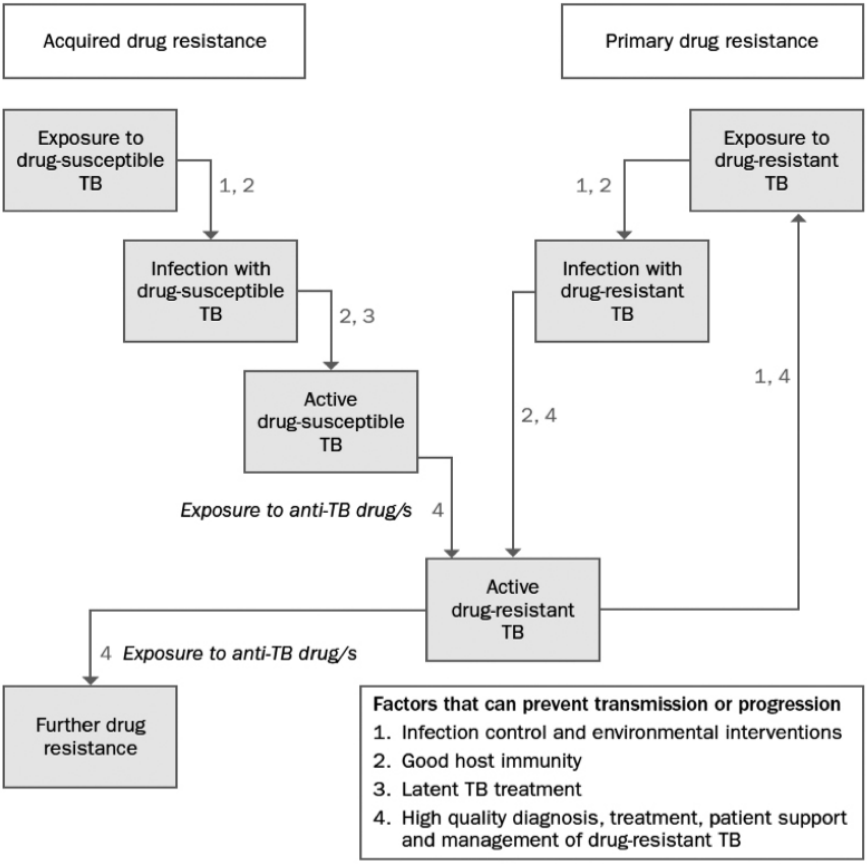
Primary drug resistance:

- Results when a person has been infected with a drug-resistant TB strain. Transmission of drug-resistant TB occurs in the same way as transmission of drug-susceptible TB. High prevalence of drug-resistant TB in the community increases the risk of drug-resistant TB exposure in the community. Undiagnosed, untreated or poorly treated drug-resistant TB contributes to sustained high drug-resistant TB prevalence as well as high proportions of infectious drug-resistant TB cases in the community.

Acquired (secondary) drug resistance:

- Results from inadequate, incomplete or poor treatment quality that allows the selection of mutant resistant strains. If drug-susceptible TB is treated with a regimen exclusively based on a single effective TB medicine, there is a risk that bacteria with drug-resistant mutations will be selected and multiply further during the course of treatment, eventually becoming the dominant strain. If a person infected with a strain initially resistant to a specific anti-TB drug is treated with the same plus a new additional anti-TB drug, there is a risk of developing resistance to the additional anti-TB drug. Step-wise additions of anti-TB drugs may eventually lead to more severe patterns of drug resistance and eventually to untreatable forms of TB.

FIGURE 3 Pathways to Development of Drug-Resistant Tuberculosis



Reference: Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant TB
Note: Arrows represent progression along the 2 pathways; numbers represent factors contributing to the prevention of progression

Outline of Issues on Drug-Resistant Tuberculosis:

1. When is Drug-Resistant TB (DR-TB) suspected in a patient?
2. How should DR-TB be diagnosed?
3. How should DR-TB be managed?
4. What is the role of surgery in the management of DR-TB?

QUESTION 1 When is drug-resistant TB (DR-TB) suspected in a patient?

Presumptive drug-resistant tuberculosis (DR-TB) refers to persons at high risk in developing DR-TB. They include any of the following new and re-treatment cases:

1. All retreatment cases – relapse, treatment failure, treatment after lost to follow-up (TALF), previous treatment outcome unknown (PTOU)
2. *New cases who are:*
   a **Non-converter of Category I** - new TB cases who remain sputum smear-positive at the end of third month of treatment;
   b **Contacts of confirmed DR-TB cases** - persons who shared enclosed space, such as the household, a social gathering place, workplace or facility, for extended periods within the day with the confirmed index DR-TB case during the three (3) months before initiation of the current DR-TB treatment;
   c **People living with HIV (PLHIV)** with signs and symptoms of TB - persons living with HIV with radiologic findings suggestive of TB and/or any of the four symptoms: cough, fever, weight loss, night sweats

(Strong recommendation, high quality evidence)

Assessment of likelihood of drug resistance based on history of prior treatment and exposure to a DR-TB case should be undertaken for all patients. *(Strong recommendation, high quality evidence)*

Summary of Evidence and Rationale

In the Philippines, the prevalence of MDR-TB among new and previously treated patients is 2% and 21% respectively. Hence one of the best infection control measures for TB is early diagnosis and early appropriate treatment. Treatment failure is high when Category II regimen is given empirically among patients with high probability of MDR-TB. In an observational study by Gler, et. al. among 4,705 previously treated patients referred from DOTS and non-DOTS providers from 2003 to 2008, MDR-TB occurred among treatment failure (97%), non-converters (91%), relapse (78%) and TALF (57%) on Category II regimen; and among treatment failures (83%), relapse

(33%) and TALF (22%) on Category I regimen. In another observational study by Sablan, et. al. at the Lung Center of the Philippines (LCP) DOTS Center from December 2006 to 2009, MDR-TB developed in 35.5% among 363 patients who received Category II treatment. Of these, the highest was among Category 1 treatment failures (45%), followed by relapse (33.3%) and TALF (27.5%).

QUESTION 2 How is DR-TB diagnosed?

- Conventional (phenotypic) Drug Susceptibility Testing (DST) on culture isolates.
  - The Lowenstein Jensen method remains the gold standard for the diagnosis of DR-TB, *preferably* in quality-assured DST centers identified by the National TB Program.
- Genotypic DST, endorsed by WHO, namely:
  - Xpert® MTB/Rif
  - Line Probe Assay (LPA)

  (Strong recommendation, high quality evidence)
- Xpert® MTB/Rif should be used as the initial diagnostic test in presumptive DR-TB. ***(Strong recommendation, high quality evidence)***

All presumptive DR-TB should be referred to the nearest DOTS facility with Programmatic Management of Drug-resistant Tuberculosis (PMDT) services or to an Xpert® MTB/Rif facility for screening and testing before initiating any form of TB treatment. (Strong recommendation, high quality evidence

Summary of Evidence

Conventional (phenotypic) drug susceptibility testing (DST) on culture isolates remains the reference standard for the diagnosis of drug resistant tuberculosis. However, its long turnaround time, cumbersome procedures and complex quality assurance requirements limits availability to the general population. In contrast, genotypic (molecular) methods offer relatively faster diagnosis, standardized testing and fewer requirements for laboratory

biosafety. Line probe assay has been endorsed by WHO in 2008 for the rapid screening for MDR-TB with the potential to substantially reduce the turnaround time of DST results. However, it requires training, supervision and adherence to stringent laboratory protocols to ensure high quality results during routine implementation. In the Philippines, there are 23 TB culture centers recognized under the NTP laboratory network as of December 2015 (refer to **Appendix B**).

In 2013, the WHO updated their recommendations for the use of Xpert® MTB/Rif as an initial test for presumptive DR-TB in adults because of its pooled sensitivity of 95% and specificity of 99% for rifampicin resistance determined by univariate analyses using 24 studies from 33 centers, involving 2,969 participants (including 555 rifampicin-resistant specimens).

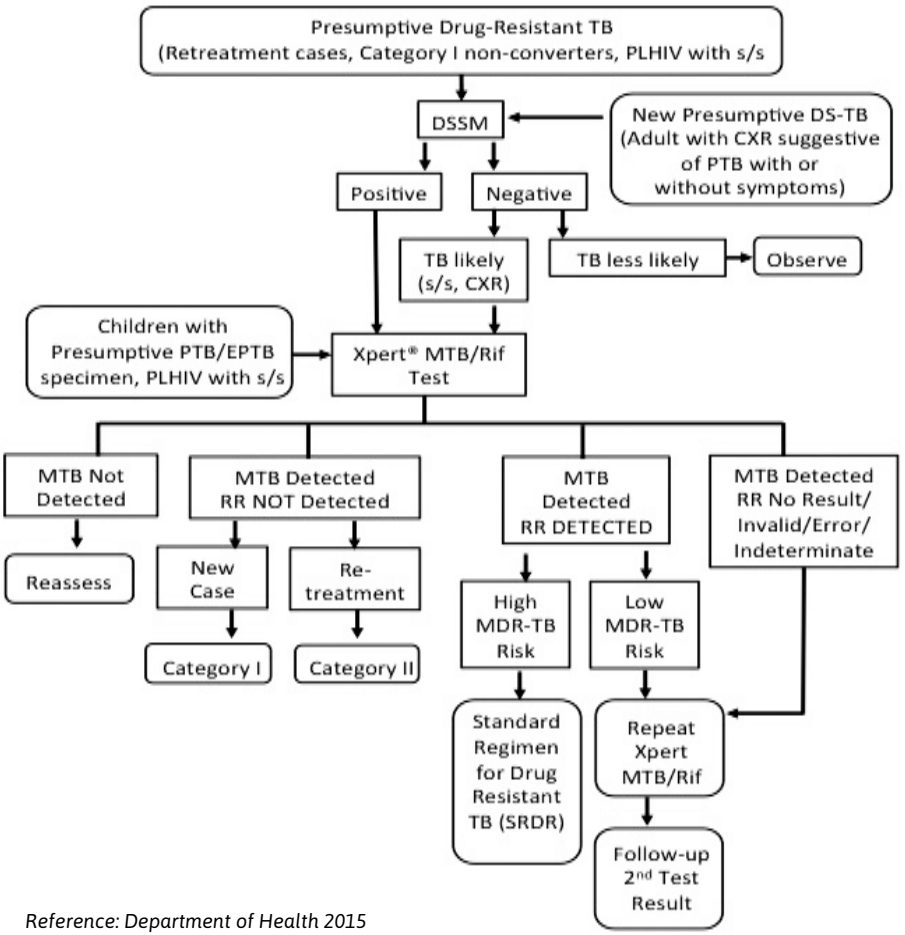
In patients with suspected MDR-TB, Xpert® MTB/Rif detected resistance to rifampicin in less than one day, while it generally took an average of 75 days for phenotypic DST results. While rifampicin resistance is a possible indicator of MDR-TB, Xpert® MTB/Rif does not eliminate the need for phenotypic DST in MDR-TB since specific drugs still need to be tested, nor does it completely eliminate conventional microscopy as this is still needed to monitor response to therapy in smear positive patient (WHO 2011).

In a local study by Gonong et al, among 446 patients seen at the LCP DOTS Center, sensitivity and specificity were 94.94% and 100% when compared to phenotypic DST. In the local study, there were 21 cases identified by Xpert® MTB/Rif that were not detected by the conventional MTB culture, and there were 6 identified by MTB culture not detected by theXpert® MTB/Rif test. The specificity of DST is even higher for Xpert/MTB/Rif compared to conventional DST which missed to detect 21 cases.

Figure 3. shows the diagnostic algorithm currently being followed by the NTP in the context of ongoing scale up of Xpert® MTB/Rif services in the public health care system.

Although DSSM is readily available at point of care and remains as the initial work-up for presumptive DR-TB to assess baseline infectiousness, there are ongoing technical discussions strongly considering simultaneous DSSM and Xpert® MTB/Rif for rapid confirmation of drug-resistant TB among retreatment cases.

