TB Innovations & Health Systems Strengthening Project

20 May 2021

Active Drug Safety Monitoring and Management (aDSM) in the Philippines

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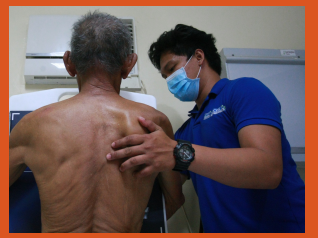
TB/DR-TB Technical Advisor

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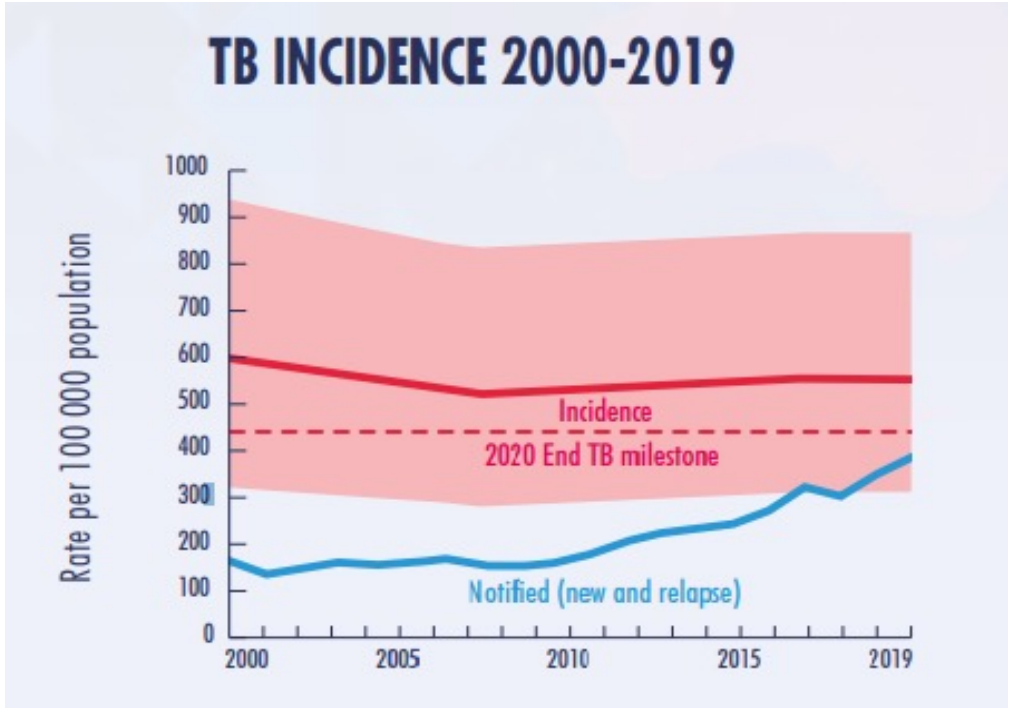
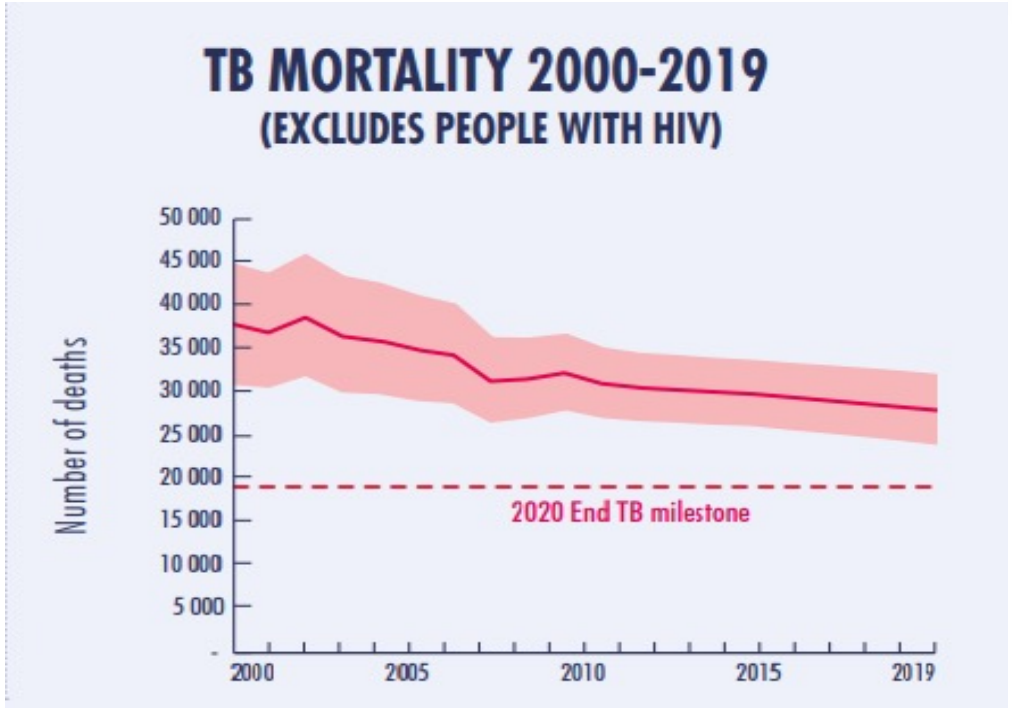
Outline of the Presentation