FIGURE 4 NTP Diagnostic Algorithm Using Xpert® MTB/Rif



Reference: Department of Health 2015

QUESTION 3 How should DR-TB be managed?

All DR-TB patients should be managed under programmatic setting. Management of DR-TB involves the use of second line drugs that are more expensive, less effective and more toxic for at least 18 months. Management outside the proper framework will only lead to further drug resistance. ***(Strong recommendation, high quality evidence)***

Immediate referral to the nearest PMDT Treatment Center or Satellite Treatment Center is mandatory. ***(Strong recommendation, high quality evidence)***

The Programmatic Management of Drug-Resistant Tuberculosis (PMDT)

PMDT is a set of strategies and activities under the National TB Control Program using DOTS framework to effectively address the problem on DR-TB. It is managed by the Department of Health in coordination with local and international partners.

The following are the basic elements of a PMDT program:

1. Sustained political commitment to treat DR-TB
2. Availability of quality-assured laboratory services for DSSM, TB culture, DST and Xpert® MTB/Rif
3. Standardized and individualized treatment strategies that utilize second line drugs under DOTS
4. Uninterrupted supply of high-quality second-line anti-TB drugs
5. Institution of parameters to promote patient adherence to treatment
6. An information system for proper data management, monitoring of performance and evaluation of the intervention

The PMDT uses two (2) strategies for treatment:

- Standardized Regimen Drug Resistant (SRDR) – for patients with confirmed RR-TB using Xpert® MTB/Rif test
- Individualized treatment approach – for patients with available comprehensive drug susceptibility testing results that warrant modification of the standardized regimen

Summary of Evidence

DR-TB patients should be referred to specialized centers trained on DR-TB management following International Standards of TB Care (ISTC). In the Philippines, this is undertaken by the PMDT of the NTP. WHO recommends the SRDR regimen based on an observational study by Gosolov among 2,125 confirmed MDR-TB cases from 2007 to 2009 who were given SRDR. Individualized regimens needed to be given based on specific DST results.

The injudicious use of flouroquinolones outside the programmatic setting has exerted a selection pressure for the emergence of resistant *M tuberculosis.* Prudent use of drugs should be strongly advocated, with flouroquinolones reserved for MDR-TB and rifampicin-resistant TB given under programmatic conditions.

The definitions of treatment outcomes for MDR-TB are summarized in **Table 27**.

TABLE 27 Treatment Outcomes for RR-TB, MDR-TB and XDR-TB Patients

OUTCOME	DEFINITION
Cured	A patient with bacteriologically-confirmed RR-TB, MDR-TB, XDR-TB who has completed at least 18 months of treatment without evidence of failure AND three or more consecutive cultures taken 30 days apart are negative after the intensive phase
Treatment Completed	A patient who completes at least 18 months of treatment without evidence of failure BUT no record that 3 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment Failed	Treatment terminated or need for permanent regimen change of at least 2 anti-TB drugs because of: • Lack of conversion** by the end of the intensive phase*, or • Bacteriological reversion** in the continuation phase after conversion** to negative, or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or • Adverse drug reactions (ADRs)
Died	A patient who dies for any reason during the course of treatment
Lost to Follow-up	A patient whose treatment is interrupted for 2 consecutive months or more
Not Evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "Transferred out" to another treatment unit and whose treatment outcome is unknown)

Reference: NTP Revised Manual of Procedures 5th Ed, Department of Health, 2014
**For Treatment Failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the intensive phase applied by the program. The intensive phase is a minimum of 6 months of second line anti-TB treatment. If the patient does not convert, a cut-off of 8 months of treatment is applied to determine the criteria for treatment failed.*
***The terms "conversion" and "reversion" of culture as used here are defined as follows: conversion (to negative): culture is considered to have converted to negative when 2 consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, 2 consecutive cultures, taken 30 days apart, are found to be positive. For the purpose or defining Treatment failed, reversion is considered only when it occurs in the continuation phase.*

QUESTION 4 What is the role of surgery in the management of DR-TB?

Surgery is an option in the treatment of TB patients with DR-TB in localized cavitary forms with continuous *M. tuberculosis* excretion, confirmed by bacterial examination and DST, after four to six months of supervised anti-TB chemotherapy. ***(Strong recommendation, moderate quality evidence)***

Surgery should be considered as integral component of MDR-TB treatment programs, even in resource-limited countries, as long as adequate surgical expertise and facilities are present. ***(Strong recommendation, moderate quality evidence)***

Multidisciplinary approach involving surgeons, anesthesiologists and specialists should be taken when a patient is being considered for surgery. ***(Strong recommendation, moderate quality evidence)***

Summary of Evidence

Based on a systemic review of 52 observational studies on surgery in DR-TB, it was expert consensus that lung resection can and should be considered when the following criteria have been met: (1) Adequate anti-TB treatment has failed to cure the patient; (2) The disease is sufficiently localized to allow anatomical lung resection; and (3) The patient has sufficient pulmonary reserve and acceptable surgical risk with which to tolerate the resection. In cases where contraindications exist for lung resection because of extensive lung involvement, collapsosurgical methods can be considered.

A recent systematic review and meta-analysis of 24 comparison studies of MDR- and XDR-TB involving 5,000 patients, showed a significant association between surgical intervention and successful outcome when compared to non-surgical treatment alone (OR 2.24, 95% CI: 1.68-2.97) (77). Sub-group analyses of studies involving XDR-TB patients revealed an even more pronounced treatment effect (OR 4.55, 95% CI: 1.32-15.7).

At the Lung Center of the Philippines, 9 patients underwent pulmonary surgery for DR-TB between July 2006 to September 2010, with mean age of 34 years, equal predominance of male and female, 83.3% had hemoptysis prior to surgery and 33% had positive culture status at the time of surgery. Of which, 6 underwent pneumonectomy with 22% morbidity (1 empyema, 1 broncho-pleural fistula); no mortality. Among those who underwent lung resection, 5 (55%) were declared cured at 8 months post-surgery, 2 (22%) failed treatment and 2 (22%) defaulted post-surgery chemotherapy.

Factors that favored success of surgery were strict infection control throughout all stages of treatment; good cooperation among chest physicians, thoracic surgeons, anesthesiologists and staff; availability of surgical expertise; patient completion of required pre- and postoperative drug regimens; observance of pre- and postoperative precautions; and careful patient follow-up

Research Recommendations:

- More research for novel short treatment regimens for DR-TB
- Identification of the most effective chemo-preventive therapy for contacts of MDR-TB cases
- Long-term surveillance of MDR-TB patients who were declared cured/ treatment success
- Determination of the outcome of drug-resistant patients who take their medicines intermittently
- Determine optimal duration of pre- and postoperative anti-TB chemotherapy
- More studies on local experience on surgery in TB and impact on cost reduction in MDR treatment

Chapter 5

TB Among HIV and Other High Risk Clinical Groups

Chapter 5
TB Among HIV and Other High Risk Clinical Groups

This new chapter highlights the importance of systematically identifying and understanding high risk clinical groups for better appreciation of how and why standard diagnostic and treatment approaches may be modified because of pre-existing medical conditions.

WHO defines a **risk group** as any group of people in which the prevalence or incidence of TB is significantly higher than the general population (WHO 2013 Systematic screening for active tuberculosis). In the latest NTP MOP, **intensified case finding** is recommended among the following individuals belonging to special or defined high risk populations, including those who consult or find themselves at the facility for other purposes:

- **Close contact** – a person who shared an enclosed space, such as household, social gathering place, workplace or facility, for extended periods within the day with the index case during the 3 months before commencement of the current treatment episode
- **High-risk clinical groups** - individuals with clinical conditions that put them at risk of contracting TB disease, particularly those with immunocompromised state (e.g. HIV/AIDS, diabetes, end-stage renal disease, cancer, connective tissue diseases, autoimmune diseases, silicosis, patients who underwent gastrectomy, solid organ transplantation, prolonged systemic steroids)
- **High-risk population** - persons with known high incidence of TB, particularly those in closed environments or living in congregate settings that promote easy disease transmission (e.g. inmates, elderly, indigenous people and urban/rural poor)

This chapter covers recommendations for the diagnosis, treatment and monitoring of TB among the following *selected* adult groups with pre-existing specific conditions that may directly or indirectly affect the clinical course, severity and even outcome of TB and vice-versa:

- persons living with HIV
- diabetes mellitus
- solid organ tumors
- pregnant and lactating women
- chronic renal disease
- chronic hepatic dysfunction
- rheumatologic patients on biologicals

Evidence for screening for the presence of latent TB infection or active disease among these patients; modifications in the dose, timing and composition of anti-TB medication regimen for either treatment or chemoprophylaxis; and appropriate monitoring of treatment response, cognizant of potential drug-drug interactions and possible adverse reactions, are reviewed.

This will further guide clinicians on their crucial role in identifying and monitoring these patients with these conditions in order to provide thorough and careful clinical management to ensure that optimal care is provided for both diseases.

Outline of Issues on TB Among HIV and Other High Risk Clinical Groups:

TB AMONG PERSONS LIVING WITH HIV (PLHIV):

1. Should routine screening for active TB be done among PLHIV?
2. How does one reliably diagnose PTB among PLHIV patients?
3. What is the recommended treatment regimen for TB among PLHIV?
4. When is the optimal time to start antiretroviral therapy in PLHIV with TB?
5. What is the management of PLHIV with presumed drug-resistant tuberculosis?

TB AND DIABETES MELLITUS:

6. Should routine TB screening be done among patients with diabetes?
7. What is the recommended treatment regimen for TB among patients with diabetes?
8. What is the recommended diagnostic work-up and most suitable treatment regimen for TB among solid organ transplant (SOT) and hematopoietic stem cell transplantation (HSCT) recipients?

TB AND CHRONIC KIDNEY DISEASES (CKD):

9. What is the appropriate regimen for TB among CKD patients?
10. When is the best time to administer anti-TB medications among CKD patients?"

TB AND CHRONIC LIVER DISEASES (CLD):

11. What is the appropriate treatment regimen for TB among CLD patients?

TB AND PREGNANCY:

12. What is the appropriate treatment regimen for TB among pregnant and lactating women?
13. Is chest radiography considered safe during pregnancy?

LATENT TB INFECTION (LTBI) AMONG HIGH RISK CLINICAL GROUPS:

14. Who should be screened and treated for LTBI among high-risk clinical groups?
15. What is the recommended screening test for LTBI among high risk clinical groups?
16. What is the recommended treatment regimen for LTBI?
17. How often should LTBI screening be for patients on biologic therapy?

QUESTION 1 Should routine screening for active TB be done among PLHIV?

All newly diagnosed PLHIV should be screened for active TB. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

Tuberculosis is strongly associated with HIV infection and is estimated to cause more than a quarter of deaths among people living with HIV (WHO, 2013). Infection with HIV increases the likelihood of progression from infection with M. tuberculosis to active tuberculosis. The risk of developing tuberculosis in people living with HIV is between 20 and 37 times greater than among those who do not have HIV infection (Getahun et al, 2010).

As of 2014, the Philippines has an HIV prevalence of 64/100,000 population while TB is 438/100,000 population. Based on the data reported by the 19 DOH-designated treatment hubs, out of the 5,995 HIV patients screened for TB, 999 (17%) were diagnosed with active tuberculosis (Global Fund, 2014).

Early identification of symptoms consistent with tuberculosis followed by prompt diagnostic evaluation and appropriate treatment of the disease among people living with HIV increases survival and improves quality of life. Thus, screening for symptoms among persons with HIV infection is crucial for identifying both tuberculosis cases and persons who should receive isoniazid preventive therapy. A comprehensive systematic review and meta-analysis found that the absence of four symptoms: current cough, night sweats, fever, or weight loss identified a large subset of PLHIV who are very unlikely to have active tuberculosis. All persons with HIV infection should be regularly screened for tuberculosis using these four symptoms at every visit to a health facility or contact with a health care worker (ISTC, 2014).

QUESTION 2 How does one reliably diagnose PTB in PLHIV patients?

- Diagnosis of PTB in PLHIV is based on symptomatic screening (i.e. cough of any duration, fever, night sweats and weight loss), chest radiograph, and sputum examination for Xpert® MTB/Rif.
- Xpert® MTB/Rif should be used as the initial diagnostic test in adults with presumed HIV-associated TB. ***(Strong recommendation, high quality evidence)***
- All presumptive HIV-TB should be referred to the nearest DOTS facility with Programmatic Management of Drug-resistant Tuberculosis (PMDT) services or to an Xpert® MTB/Rif facility for screening and testing before initiating any form of TB treatment. ***(Strong recommendation, high quality evidence)***
- If Xpert® MTB/Rif is negative, diagnosis for PTB will be based on a high index of clinical suspicion. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

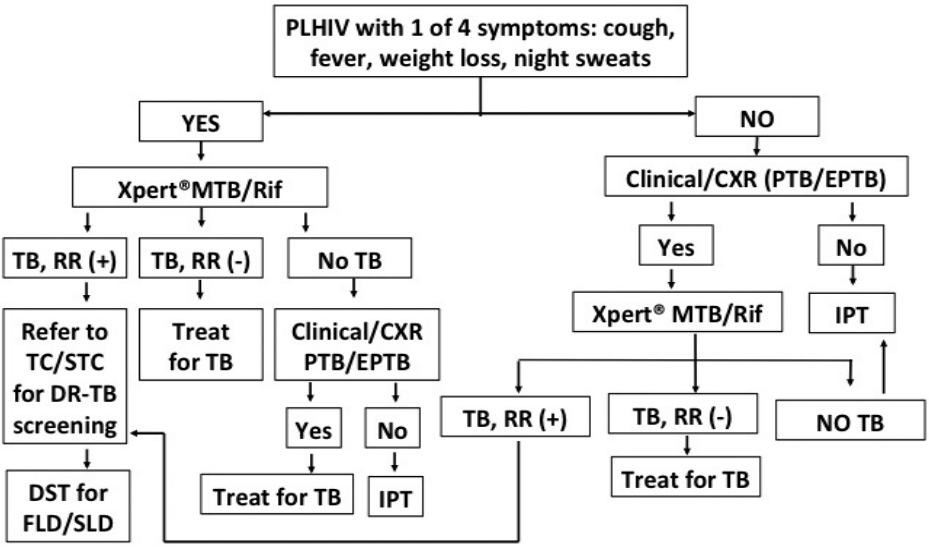
According to WHO, adults and adolescents living with HIV should be screened for TB with a clinical algorithm; those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases (WHO, 2012). The diagnostic evaluation for tuberculosis should be done in accordance with the national guidelines specific for PLHIV as shown in **Figure 5.**

Even in the absence of pulmonary symptoms or signs, the initial evaluation of a patient presumed to have HIV-related TB should always include a chest

radiograph since pulmonary involvement is common whatever the CD4 cell count (IDSA, 2015). The radiographic representation of chest x-ray is also dependent on the stage of HIV disease. However, chest radiography is an imperfect screen for sputum culture-positive TB, particularly in patients with advanced immunodeficiency. Upper lobe pulmonary involvement in HIV-seropositive patients was less frequent than HIV-seronegative persons due to their immunodeficiency (Ahmadi et al, 2012).

HIV patients have higher rates of sputum smear-negative disease. Smear-negative, culture-positive TB is more common with advanced immunosuppression. Rates of AFB smear-negative disease is as high as 66% (Hassim et al, 2010). In general, the rate of smear positivity correlates with the extent of radiographic disease. However, it is not true when it comes to PLHIV. These co-infected populations are less likely to have positive sputum microscopy, while not significantly altering the sensitivity and specificity of Xpert® MTB/Rif (WHO, 2011; WHO 2013).

FIGURE 5 National Guidelines on the Collaborative Approach of TB and HIV Prevention and Control



RR-rifampicin resistant, TC-treatment center, STC-satellite treatment center, DR-drug resistant, DST-drug susceptibility testing, FLD-first line drugs, SLD-second line drugs, IPT-INH prophylactic treatment

Reference: Department of Health 2015

In 2013, the WHO updated their recommendations for the use of Xpert® MTB/Rif as an initial diagnostic test for TB in adults with HIV. It improves the quality of rapid TB diagnosis among PLHIV by providing bacteriologically confirmed diagnosis in 36 – 75% of pulmonary TB patients who are smear-negative. Xpert® MTB/Rif is sensitive and specific for the detection of pulmonary TB when used as the initial diagnostic test in adults presumed to have HIV-associated TB. It detects 79% of the pulmonary TB cases among PLHIV, which is far superior to smear microscopy (WHO, 2014).

QUESTION 3 What is the recommended treatment regimen for PTB among PLHIV?

The recommended treatment regimen for PTB among PLHIV is the same as the general population. (*See Chapter 3: Treatment Recommendations).*

Co-trimoxazole prophylaxis at a total daily dose of 800 mg sulfamethoxazole + 160 mg trimethoprim should also be given to prevent *Pneumocystis jirovecii* pneumonia among PLHIV regardless of CD4 count. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

Treatment of TB in PLHIV should include an initial four-drug combination of isoniazid, rifampicin, pyrazinamide, and ethambutol; similar to the general population who are HIV-negative. Patients with HIV-related tuberculosis should be treated with a regimen including a rifamycin for the full course of tuberculosis treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifampicins. Regimens without rifampin or in which rifampin was only used for the first two months resulted to higher rates of treatment failure and relapse (Jindani, 2004). Use of Efavirenz 600mg with 2 NRTIs, along with rifampin-based tuberculosis treatment is the preferred strategy for co-treatment of HIV and tuberculosis.

Co-trimoxazole is given as prophylaxis against *Pneumocystis jirovecii* pneumonia (formerly known as Pneumocystis carinii pneumonia) and toxoplasmosis. Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts[15] and clinical stage of the HIV disease [A-I]. The recommended dose of co-trimoxazole for PLHIV is 960 mg daily (800 mg sulfamethoxazole + 160 mg trimethoprim, either as a 960-mg double-strength tablet or two 480-mg single-strength tablets).

Health authorities suggested a cut-off of CD4 count of above 200 and clinically stable without WHO Clinical Stage 2, 3 or 4 events for one year while on ART with evidence of immune recovery and/or viral suppression to stop prophylaxis. Some studies showed that continuing co-trimoxazole above CD4 count of 350 reduced hospitalisation, malaria, pneumonia and diarrhea in settings where malaria and/or serious bacterial infections were highly prevalent. However, it did not affect mortality and new stage 3 or 4 events (Campbell, 2012; Polyak, 2014). Other studies showed that continuing co-trimoxazole did not affect rates of *Pneumocystis jirovecii* pneumonia and death among people receiving ART who achieved CD4 cell counts above 100 cells/mm^3 (Chaiwarith, 2013; Mocroft, 2010).

QUESTION 4 When is the optimal time to start antiretroviral therapy in PLHIV with TB?

Antiretroviral therapy should be initiated **after the second week** of TB treatment regardless of CD4 count.

For patients with TB meningitis, antiretroviral therapy should be initiated **after the intensive phase** of TB treatment.

Efavirenz is the preferred NNRTI for HIV patients on TB treatment. Avoid the use of nevirapine because of drug-drug interactions.

(Strong recommendation, high quality evidence)

Summary of Evidence

Antiretroviral Therapy (ART) should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in PLHIV. ART is life-saving among PLHIV with tuberculosis. PLHIV should be referred to DOH-designated treatment hubs and satellite treatment hubs for management and provision of ART.

In one randomized controlled clinical trial among HIV-infected adults in South Africa, initiating ART during anti-TB therapy reduced all-cause mortality by 56% and was beneficial regardless of CD4 count (Abdool, 2010). Other studies also supported that earlier initiation of ART significantly reduced mortality in persons with (non-meningitis) HIV-TB and CD4 cell count below 50 (Blanc, 2011; Havlir, 2011; Torok, 2011).

The 2012 WHO policy on collaborative TB-HIV activities states that TB treatment should be started first, followed by ART, as soon as possible

within the first eight weeks. Important issues associated with concomitant therapy include overlapping toxicity profiles for the drugs used, drug-drug interactions (especially with rifampicin and protease inhibitors), potential problems with adherence to multiple medications, and immune reconstitution inflammatory reactions (ATS, 2003; Harries, 2009).

There are few drug interactions with tuberculosis drugs and the nucleoside reverse transcriptase inhibitors (NRTIs) and no specific changes are recommended. However, rifampicin reduces drug levels of both non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors through induction of the cytochrome P450 liver enzyme system. Therefore, Efavirenz should be used as the preferred NNRTI since its interactions with anti-TB drugs are minimal. In several studies, ART with standard-dose efavirenz and two nucleosides was well tolerated and highly efficacious in achieving viral load suppression (WHO, 2009).

Patients should also be closely monitored to identify adverse drug reactions and to observe for immune reconstitution inflammatory syndrome (IRIS). Although some studies reported increased risk of IRIS when ART is started earlier, the mortality benefit of earlier ART initiation outweighs the IRIS risk, which usually is self-limited (Laureillard, 2013).

QUESTION 5 What is the management of PLHIV with presumed drug-resistant tuberculosis?

PLHIV with drug-resistant TB should be referred to PMDT treatment facilities immediately. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, prescription of an incorrect or inadequate regimen, sub-therapeutic drug levels due to malabsorption or drug interactions, superinfection with drug-resistant *M. tuberculosis*, and acquired drug resistance. Treatment of MDR-TB should only be undertaken in specialized centers who are specifically trained and experienced in the holistic management of drug-resistant TB. Any form of treatment outside programmatic setting will only lead to further emergence of resistance.

QUESTION 6 Should routine screening for TB be done among patients with diabetes?

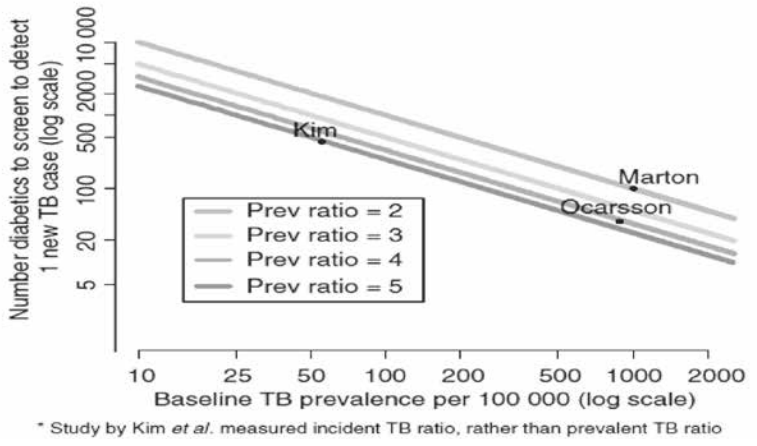
Screening for TB in people with DM may be considered due to the high TB prevalence in the Philippines. *(Weak recommendation, low to moderate quality evidence)*

Summary of the Evidence

In 2011, the WHO recommended that screening for TB in patients with DM should be considered in settings with high TB prevalence. A systematic review revealed that screening for TB in persons with DM demonstrated a prevalence of 1.7% to 36%, and noted to be increasing with rising TB prevalence in the underlying population as well as with DM severity. In a study done in India, screening for TB among patients with DM yielded a prevalence of 2.7%. (Jali etal, 2013)

The utility of screening for TB among those with DM is greatest when the population has a relatively high TB prevalence. One can get a better idea of its usefulness by deriving the number needed to screen, or the number of people with DM who would need to be screened to detect one additional case of TB from the nomogram below.

FIGURE 6 Nomogram of the Number of People with Diabetes to Screen to Detect One Additional Case of TB by Varying Baseline Tuberculosis Prevalence



* Study by Kim *et al*. measured incident TB ratio, rather than prevalent TB ratio

Reference: Jeon C, etal. Bi-directional screening for tuberculosis and diabetes: a systematic review. Tropical Medicine and International Health. Vol. 15 no 11 pp 1300–1314 November 2010).