- Burden of tuberculosis (TB) in the Philippines
- Key challenges in the implementation of the Programmatic Management of Drug-Resistant TB (PMDT)
- Active TB-Drug Safety Monitoring and Management (aDSM) Framework
- Essential Activities of aDSM
- Status of aDSM implementation – progress made so far

Burden of TB in the Philippines



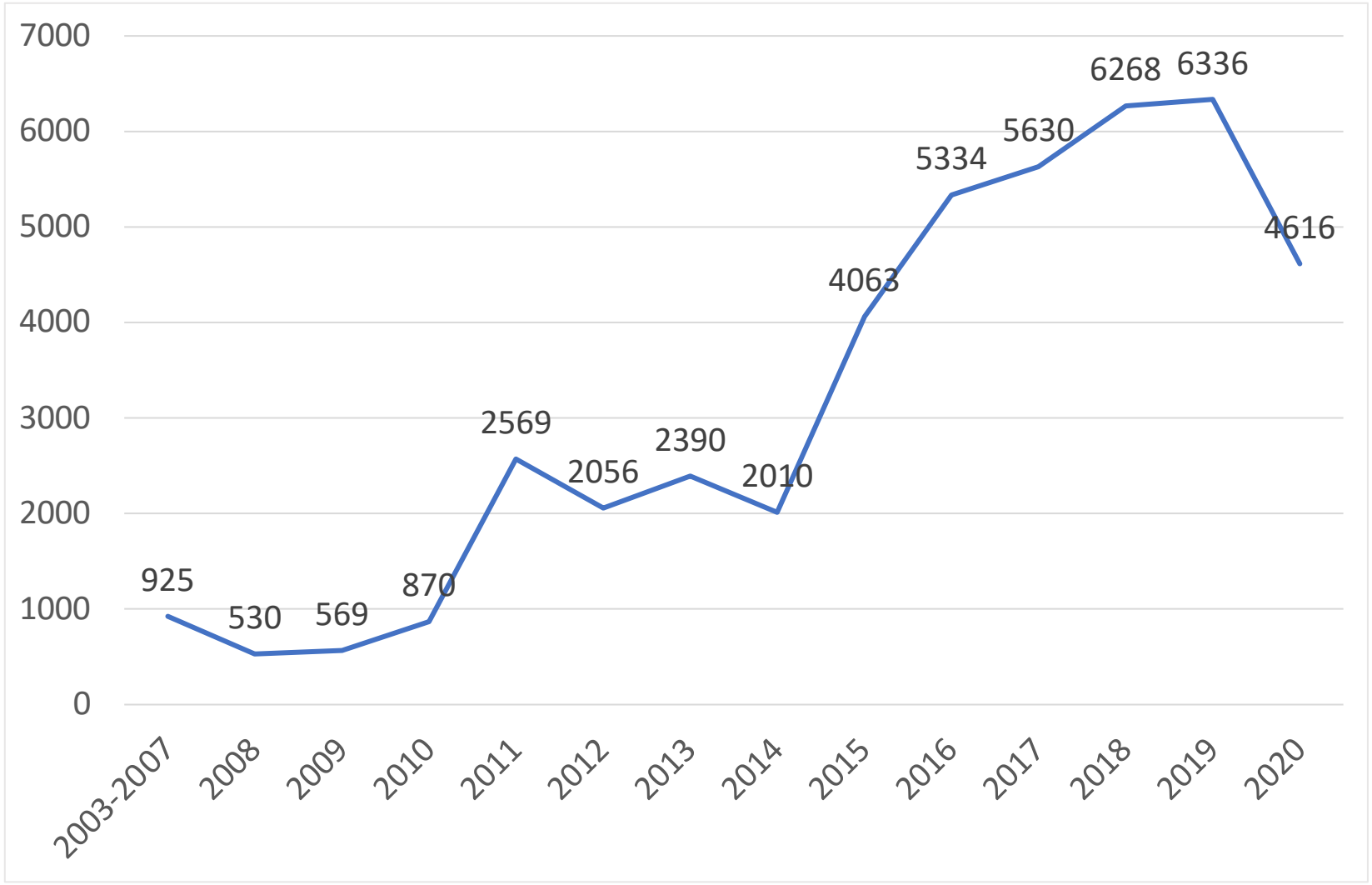


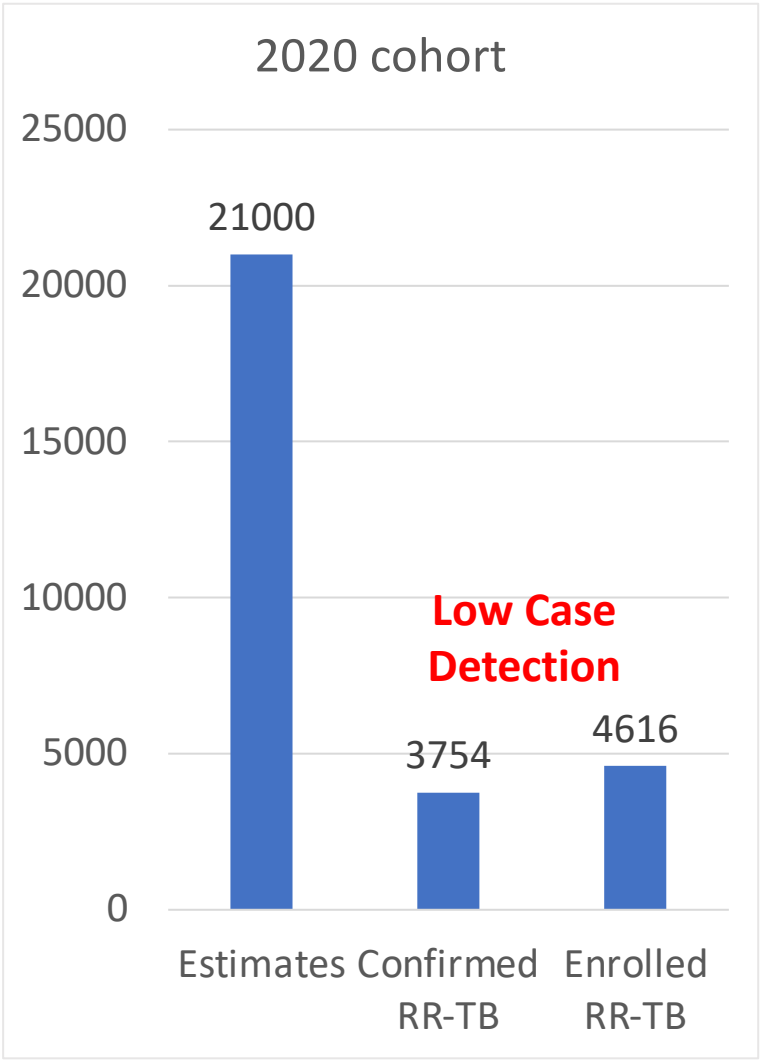
Total TB Incidence:
554 per 100,000 population

MDR/RR-TB Incidence:
19 per 100,000 population

HIV-negative TB mortality:
25 per 100,000 population

Key Challenges in PMDT Implementation (1)