In settings in which TB prevalence is <25 per 100 000 persons, at least 1000 people with DM would need to be screened to find a single additional case of TB. In contrast, in places with higher TB burden, such as India, where TB prevalence is estimated at 283⁄100 000, screening 90–350 people with DM would yield one or more cases of TB. (Jeon etal, 2010)

In the Philippines, the prevalence of TB in 2007 was 2.0 per 1000 for smear-positive TB and 4.7 per 1000 for culture-positive TB, or 470/100,000 population (WPRO. The TB Profile of the Philippines, 2003-2011). Thus, approximately 75-200 patients with DM have to be screened to identify 1 case of TB based on the nomogram in **Figure 5.** The cost-effectiveness of this strategy though has not yet been investigated.

DM is included as one of the risk factors that may increase the risk of progression of latent to active TB (Hauck etal, 2009). The relative risk of progression to active TB is 2.0-4.1 (ATS/CDC, 2000). Finally, certain subsets of diabetic individuals may be at higher risk of tuberculosis for which the benefit of routine screening might be greater. These include Type 1 diabetics, Type 2 diabetics on insulin therapy or with poor glycemic control, those with exposure to household contacts with TB, diabetics who smoke. (ATS/CDC 2000; Olmos etal, 1989; Dobler etal, 2012; Jeon etal, 2010; Boucot etal, 1952)

QUESTION 7 What is the recommended treatment regimen for TB among patients with diabetes?

The treatment regimen for TB among patients with DM is the same as the general population *(Please see Chapter 3: Treatment). (Strong recommendation, high quality evidence)*

Glucose control for diabetic individuals with TB should be optimal. In difficult to control diabetes mellitus, referral to a diabetes specialist is recommended to achieve optimal glucose control.*(Strong recommendation, moderate quality evidence)*

Summary of the Evidence

Given the lack of rigorous intervention studies, the International Union Against Tuberculosis and Lung Disease and the WHO concluded that there is insufficient evidence to support changing the recommended standard TB treatment regimens or making specific recommendations for clinical case management of TB in people with diabetes (WHO/IUATLD, 2011). Although no published studies report on the efficacy of prolonged

treatment, investigators in the Pacific Islands TB Controllers Association have observed that TB patients with DM frequently remain sputum culture positive at 2 months (Blumberg etal, 2013). The Official Joint Statement of the American Thoracic Society, US CDC and the Infectious Diseases Society of America states that patients who have cavitation on initial chest radiograph and who have a positive culture at completion of 2 months of therapy are at substantially increased risk of relapse. For these patients it is recommended that the continuation phase of treatment be prolonged to 7 months, making a total treatment period of 9 months. Study done in Taiwan showed that among diabetic patients treated for TB in DOTS setting, the outcome was the same for both patients receiving a 6-month and a 9-month treatment regimen (Wang etal, 2015). In the same study, in non-DOTS setting, the additional 3 months (9-month regimen) showed additional treatment benefit over the 6-month regimen.

Poor glucose control (HbA1c >7) increases the risk of poor outcomes. There is no direct evidence from randomized trials or observational studies that better glycemic control during concurrent TB treatment will lead to better outcomes. Upon consult, HbA1c and FBS may be used to assess the level of glucose control. Insulin therapy will be a better option to achieve optimal glucose control. If glucose is controlled, upon consult, then patients may be continued on their current oral anti-diabetic agents. The general target is HbA1c of <7 and FBS <100 mg/dL (70-130 mg/dL). On follow-up, when patient is already sputum or culture negative for TB, based on physician's discretion and patient's level of glucose control, insulin may be shifted to oral anti-diabetic agents. Otherwise, patients may be maintained on insulin during the entire treatment course.

Another issue arises from the possible drug interactions between the oral hypoglycemic drugs and the anti-Koch's medications. Rifampicin accelerates the metabolism of sulphonylureas and biguanides which subsequently lowers their plasma levels leading to hyperglycemia. Isoniazid antagonizes sulphonylureas causing worsening glycemic control. The interaction also impairs the release and action of insulin leading to hyperglycemia even in non-diabetics. Therefore, the dosage of insulin should be adjusted while adding and removing these drugs from the patients' prescriptions. Dipetidyl peptidase IV inhibitors (gliptins), have a theoretical possibility of reducing immunocompetence because of their mechanism of action, and could possibly worsen the outcome of patients with TB (Niazi etal, 2012). Hence, patients will benefit from insulin therapy during the intensive phase of TB treatment. For those with acceptable blood sugar control, with nephropathy or any risk for hypoglycemia,

physician discretion on the use of insulin is advised. Referral to a specialist adept at intensive glycemic control will be needed. Once patient is sputum or culture negative and if blood glucose level is acceptable, physician may shift from insulin therapy to oral hypoglycemic agents.

QUESTION 8 What is the recommended diagnostic work-up and most suitable treatment regimen for TB among solid organ transplant (SOT) and hematopoietic stem cell transplantation (HSCT) recipients?

Diagnostic work-up for TB will follow the recommendations for the general population.

Treatment regimen for kidney and liver transplant candidates will need dose adjustments based on drug and disease severity. ***(Strong recommendation, moderate quality evidence)***

For post-SOT recipients without risk factor for drug resistance (i.e. mild non-cavitary, non-miliary, not extra-pulmonary, and clinically diagnosed), the anti-TB treatment recommended is the combination of Isoniazid, Ethambutol and Pyrazinamide (HEZ) for the intensive phase in the first 2 months followed by Isoniazid and Ethambutol for 12-18 months. ***(Weak recommendation, moderate quality evidence)***

For more **severe cases** of tuberculosis (i.e. disseminated TB, cavitary, and bacteriologically-positive), the addition of Rifampicin (HEZ + R) may be considered for the intensive phase in the first two months followed by Rifampicin and Isoniazid for 4-9 months. (***Weak recommendation, moderate quality evidence)***

Summary of Evidence

Tuberculosis is a serious opportunistic infections among solid organ transplant recipients with reactivation as the most common mode of infection. Other modes of infection identified include infected transplanted organs, from living donors and very rarely through nosocomial transmission. Risk factors for post-transplant tuberculosis identified include: presence of chronic liver disease, co-existing infections such as deep mycoses, *Pneumocystis jirovecci* and Nocardia, OKT3 and CMV; presence of diabetes mellitus, type of immunosuppressive therapy with OKT3 and anti-T cell antibodies; history of exposure to M. tuberculosis; recipient donor with positive PPD test and radiologic evidence of previously untreated TB.(Munoz etal, 2005; Aguado etal, 2009)

The incidence of active TB disease among solid organ transplant recipients varies according to geographical locations. Post SOT tuberculosis is reported

to be 3.1 to 15% in Asia, 1.5 to 8.5% in South Africa, 1.5 to 3.5% in the Middle East, 1.7 to 5% in Europe and 1.5% in the United States. The actual burden may be much higher in the developing countries. Underreporting may be due to poor maintenance of records and follow-ups. (EBPG Expert Group on Renal Transplantation, 2002)

About 45-60% of TB occurs in the first year after transplantation. A global review on TB estimated the median time for onset at nine months post transplantation. Studies have shown the median onset to be 26 months for those who received azathioprine and prednisolone as immunosuppression and 11 months for those who received cyclosporine along with other immunosuppressive agents. (Aguado etal, 2009)

TB in liver transplant recipients presents unique challenges, including a delayed diagnosis secondary to insensitive testing and treatment complications due to anti-TB drug toxicities and interactions with immunosuppressive agents. Rates of 0.47% to 2.3% for active TB in adult liver transplant recipients has been reported. Because of the difficulty of accurately diagnosing symptomatic TB, these figures most likely underestimate the burden of the disease (EBPG Expert Group on Renal Transplantation, 2002). Vigorous search for active TB should be done and treated prior to transplant.

The search for evidences to support the recommendations for treatment of tuberculosis among post SOT recipients yielded consensus statements, based on experts' opinions. One CPG published last 2010 in Thorax was assessed to have fair quality of presentation and completeness or reporting and the recommendation of which may not be applicable in our setting because of the high rates of quinolone resistance of 35.3% in our country.

The recommendations for the treatment of active tuberculosis among post SOT recipients are made based on consensus guidelines by experts in the fields of organ transplantation and infectious diseases. The Spanish group of experts recommend the exclusion of Rifampicin for the treatment of post SOT recipients with uncomplicated tuberculosis based on the increased risk of hepatotoxicity with Rifampicin. A retrospective cohort study in Brazil identified the use of Rifampicin at 600 mg or higher dose as an independent risk factor for liver toxicity (OR 2.47) (Schultz, 2014). Another significant concern with the use of Rifampicin is its interaction with immunosuppressive agents, increasing the chance of graft rejection (Milburn, 2010). There were no published RCT's to compare the outcome of patients on HEZ to those on Rifampicin-containing regimen. However,

a retrospective matched cohort study conducted in Barcelona, which looked at the risk factors for tuberculosis-related deaths among post-SOT recipients, included a sub-analysis of treatment regimens. The outcome of post-transplant patients who received HEZ was compared to the matched patients from the general population who received HREZ. Sub-analysis showed that there was no relapse among post-SOT recipients and all patients were considered to be cured, though they understandably had longer duration of therapy. (Benito, 2015)

The consideration of adding Rifampicin was included in the recommendation by the Spanish experts for disseminated tuberculosis or for transplant recipients with more severe cases. The expert panel of the British Thoracic Society was more aggressive to adopt Rifampicin-containing regimen (2RHEZ->4RH) for all post-SOT recipients with frequent drug level determination and dose modification of immunosuppressive drugs. Longer duration of treatment was recommended for diseases involving the CNS and skeletal system. (British Society Standards, 2010; EBPG Expert Group on Renal Transplantation, 2002)

QUESTION 9 What is the appropriate treatment regimen for TB among patients with chronic kidney disease (CKD)?

Patients with CKD diagnosed to have active TB should receive the standard anti-TB regimen using first line drugs with dose modifications where appropriate. CKD patients on second-line drugs should receive doses adjusted based on renal function. ***(Strong recommendation, high quality evidence)***

Summary of Evidence

The recommended initial TB treatment regimen for patients with kidney disease is two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of isoniazid and rifampicin. No change in dosing is necessary for isoniazid and rifampicin since these drugs are eliminated via biliary excretion. However, patients with kidney disease who are receiving isoniazid should also receive pyridoxine 10-25 mg/day to prevent isoniazid-induced peripheral neuropathy (WHO, 2009).

Ethambutol and metabolites of pyrazinamide are excreted through the kidneys in significant amounts hence dose adjustment for these two drugs is necessary. Three times per week (instead of daily) administration of

pyrazinamide and ethambutol is recommended (WHO, 2009; ATS/CDC/IDSA 2003). Patients receiving pyrazinamide may develop some degree of hyperuricemia as a result of inhibition of renal tubular secretion but this may be reduced by intermittent administration of the drug. Baseline determination and periodic monitoring of serum uric acid levels for these patients is recommended.

Ethambutol, on the other hand, may cause dose-dependent optic neuritis that can result in impairment of visual acuity and color vision and can eventually lead to blindness. All patients receiving ethambutol should be advised to discontinue taking the drug immediately and report to their physicians as soon as they experience deterioration of vision or color perception. Baseline and periodic ophthalmologic evaluation of patients receiving ethambutol is also advised (WHO, 2009).

For patients with advanced CKD (i.e., those with GFR < 30mL/min), single formulation anti-TB drugs is preferred over fixed-dose combination anti-TB drugs to facilitate proper dose adjustment of these medications.

Patients with or highly likely to have drug-resistant TB or those who develop severe adverse reactions to first-line anti-TB medications should be referred to PMDT.

Patients, including patients with kidney disease, with or highly likely to have drug-resistant TB or those who develop severe adverse reactions to first-line anti-TB medications should be treated with specialized regimens containing second-line anti-TB drugs. These regimens should be administered after consultation with a TB specialist with expertise on the use of second-line anti-TB drugs.

QUESTION 10 When is the best time to administer anti-TB medications among patients undergoing dialysis?

For patients on hemodialysis who are undergoing treatment for TB, anti-TB medications should be administered immediately *after* hemodialysis session.

For patients on peritoneal dialysis, anti-TB medications may be administered regardless of PD schedule; begin with doses similar to those recommended for patients on hemodialysis. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

For patients undergoing hemodialysis, anti-TB drugs should be given after dialysis to avoid premature removal of these drugs during hemodialysis (BTS, 2010; ATS/CDC/IDSA, 2003; Launay-Vacher etal, 2005). For patients on peritoneal dialysis, however, no clear recommendations as to the dose adjustment of anti-TB drugs are available at present due to the paucity of information concerning the effects of peritoneal dialysis on the clearance of these drugs. Currently, the recommendation for patients on peritoneal dialysis is to begin with doses similar to those recommended for patients receiving hemodialysis (see **Table 28**). (ATS/CDC/IDSA, 2003)

TABLE 28 Recommended doses of first-line anti-TB drugs for patients with kidney disease

DRUG	REFERENCE DOSE (NORMAL RENAL FUNCTION)	DOSE ADJUSTMENT AND TIMING			
		GFR≥ 30ML/MIN	*GFR< 30ML/MIN*	*HD*	*PD*
Isoniazid+	5 (4-6) mg/kg, 400 mg daily	None	None	AD	None
Rifampicin	10 (8-12) mg/kg, 600 mg daily	None	None	AD	None
Pyrazinamide	25 (20-30) mg/kg, 2 g daily	None	25-35 mg/kg, 3x/week	25-35 mg/kg, 3x/week, AD	25-35 mg/kg, 3x/week
Ethambutol	15 (15-20) mg/kg, 1.6 g daily	GFR > 70 mL/min: None GFR < 70 mL/min: 15-25 mg/kg, 3x/week	15-25 mg/kg, 3x/week	15-25 mg/kg, 3x/week, AD	15-25 mg/kg, 3x/week

+ Should be given along with Pyridoxine 10-25 mg/day
^ AD, after dialysis session on days with dialysis
GFR, glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis

QUESTION 11 What is the appropriate treatment regimen for TB among patients with chronic liver disease (CLD)?

- The more advanced the liver disease, the less the number of hepatotoxic drug that should be used.
- Among patients with compensated liver cirrhosis, the following are recommended treatment options for TB: 2HRSE/6HR; 2HSE/10HE or 9HRE

- In patients with decompensated liver cirrhosis, referral to specialized centers is warranted because of the possible use of second line TB drugs.

(Strong recommendation, low quality evidence)

Summary of Evidence

Challenges in the treatment of TB in patients with CLD arise because three of the first-line anti-TB drugs are potentially hepatotoxic. These drugs can lead to worsening liver function with decompensation of stable cirrhosis and sometimes cause fulminant hepatic failure, with a high mortality. There is no consensus on the drugs to be given for different grades of liver injury.

Broadly, the more advanced the liver disease the less the number of hepatotoxic drug should be used. It must be remembered that pyrazinamide has the highest hepatoxicity followed by rifampin and isoniazid. Safer anti-TB drugs are ethambutol, quinolones, aminoglycosides and cycloserine. (Dhingra, 2006).

Due to better functional reserve, patient with compensated cirrhosis (Childs A) have more treatment options and better tolerability (WHO, 2010).

There have been no studies to date comparing the full anti-tuberculosis therapy course with regimens containing only two potentially hepatotoxic drugs. It is prudent to use only two hepatotoxic drugs in treating compensated cirrhosis until a randomized controlled trial (RCT) proves the safety of low-dose pyrazinamide-containing combinations of three potentially hepatotoxic drugs.

Treatment of TB in patients with decompensated liver cirrhosis may lead to hepatotoxicity and progressive TB may lead to liver decompensation. One or two hepatotoxic drugs may be used in moderately severe disease (e.g., Child B cirrhosis) whereas hepatotoxic drugs are completely avoided in decompensated Child C cirrhosis.

Second line anti-TB drugs are recommended among patients with liver cirrhosis with encephalopathy (ATS, 2003) and among patients with decompensated liver cirrhosis (Kumar etal, 2014). Thus, the consensus is to refer these patients to specialized TB centers with expertise and access to second line TB drugs.

QUESTION 12 What is the appropriate treatment regimen for TB among pregnant and lactating women?

The treatment regimen for pregnant and lactating women is the same as the general population. Streptomycin, however, is contraindicated in pregnant and lactating women.

Supplementation with pyridoxine to pregnant and lactating women at a dose of 10-25 mg/day is recommended to prevent peripheral neuropathy. ***(Strong recommendation, moderate quality evidence)***

Summary of Evidence

The treatment of active PTB among pregnant and lactating women should follow the same standardized first-line regimen used for non-pregnant patients. (refer to **Chapter 3** on Treatment). Pregnant and breastfeeding women are at increased risk of peripheral neuropathy associated with isoniazid. Hence, it is recommended to supplement pyridoxine at a dose of 10 mg per day up to 25 mg per day as prophylaxis. Patients who develop polyneuritis should be treated with 100-200 mg/day of pyridoxine (Arbex, 2010) (WHO, 2010).

Women on first-line regimen are encouraged to breastfeed provided they have been treated appropriately for 2 weeks or more and are no longer infectious (Loto, 2012) (WHO, 2010) (Blumberg, 2003). Breastfeeding recommendation for women on second-line drugs must be individualized. Women should be counseled that there are minimal data on long-term safety, breast milk concentration or potential adverse effects to the infant (Mathad, 2012). Caution must be exercised during breastfeeding of infants concomitantly given anti-tuberculosis regimen with their mothers (Loto, 2012).

The treatment regimen for pregnant patients suspected to have MDR-TB should be individualized depending on the drug sensitivity test (DST) results, clinical assessment, the age of gestation and the drug effects to the developing fetus (Albanna & Menzies, 2011) (Caminero, 2006). Women should be counseled regarding the necessity of treatment, the effects of treatment to the developing fetus versus the risk of an adverse outcome from withholding treatment, as well as the risk of transmission to the neonate during the postpartum period. Candidates for MDR-TB treatment may start with a non-injectable regimen and continue until delivery when an injectable agent may be added "(Duff, 1997) (Drobac, 2005) (Drobac, 2005) (Arbex etal, 2010).

Another option is to delay initiating treatment to the second trimester where possible (Loto, 2012). Mothers on second-line anti-tuberculosis agent should avoid breastfeeding (Drobac, 2005) (Mukherjee, 2003).

Literature is lacking in terms of assessment of safety, tolerability, and long-term treatment outcome of tuberculosis during pregnancy and the postpartum period. The risk to the fetus from untreated tuberculosis is greater than the risk of treatment of the disease. Available data do not suggest need for dose adjustment during pregnancy (Loto, 2012) (Mathad, 2012; Blumberg, 2003)

QUESTION 13 Is chest radiography considered safe during pregnancy?

Chest radiography with abdominal shield, if indicated, is considered to be relatively safe during pregnancy. An informed consent is necessary. Pregnancy should neither deter nor delay the diagnosis and management of PTB. *(Strong recommendation, low quality evidence)*

Summary of Evidence

Data on the potential adverse effects of radiation to pregnancy are mostly from those of the fetal outcome reported after the bombing of Hiroshima and Nagasaki (Eskandar, 2010) (Toppenberg, 1999). There are three areas of concern after exposure to ionizing radiation during pregnancy, these are teratogenicity or birth defects, cancer, and germline mutation in the exposed fetus. (WAPC, 2006) (Toppenberg, 1999) (ACOG, 2004) Several current literature agree that ionizing radiation, particularly to the chest, poses negligible risk to the fetus. According to the American College of Radiology (ACR), "No single diagnostic procedure results in a radiation dose that threatens the well-being of the developing embryo and fetus." (WAPC, 2006) (ACOG, 2004) Therefore, the risk from exposure should not delay the use of appropriate imaging studies.

The accepted cumulative dose of ionizing radiation below which clinically manifest effects are not observed is <5 rads. (WAPC, 2006) (Toppenberg, 1999) Current evidence suggest that there is no increased risk of major malformations, growth restriction or miscarriage from radiation <5 rads scompared with background risk in nonexposed fetuses which are 3%, 4%, and 15%, respectively. The potential for increased risk of teratogenicity or birth defect primarily affecting the CNS is commonly observed at exposures of >50 rads during the critical period of 10 – 17 weeks gestation, with less risk at 18 – 27 weeks.

There is no proven risk before 10 weeks or after 27 weeks. The estimated fetal dose per chest x-ray examination is 0.00007 rads and therefore should require >71000 number of examinations to reach the cumulative 5 rad threshold. Although it has been estimated that exposure to as little as 1 – 2 rads is associated with an increase rate of leukemia in children to 5 per 10000, there is conflicting evidence on the association of fetal irradiation and increased occurrence of leukemia as found in population. Further, data are likewise not consistent on the association of ionizing radiation and occurrence of new genetic mutation. (WAPC, 2006) (Toppenberg, 1999) (ACOG, 2004)

For diagnostic radiologic procedures outside of the abdomen/ pelvis, the only radiation to which the conceptus is exposed is that of scattered radiation, which characteristically results in a very low dose (ACR-SPR, 2014). A plain CXR generally exposes the fetus to very small amounts of radiation. Estimated fetal exposure from CXR (2 views) is 0.02–0.07 mrad. It is common to shield the pregnant uterus during non-pelvic procedures (ACOG, 2004). (ACOG, 2004). Hence, in general, radiological examinations render exposures to a pregnant uterus that are so low that pregnancy status need not alter the decision to proceed with a medically indicated examination, as long as the beam is properly collimated and the patient is positioned to avoid direct irradiation of the pelvis. (ACR-SPR, 2014)

QUESTION 14 Who should be screened and treated for latent TB infection (LTBI) among high risk clinical groups?

The following high risk groups should be screened and treated for LTBI:

- PLHIV (When active disease is ruled out, patient is treated for presumed LTBI, no screening needed) ***(Strong recommendation, moderate quality evidence)***
- Solid organ and hematopoietic stem cell transplant recipients (***Strong recommendation, low quality evidence)***
- Patients with rheumatoid arthritis on biologicals ***(Strong recommendation, low quality evidence)***
- Patients on chronic dialysis ***(Strong recommendation, low quality evidence)***
- Patients with Type 1 diabetics, Type 2 diabetics on insulin therapy with poor glycemic control, diabetics exposed to active TB or those who are smokers ***(Weak recommendation, moderate quality evidence)***

- Pregnant patients with known exposure to active TB, injection drug users, or immunocompromised. *(Strong recommendation, low quality evidence)*
- Pregnant women with known exposure to active TB, injection drug users, and/or residence in congregate setting *(Weak recommendation, low quality evidence)*
- Pregnant women with HIV similar to non-pregnant PLHIV *(Strong recommendation, moderate quality evidence)*

At present, the National TB Program prioritizes LTBI treatment for PLHIV.

Summary of Evidence

PLHIV

The estimated annual risk of active TB among PLHIV with LTBI is 3 to 12 times higher compared to the general population (ATS, 2000; Horsburgh, 2004). Furthermore, development of HIV-related TB increases viral load and the risk of HIV disease progression and death compared with CD4-matched, HIV seropositive controls (Day, 2004; Lopez-Gatell, 2008). Among HIV-infected individuals, treatment of LTBI decreases the risk of TB disease by 62% and the risk of death by 26% (Akolo etal, 2010). Therefore, prevention of TB disease by screening for and appropriately treating LTBI is a key component of HIV care. The combined use of IPT and antiretroviral therapy (ART) among PLHIV significantly reduces the incidence of tuberculosis. The combined use of ART and IPT can reduce tuberculosis incidence among PLHIV by up to 97% particularly among persons with positive tuberculin skin tests (Golub, 2007; Golub, 2009).

A TST is not required for initiating IPT in PLHIV.

SOLID ORGAN AND HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Based on systematic reviews, solid organ and hematopoietic stem cell transplant recipients were identified as one of the pre-defined high risk groups with evidence of increased incidence of active TB (WHO, 2015). Vigorous search for active PTB should be undertaken before, during and after transplant procedures."

CONCOMITANT USE OF BIOLOGICALS AMONG PATIENTS WITH RHEUMATOID ARTHRITIS

The seroconversion of LTBI among patients receiving biologic therapy is 30%; therefore, annual screening should be done if negative (AGREE

rating: Recommend=1, No Recommendations=6). Patients may remain TST or IGRA positive after successful treatment of TB; hence, monitoring for clinical signs and symptoms of recurrent TB should be considered (ACR 2012). In a prospective cohort study of 70 patients with rheumatoid arthritis on anti-TNFs with negative baseline TB screening (TST, TB Spot TB, QFT-GIT), 29% (20 patients) had conversion of at least 1 screening assay 12 months after initiation of anti-TNF therapy - TST 9 (13%), T-Spot TB 7 (10%) and QFT GIT 5 (7%) (Hatzara 2014).

DIABETES MELLITUS

LTBI screening is likely to be specifically beneficial among diabetic patients who are Type I, Type 2 with poor glycemic control despite insulin therapy, contacts of active TB and smokers.

In 10 case-control studies, the pooled odds ratio among DM cases was 2.2 (1.16 to 7.81); while in 4 cohort studies, the pooled relative risk was 2.52 (95% CI: 1.53 to 4.03) [5,32]. Patients with type 1 DM are more susceptible to TB than those who have type 2 DM. This susceptibility is related to a longer duration of disease and relative difficulty to achieve glucose control among type 1 compared to type 2 DM. Poor glycemic control has been significantly associated with the occurrence of TB. There is a correlation between active TB and the level of glycosylated hemoglobin (HbA1c) with a hazard ratio of 1.39 (95% CI, 1.18-1.63) per unit increase. The risk of TB is higher among patients on insulin, particularly those who need higher doses, with a TB prevalence ratio from 2.8 to 20.9 observed among diabetic patients who were insulin-dependent as compared to non-insulin dependent.

Poor glycemic control has been significantly associated with the occurrence of TB. There is a correlation between active TB and the level of glycosylated hemoglobin (HbA1c) with a hazard ratio of 1.39, 95% CI: 1.18-1.63 per unit increase. The risk of TB is higher among patients on insulin, particularly those who need higher doses. The TB prevalence ratio ranging from 2.8 to 20.9 were observed among diabetic patients who were insulin-dependent as compared to non-insulin dependent. Poor glycemic control has been significantly associated with the occurrence of TB. In one study, there was a correlation between active TB and the level of glycosylated hemoglobin (HbA1c) (hazard ratio 1.39, 95% CI: 1.18-1.63 per unit increase).

Smoking history is also very important among patients with both DM and TB, where DM and cigarette smoking independently increased the risk of death. Compared with non-smokers, current smokers had increased

mortality from TB with a hazard ratio of 1.6 (1.3, 2.0) for men and 1.6 (1.0-2.4) for women. Estimating the combined impact of DM and smoking yielded a hazard ratio of 5.78.

PREGNANCY

Latent tuberculosis screening is **not routinely recommended** during pregnancy. Screening should be considered for pregnant women with known exposure to active TB, are injection drug users and with an immunosuppressive condition. For pregnant women with HIV, recommendations should follow LTBI HIV management guidelines.

Effects of Pregnancy on Tuberculosis

Researchers demonstrated no net benefit or adverse effect of pregnancy on the progression of TB. However, frequent, consecutive pregnancies may have a negative effect, as they may promote recrudescence or reactivation of latent tuberculosis. It is important to note that the diagnosis of tuberculosis in pregnancy may be more challenging, as the symptoms may initially be ascribed to the pregnancy. The weight loss associated with the disease may also be temporarily masked by the normal weight gain in pregnancy (Loto, 2012).

Effects of Tuberculosis on Pregnancy

The effects of TB on pregnancy may be influenced by many factors, including the severity of the disease, how advanced the pregnancy has gone at the time of, the presence of extra-pulmonary spread, and HIV co-infection and the treatment instituted. Obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, small for date uterus, suboptimal weight gain in pregnancy, preterm labor, low birth weight and increased neonatal mortality (Loto, 2012).

Latent tuberculosis prevalence in pregnancy likely mirrors that of the general population; reported at 4.2% in low-burden countries such as the United States to as high as 19-34% in high-burden countries such as India (Mathad, 2012).

In low-burden countries, the CDC recommends LTBI screening only for high-risk women - those with known or suspected tuberculosis contacts, injection drug use, HIV or other immunosuppression, foreign birth, and/or residence in congregate settings. In high-burden countries, LTBI is not routinely recommended since pregnancy by itself is not considered high-risk.

QUESTION 15 What is the recommended screening test for LTBI among high risk clinical groups?

Tuberculin skin test (TST) is the preferred screening test for LTBI in resource-limited setting like the Philippines. *(Strong recommendation, low quality evidence)*

Summary of Evidence

TST is comparable to IGRAs as screening test for LTBI. IGRAs are costly and technically complex to do than the TST. However, active disease should be ruled out first before LTBI is screened and treated by asking about TB symptoms, and requesting for chest radiography. (WHO 2011)

QUESTION 16 What is the recommended treatment for LTBI??

Isoniazid 300 mg daily for 6 months under supervised treatment is the recommended regimen for LTBI *(Strong recommendation, moderate-high quality evidence)*

Pyridoxine at a dose of 25 mg/day is recommended to prevent peripheral neuropathy. *(Strong recommendation, low quality evidence)*

Summary of Evidence

INH is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults, not to exceed 300 mg per dose. The six-month regimen was found to be equivalent to 9-month isoniazid in terms of efficacy and safety. The shorter duration regimen is preferred due to resource requirements, feasibility and acceptability by patients (WHO, 2015). Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months.

Isoniazid can potentiate the risk of peripheral neuropathy when used with some antiretroviral (ARV) drugs, most notably the dideoxynucleosides (didanosine, stavudine), which are seldom used in clinical practice in the United States. Hence, it should be supplemented with pyridoxine at a dose of 25 mg/day to prevent peripheral neuropathy.

Contraindications of IPT include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy.

INH, when used with efavirenz- or nevirapine-based regimens, does not significantly increase risk of hepatitis, the most important adverse reaction.

Providing INH-prophylactic therapy (IPT) to PLHIV does not increase risk of developing INH-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a reason not to provide IPT.

Research Recommendations:

- More trials to evaluate modified treatment regimens for this special population

Chapter 6

Prevention and Control of Tuberculosis in the General Population

Chapter 6
Prevention and Control of Tuberculosis in the General Population

Outline of Issues on Prevention and Control for TB:

1. Will the observance of proper cough etiquette help minimize transmission of PTB?
2. Will the use of face masks by patients and/or exposed individuals decrease TB transmission?
3. Is routine screening among household contacts of active TB cases mandatory?
4. What risk factors need to be addressed to decrease TB infection and progression to disease among patients with no known co-morbid conditions?
5. Do we need to treat LTBI in the general population?
6. What is the role of BCG re-vaccination among adults to prevent TB infection?
7. When is isolation recommended?
8. What infection control measures must be observed in health care facilities?
9. What infection control measures must be observed when handling TB biological specimens?
10. How should job applicants/students be managed if pre-employment/ pre-enrollment screening suggests tuberculosis?

QUESTION 1 Will the observance of proper cough etiquette help minimize transmission of PTB?

Covering one's mouth when coughing minimizes the spread of potentially infectious aerosols, including those laden with MTB. ***(Strong recommendation, low quality evidence)***

Summary of Evidence

Most infection control guidelines highlight the need to observe cough etiquette. (WHO, 2009; Jensen, 2005) In a cohort study, simple control measures including covering the mouth when coughing, were effective in significantly reducing nosocomial transmission of MDRTB among HIV patients (28.9% vs. 0%). (Moro, 2000). However, in a recent open bench, observational study, cough etiquette maneuvers did not block the release and dispersion of a variety of different diameter droplets to the surrounding environment. (Zayas, 2013)

QUESTION 2 Will the use of face masks by patients and/or exposed individuals decrease TB transmission?

- Surgical face masks should be used among patients presumed or confirmed to have infectious PTB until they are deemed non-infectious.
- Patients with active PTB should NOT wear face-piece respirator masks since these masks are primarily meant to prevent inhalation of the infectious droplets. (Strong recommendation, low quality evidence)
- There is no evidence that the use of 2 or more surgical face masks in layers provide additional protection. (Strong recommendation, moderate quality evidence)
- Exposed health care workers should use filtering face-piece respirator masks (i.e., N95 or FFP2) when performing procedures with high risk of aerosolization.
- Surgical masks do not offer significant protection on personnel performing aerosol-producing procedures.
- Users of filtering face-piece respirator masks should undergo regular fit testing to ensure proper use. (Strong recommendation, high quality evidence)

Summary of evidence

Surgical face masks reduce the aerosolization of droplet nuclei from patients. A prospective cohort observational study on guinea pigs exposed to MDR-TB patients showed 56% reduction of TB incidence compared to those not wearing masks. (Dharmadhikari, 2012)

In a prospective cohort study, transmission is highest among TB patients with cavitations or bacteriologically proven disease [i.e., positive AFB

smears or positive TB culture] (Loudon and Spohn, 1969). Thus, patients with this type of TB disease should wear masks.

The presence of cavitary PTB, sputum AFB smear positivity and frequent cough are likely causal factors for infectivity. (ATS/CDC/IDSA, 2005)

In one retrospective cohort study and a sensitivity analysis of an observational study, sputum smear-negative pulmonary TB, especially those culture-positive, account for 13% (Tostmann, 2008) to 17% (Behr, 1999) of disease transmission.

In quantitative bacteriologic studies using multiple regression analyses, most patients (at least those with infection attributable to isolates susceptible to isoniazid) who have received treatment for as few as 2 days with the standard regimen (i.e., isoniazid, rifampin, ethambutol, and pyrazinamide) could be assumed to have an infective potential that averages 10% of that at the time of diagnosis. After 14 to 21 days of treatment, infectiousness averages less than 1% of the pretreatment level. (Jindani, 1999 and 2003)

Filtering face-piece respirator mask (N/R/P 95/99/100 or FFP2, FFP3 filter level) decreases the incidence of TB among healthcare workers exposed to MTB. It should be worn when aerosols cannot be safely contained or when handling positive cultures (Jensen, 2005). In a recent RCT, the continuous use of N95 by health workers on-duty significantly reduce clinically evident respiratory illness compared to those who use it only during high risk procedures (7.2% vs 11.8%) (MacIntyre, 2013). Use of surgical mask does not offer significant protection on personnel performing aerosol-producing procedures.

QUESTION 3 Why and how should household contacts of active TB be screened?

Household contacts of active TB cases are at increased risk of infection and disease should be screened for disease activity according to CPG recommendations (Refer to chapter on Diagnosis); or at least by CXR, especially if the index case is bacteriologically confirmed, cavitary disease, with frequent coughs and has yet to receive or in the early stages of the recommended treatment regimen. ***(Strong recommendation, high quality evidence)***

Summary of evidence

In a recent systematic review and meta-analysis of all studies reporting the prevalence of TB and latent TB infection, and the annual incidence of TB among contacts of TB patients, the prevalence of active TB in all contacts was 3.1%, microbiologically proven TB was 1.2% and latent TB infection was 51.5% . TB prevalence among household contacts was 3.1% and among contacts of patients with multidrug-resistant or extensively drug-resistant TB was 3.4%. Incidence of TB infection was greatest in the first year after exposure. (Fox, 2013)

The presence of cavitary PTB, sputum AFB smear positivity and frequent cough are likely causal factors for infectivity. (ATS/CDC/IDSA, 2005)

QUESTION 4 What factors increase the risk of contracting TB infection and promote its progression to disease?

Smokers, alcoholics (i.e., $\geq$ 40 g/day) and underweight individuals (i.e., BMI $\leq$ 20) have slightly increased risk of contracting TB and progressing to disease compared to the general population. As modifiable risk factors, clinicians must address these appropriately - i.e., identify and advise smokers to quit; and offer dietary or lifestyle modifications.

The risk of progression to disease is strongly significant among persons with recent TB infection (i.e., < 2 years) and upper lobe fibro-nodular disease on chest x-ray. Periodic monitoring for symptoms suggestive of disease activity and a repeat chest x-ray after 4-6 months to establish radiographic stability is recommended for early detection of disease activity in these individuals.

(Strong recommendation, moderate quality evidence)

Summary of Evidence

Certain groups of individuals are particularly at higher risk for contracting TB infection and developing active disease compared to the general population. (Lobue and Menzies, 2010)

TABLE 29 Risk Factors for Contracting TB Infection and Developing Active Disease Compared to General Population

RISK FACTOR	ESTIMATED RISK FOR TB RELATIVE TO PERSONS WITH NO KNOWN RISK FACTORS	STUDIES
HIGH RISK		
Recent TB infection (<2 yrs)	15	Sutherland I, 1976, 1966
Abnormal CXR –with upper lobe fibronodular disease typical of healed TB infection	6-19	Nolan et.al, 1988 Grzybowski, 1971 Grzybowski, 1966
SLIGHTLY INCREASED RISK		
Underweight (<90% ideal body weight; for most persons, this is BMI < 90% IBW; for most persons, this is a BMI ≤ 20	2-3	Comstock, 1975
Cigarette smoker (1 pack/day)	2 – 3	Maurya, 2002 Gajalakshmi, 2003
	1.73 (for TB infection) 2.33-2.66 (for TB Disease) 1.4-1.6 (TB disease among TB infection) OR 2.53 for TB relapse	Bates, 2007 Batista, 2008
Underweight (BMI ≤ 18.5) and smoker	4.95 (women), 2.34 (men)	Patra, 2014
DM and underweight (BMI ≤ 18.5)	10 (women), 6.43 (men)	Patra, 2014
Alcohol intake of more than 40 g/day or with clinical Dx of alcohol use disorder	2.94	Lonnroth, 2008
Abnormal chest x-ray - granuloma	2	Grzybowski, 1971 Horwitz, 1969
LOW RISK		
Infected person, no known risk factor, normal CXR ('low-risk reactor')	1	Comstock, 1974
VERY LOW RISK		
Person with positive 2-step (booster), no other known risk factor, and N CXR	0.5	Comstack, 1974 Ferebee, 1970

QUESTION 5 Do we need to treat LTBI in the general population?

Treatment of latent TB infection in the general population is **NOT** recommended. ***(Strong recommendation, moderate quality evidence)***

Summary of evidence

In a systematic review, IPT was found to be cost effective to pursue in high-resource countries but there are limited studies to justify recommending LTBI treatment in low-resource countries. (Chavan, Newland and Smith, 2011)

QUESTION 6 What is the role of BCG re-vaccination among adults to prevent TB infection?

BCG re-vaccination is **NOT** recommended. ***(Strong recommendation, moderate quality evidence)***

Summary of evidence

In a cross-sectional study on the prevalence of LTBI among HIV-negative men, using QuantiFERON-TB Gold In-Tube (QFT-GIT), BCG vaccine seem to have a protective effects in adults decades after vaccination according to the number of recent infections (QFT-IT >/= 0.7 IU/ml). There is an inverse correlation between the number of BCG scars and the prevalence of positive QFT-IT in all age groups (18-34, 35-54 and > 55 years), which indicates a lasting protective effect of BCG against TB infection into adulthood; and thus, precludes the need to revaccinate (Chan, 2013).

QUESTION 7 When should isolation be recommended?

Isolation is recommended for the following TB cases:

- Bacteriologically confirmed PTB cases who have not started or are in the early stages of anti-TB treatment (including EPTB cases with potential for aerosol generation)
- Presumptive DRTB or known MDR/XDR-TB cases

- Documented HIV/AIDS cases or those with strong clinical evidence for HIV/AIDS should be isolated from active TB cases. Refer to CPG recommendations on when to transfer out a patient from isolation.

(Strong recommendation, moderate quality evidence)

Summary of evidence

Infectious patients should be separated from other individuals. Patients living with HIV or with strong clinical evidence of HIV infection, or with other forms of immunosuppression, should be physically separated from those with suspected or confirmed infectious TB. Patients with culture-positive drug-resistant TB, especially MDR and XDR-TB, or people suspected of having drug-resistant TB should be separated (preferably according to the drug resistance profile) or isolated from other patients, including other TB patients. (WHO, 2009)

QUESTION 8 What infection control measures must be observed in health care facilities?

Recommendations of the Philippine Guidelines on Infection Control for TB and Other Airborne Infectious Diseases must be observed in all health facilities dealing with presumptive and confirmed TB cases. These include the following:

- Observe administrative control through -
  - Identification of people with TB symptoms (triage)
  - Separation of infectious cases
  - Time is minimized in health care facilities (also ensure effective Treatment)
  - Cough etiquette promotion
- Conduct surveillance of TB disease among health workers, and conduct assessment at all levels of the health system and in congregate settings
- Ensure environmental controls are in place such that health facility design, construction, renovation and use are appropriate, e.g., good ventilation is assured.
- Provide appropriate personal protective equipment for health care workers in areas at high-risk for TB transmission

(Strong recommendation, low quality evidence)

QUESTION 9 What infection control measures must be observed when handling TB biological specimens?

- Hand hygiene must be strictly observed.
- Appropriate use of personal protective equipment is recommended to avoid direct contact with patient's blood, body fluids, secretions, and non-intact skin – i.e., use gloves, wear lab gown and N-95 mask in high risk areas.
- Filtering respirator face-masks are not required for use during the preparation of sputum smears.
- Biological safety cabinets (BSCs) are not mandatory when performing DSSM.
- Observe proper cleaning and disinfection of the environment and equipment, including the use of:
  - Sodium hypochlorite (1-5%) or bleaching solution for 1 minute; ethyl and isopropyl alcohols in high concentrations (70%), and iodine in disinfecting surfaces like contaminated containers
  - Soaking in 5% phenol or 5% formaldehyde for at least 10 minutes, or 30 minutes in 2% glutaraldehyde solution.
- Inactivate (e.g., by disinfection, autoclaving or incineration) and dispose infectious wastes appropriately.
- Only trained personnel should handle TB clinical specimens.

(Strong recommendation, low quality evidence)

Summary of evidence

The relative risk of becoming infected with TB for technicians performing DSSM compared with the general population was 1.4x and 21.5x for technicians performing DST (Kim, 2007)

Laboratory-acquired infection (LAI) with MTB is 100x greater than for the general population (Reid, 1957) and 3-9 times higher as compared to those handling other clinical specimens (Saint-Paul, 1972; Harrington & Shannon, 1976; Sepkowitz, 1995; Shinnick, 1995; Germanaud & Jamet, 1994)

Though only 1% of clinical specimens submitted for MTB tests really contain pathogenic mycobacteria, the infectious dose in humans is very

low (ID_{50} 1-10 bacilli) and sputum can contain several millions of bacilli per mL (Riley, 1957; Riley, 1961)

Procedures that generate aerosols can also be a source of MTB-laden droplet nuclei.

- sputum collection, nebulization among infectious cases, and handling of biological specimens – especially liquid) (WHO, 2008)
- Sputum smear fixation on slides (by heat or methanol) but not likely thereafter, despite the possibility of still having viable bacilli. (Allen, 1981) Viable TB bacilli can also be potentially be excreted by cockroaches following ingestion from heat-fixed smears not stored properly. (Allen, 1987)

Due to the viscosity of sputum specimens, the likelihood of generating an infectious aerosol while manipulating such specimens is much lower than the likelihood of generating an infectious aerosol from a liquid culture. (WHO, 2012)

Large air droplets do not dry easily, and rapidly contaminate laboratory surfaces and fingers and possible consequent secondary contamination of mouth and nasal cavities (Collins, 1988; Wells, 1941)

Survival of MTB outside the host can be particularly long, ranging from 90 to 120 days on dust, 45 days on manure, 105 days on paper, 6 to 8 months in sputum (stored in a cool, dark location) and 45 days on clothing (Rubin, 1991)

Outer surface of sputum containers is frequently contaminated by MTB (6.5%) or by other airborne pathogens (15%); may also leak during transport and, therefore, require proper protection during handling. (Allen and Darell, 1983)

After settling on surfaces, droplet nuclei are not re-aerosolized and are considered noninfectious. (Olson, 1967; Qian, 1997; Segal-Maurer, 1994)

Biological safety cabinets (BSCs) are not mandatory when performing DSSM. DSSM may be performed on an open bench, provided that adequate ventilation can be assured; smear-preparation should be separated from other benches in the laboratory. (CDC, 2012)

Ventilation can be ensured by opening windows. Unidirectional airflow is desirable in designing ventilation systems. Access to the laboratory should be restricted to authorized persons (WHO,2012)

TABLE 30 Assessment of Risk of Laboratory Activities Based on Risk Level of TB Laboratory

RISK LEVEL OF TB LABORATORY	LABORATORY ACTIVITIES	ASSESSMENT OF RISK
Low Risk	Direct sputum smear microscopy; preparation of specimens for use in an automated nucleic acid amplification test cartridge (such as the Xpert® MTB/Rif assay)	Low risk of generating infectious aerosols from specimens; low concentration of infectious particles
Moderate risk	Processing and concentration of specimens for inoculation on primary culture media; direct DST (for example, line-probe assays on processed sputum)	Moderate risk of generating infectious aerosols from specimens; low concentration of infectious particles
High risk (TB-containment laboratory)	Culture manipulation for identification; DST or line-probe assays on cultured isolates	High risk of generating infectious aerosols from specimens; high concentrations of infectious particles

QUESTION 10 How should job applicants/students be managed if pre-employment/pre-enrolment screening suggest tuberculosis?

- Job applicants/students who fulfill the criteria for presumptive TB are to be worked up and treated (if diagnosed) according to the latest CPG recommendations (See sections on diagnosis and treatment).
- Job applicants/students may be cleared for employment/ enrolment when deemed non-infectious (See section on treatment)
- In cases where disease activity is not entirely ruled out, these individuals may be given conditional clearance, placed on periodic monitoring and re-evaluated if necessary. A repeat CXR after 4-6 months is recommended to establish radiographic stability
- For prospective overseas Filipinos, policies of host countries apply and will prevail.

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APPENDIX A: Procedure for Sputum Collection for DSSM, Xpert® MTB/Rif

1. Motivate the presumptive TB to undergo DSSM. Explain the importance of the procedure and that of submitting two (2) sputum specimens. The only contraindication to collecting sputum for DSSM is massive hemoptysis which is expectoration of large volumes of blood (200-600 ml in 24 hours) from the respiratory tract. Blood streaked sputum can still be examined. For PLHIV with signs and symptoms of TB, refer the patient to a DOTS Facility with PMDT services for screening or to an Xpert site for testing.

2. Prepare the sputum cups and the **Form 2a. NTP Laboratory Request Form.** Label the body of the sputum cup (i.e., not the lid), indicating patient's complete name, and order of specimen collection (1st and 2nd). For Xpert® MTB/Rif prepare a sputum cup or 50ml conical tube and **Form 2a. NTP Laboratory Request Form.** Label the body of the sputum cup/conical tube, indicating patient's complete name and indicating specimen for Xpert® MTB/Rif
3. Demonstrate how to produce quality sputum. Mucus from the nose and throat, and saliva from the mouth are NOT good specimens. Advise the patient to:
    a. Clean mouth by thoroughly rinsing with water. Food particles or other solid particulates may inhibit the test for Xpert® MTB/Rif .
    b. Breathe deeply, hold breath for a second or two, and then exhale slowly. Repeat the entire sequence two (2) more times.
    c. Cough strongly after inhaling deeply for the third time and try to bring up sputum from deep within the lungs.
    d. Expectorate the sputum into a container with a well fitted cap.
    e. Collect at least 1 teaspoonful (5-10mL) for DSSM. For Xpert® MTB/Rif sputum sample should not be less than one (1) mL.
    f. Examine the specimen to see that it is not just saliva. Repeat the process if necessary.

    Sputum induction for individuals unable to expectorate should be done only in facilities where the staff is trained, supplies and equipment are available and infection control measures are in place.
4. Observe proper precautions against infection during the demonstration. Stay behind the patient. Collect specimen in a well-ventilated designated sputum collection area, or outside the DOTS facility.
5. Collect the first specimen (i.e., spot) at the time of the first consultation. Collect the second spot specimen after at least an hour, or the following morning. If the second sputum specimen is not submitted within three days from the first specimen, a new set of two (2) sputum specimens should be collected unless the first specimen already tests positive for AFB.
6. Check quantity and quality of sputum. Wipe off the external surface of the sputum cup if needed and wash your hand thoroughly with soap and water.
7. Seal the sputum specimen container, pack it securely, and transport it to a microscopy center or Xpert site together with the completely filled up **Form 2a. NTP Laboratory Request Form.**
8. If specimen cannot be sent to a microscopy unit early enough, prepare the smears immediately and then store them appropriately. Smearing can be done by trained volunteers before transport to the microscopy center.
9. Inform the patient when to return for follow-up consultation regarding the results

APPENDIX B:
List of TB Culture Centers in the Philippines under the NTP Laboratory Network as of December 2015

GOVERNMENT FACILITIES (17) PER REGION		PRIVATE FACILITIES (6) PER REGION	
NCR	Lung Center of the Philippines	NCR	Philippine Tuberculosis Society Inc. - Quezon Institute
	San Lazaro Hospital	4-A	De La Salle Health Sciences Institute
	UP PGH Medical Research Lab	5	Sorsogon MMG Hospital and Health Services Cooperative
	National TB Reference Laboratory	6	Dr. Pablo O. Torre Memorial Hospital
CAR	Baguio General Hospital & Medical Center	10	CDO Polymedic Medical Plaza
1	Region I Medical Center	12	Dr. Arturo Pingoy Medical Center
2	DOH-Region II TB Laboratory		
3	DOH- Region III TB Laboratory		
4-A	Batangas Medical Center		
5	Bicol TB Regional Laboratory		
6	Western Visayas Medical Center		
7	Cebu TB Reference Laboratory		
9	Zamboanga City Medical Center		
10	Northern Mindanao TB Reference Lab		
11	Davao TB Reference Laboratory		
	Davao Regional Hospital		
13	RO XIII TB Culture Laboratory		

Reference: National TB Reference Laboratory

APPENDIX C: List of Xpert® MTB/Rif Centers in the Philippines under the NTP Laboratory Network as of December 2015

NOTE: All referrals for Xpert® MTB/Rif under the NTP Laboratory Network should be endorsed by a TB-DOTS Providing or Referring Hospital, DOTS Clinic, health center or rural health unit.

NCR
Caloocan City QA Center
Dr. Elvira Lagrosa
Dr. Jose N. Rodriguez Memorial Hosp.
E.Aldana Health Center
East Avenue Medical Center
Gat. Andres Bonifacio Memorial Medical Center
Lacson HC and HTC
Lung Center of the Philippines (LCP)
Manila Public Health Lab.
Marikina City Health Office
Moonwalk Health Center
National Bilibid Hospital (ICRC)
National Children's Hospital
National Tuberculosis Reference Laboratory
North Daang Hari Super Health Center
Pasig City General Hospital
Philippine Orthopedic Center
Philippine Tuberculosis Society Inc. (PTSI)
Quezon City Jail
San Lazaro Hospital (SLH)
San Lorenzo Ruiz Women's Hospital
Tondo Foreshore HC
Tropical Disease Foundation (TDF)
Tumana Navotas Xpert Site
Tunasan PPMD
UP – Philippine General Hospital
V. Luna General Hospital (AFRIMS)
Valenzuela Medical Center
Welfareville HC - Mandaluyong City Health Lab.

CAR
Baguio General Hospital and Medical Center
Abra Provincial Hospital
Amma Jadsac District Hospital
Benguet PHO
Bontoc General Hospital
Kalinga Provincial Hospital
Panopdopan District Hospital

Region 1
Ilocos Training & Regional Medical Center
Bantay MHO
Batac City Health Office
Ilocos Sur Provincial Hospital-Gabriela Silang
Region 1 Medical Center
Urdaneta District Hospital

Region 2
RO II TB Culture Laboratory
Southern Isabela General Hospital
Veterans Regional Hospital

Region 3
Paulino J. Garcia Memorial Research & Medical Center
Bataan General Hospital
Bulacan Medical Center
Dinalupihan Rural Health Unit II STC
Iba Rural Health Unit
Jose B. Lingad Memorial Regional Hospital
Maria Aurora Community Hospital
Olongapo City Health Office
Pampanga San Jose Birthing Station 3
RHU 1 Guimba Satellite Treatment Center
RHU 1 Mabalacat
RHU Lourdes Sur East
RO III TB Culture Laboratory
Rogaciano M. Mercado Memoorial Hospital
San Jose City General Hospital
Tarlac Provincial Hospital

Region 4A
Batangas Medical Center
Antipolo City Health Office
Binangonan GX Site
Bondoc Peninsula District Hospital
Cainta Municipal Health Hospital
CHO Calamba
De La Salle Health Sciences Institute (DLSHSI)
General Emilio Aguinaldo Memorial Hospital
Gumaca District Hospital
Lipa City DOTS Clinic
Los Banos Rural Health Unit
Naic RHU
Quezon Medical Center
Rodriguez CCH-RHU
San Juan RHU
Sta. Rosa City Health Office I
Taal RHU
Tanay GX Site

Region 4B
Oriental Mindoro Provincial Hospital
CHO Palawan - PPC Community Base -Detect TB
CHO Palawan Facility Base -Detect TB
Narra RHU
Northern Palawan Provincial Hospital- Facility Base (Detect TB)
Oriental Mindoro Southern District Hospital
Ospital ng Palawan -Facility Base
PHO Palawan Mobile Bus (Detect TB)- Community Base
Romblon Provincial Hospital
Southern Palawan Provincial Hospital- Facility Base (Detect TB)

Region 5
Bicol Medical Center
Bicol Diagnostic and Reference Lab.
Sorsogon Medical Mission Group of Hospital

Region 6
Dr. Rafael S. Tumbokon Memorial Hospital
Bacolod City Health Office (UNITAID)
Roxas City Health Office
San Carlos City Health Office
San Jose Rural Health Unit
Teresita L. Jalandoni Provincial Hospital
Western Visayas Medical Center

Region 7
Bohol Provincial Health Office
Bogo City Health Office
Car Car Provincial Hospital
Cebu City Health Office (QA Center)
Cebu TB Reference Laboratory
Don Emilio Del Valle Memorial Hospital
Eversly Child's Sanitarium (ECS), Mandaue City
Negros Oriental Provincial Hospital (NOPH)

Region 8
Eastern Samar Provincial Hospital
Calbayog City Health Office
Eastern Visayas Regional and Medical Center
Northern Samar Provincial Hospital
Ormoc City Health Office
RO VIII TB Culture Laboartory
Salvacion Oppus Yniguez Memorial Provincial Hospital

Region 9
Dr. Jose Rizal Memorial Hospital
Margosatubig Regional Hospital
Zamboanga City Medical Center

Region 10
Iligan Society of Internist
Bukidnon Provincial Medical Center (BPMC)
Mayor Hilarion A. Ramiro Senior Regional Teaching and Training Hospital
Northern Mindanao TB Reference Laboratory
Xavier University

Region 11
Davao Regional Medical Center (former DRH)
Davao Chest Center
Davao Del Sur Provincial Hospital

Davao Malita Satellite Treatment Center
Davao Oriental Provincial Medical Center
Davao TB Reference Laboratory

Region 12
Cotabato Regional Medical Center
General Santos City Hospital
Koronadal City Health Office

Region 13
Butuan Medical Center
Adela Serra Ty Medical Center
Agusan Del Norte Provincial Health Office- PPMD
Bislig District Hospital
Democrito O. Plaza Memorial Hospital
DOH XIII TB Culture Laboratory

ARMM
Sulu Provincial Hospital

APPENDIX D: ICD 10 Codes for Tuberculosis Cases (for PhilHealth)

ANATOMIC SITE	DIAGNOSTIC CRITERIA	DEFINITION OF TERMS		ICD 10 CODE/S
Pulmonary (PTB)	**Bacteriologically confirmed**	Smear-positive	A patient with at least one (1) sputum specimen positive for AFB, with or without radiologic abnormalities consistent with active TB	A 15.0
		Culture-positive	A patient with positive sputum culture for MTB complex, with or without radiologic abnormalities consistent with active TB	A 15.1 Note: if confirmed by both culture and smear, code should be A 15.0
		Rapid Diagnostic test-positive	A patient with sputum positive for MTB complex using rapid diagnostic modalities such as Xpert ÒMTB/ Rif, with or without radiographic abnormalities consistent with active TB	A 15.0
	Clinically diagnosed	A patient with two (2) sputum 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 TBDC and/or physician) to have TB disease activity requiring a full course of anti-TB chemotherapy OR A child (<15y/o) with two (2) sputum specimens negative for AFB or with smear not done, who fulfills three (3) of the five (5) criteria for disease activity namely: signs and symptoms suggestive of TB; exposure to an active TB case; positive tuberculin test; abnormal chest radiograph suggestive of TB; and other laboratory findings suggestive of tuberculosis 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 patient with laboratory or strong clinical evidence for HIV/AIDS with two (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 activity requiring a full course of anti-TB chemotherapy		A 16.0 (if smear or MTB culture was done but negative) A 16.1 (if smear or culture was not done) For cases of clinically diagnosed PTB resulting from HIV, the following codes shall be used: B20.0, A16.0 (if smear or culture negative) B20.0, A16.1 (if smear or culture not done) B20.0, A16.2 (without mention of smear or culture confirmation)
Extra-pulmonary (EPTB)	Bacteriologically confirmed	A patient with a smear/culture/new diagnostic test from a biological specimen in an extra-pulmonary site (i.e., organs other than the lungs) positive for AFB or MTB complex		A15.4 – A15.6, A15.8 Note: 4th character of ICD 10 Code depends on the site
	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		A16.3 – A16.6, A16.8, A17-A19

http://www.philhealth.gov.ph/circulars/2014/annexes/circ14_2014/annex2ICD10CodesForTbCases.pdf

APPENDIX E: The World Health Organization (WHO) END TB Strategy

VISION	A WORLD FREE OF TB (ZERO DEATHS, DISEASE, AND SUFFERING DUE TO TB)			
GOAL	**End the global TB epidemic**			
INDICATORS	**Milestones**		**Targets**	
	2020	2025	SDG 2030	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100,000)	50% (<55/100,000)	80% (<20/100,000	90% (<10,000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero
PRINCIPLES				
Government stewardship and accountability, with monitoring and evaluation Strong coalition with civil society organizations and communities Protection and promotion of human rights, ethics and equity Adaptation of the strategy and targets at country level, with global collaboration				
PILLARS AND COMPONENTS				
1. INTEGRATED, PATIENT-CENTERED CARE AND PREVENTION A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support C. Collaborative TB/HIV activities and management of co-morbidities D. Preventive treatment of persons at high risk, and vaccination against tuberculosis				
2. BOLD POLICIES AND SUPPORTIVE SYSTEMS A. Political commitment with adequate resources for tuberculosis care and prevention B. Engagement of communities, civil society organizations, and public and private care providers C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control D. Social protection, poverty alleviation and actions on other determinants of tuberculosis				
3. INTENSIFIED RESEARCH AND INNOVATION A. Discovery, development and rapid uptake of new tools, interventions and strategies B. Research to optimize implementation and impact, and promote innovations				

A joint initiative of the Philippine Coalition Against Tuberculosis (PhilCAT),
the Philippine Society for Microbiology and Infectious Diseases (PSMID),
the Philippine College of Chest Physicians (PCCP)
and the Department of Health (DoH)

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