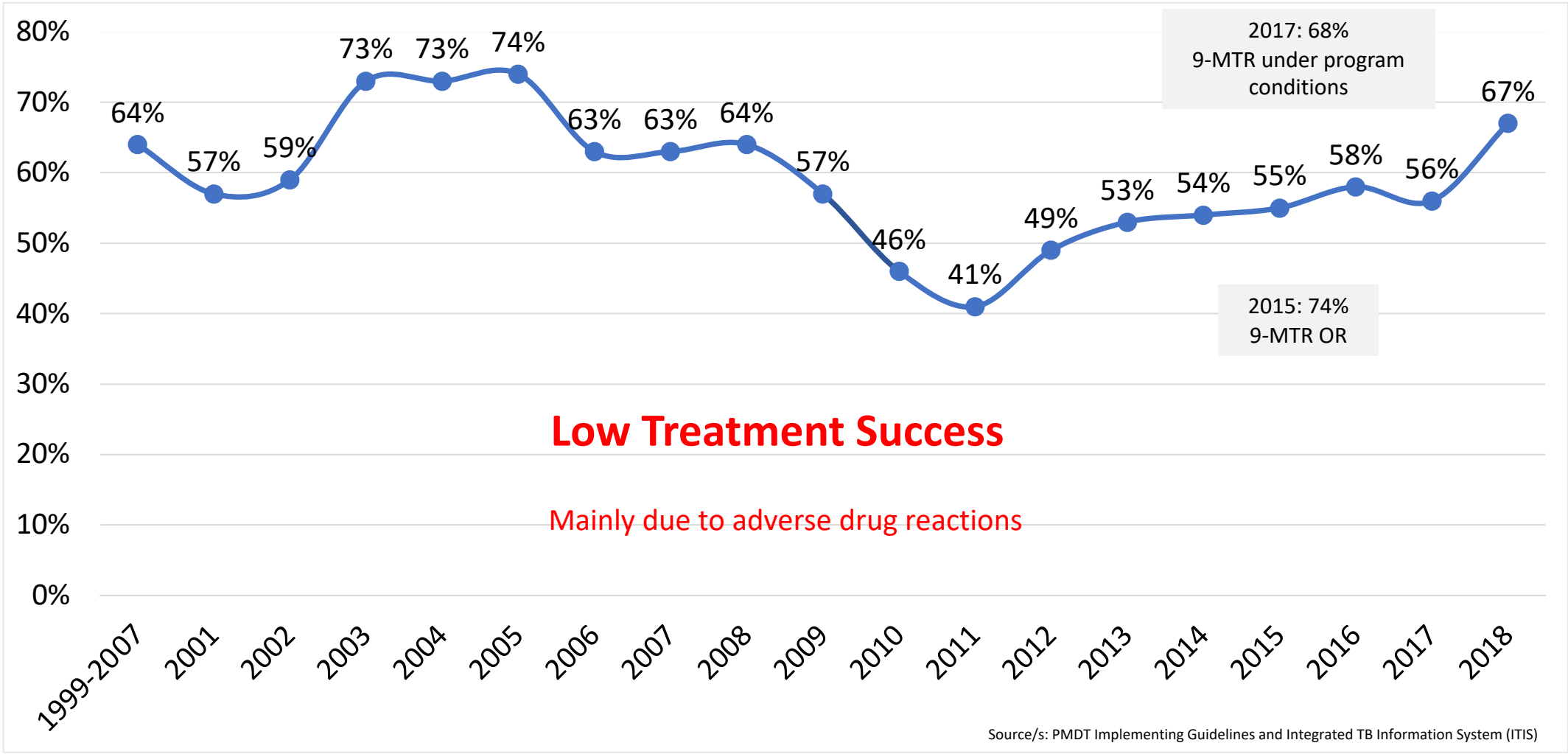




Trend of Enrolment under PMDT, Philippines, 2003-2020

Source/s: PMDT Implementing Guidelines and Integrated TB Information System (ITIS)

Key Challenges in PMDT Implementation (2)



Trend of Treatment Success Rate under PMDT, Philippines, 1999-2018

To ensure successful treatment outcome of patients with DR-TB….

Key Strategies

- Establishment of Health Care Provider Network (HCPN) offering full TB care continuum
- Adoption of patient-centered care
- **<u>Strengthen active Drug Safety Monitoring and Management (aDSM)</u>**
- TB-HIV collaboration

Updated PhilSTEP1: ≥85% TSR by 2023

Policies and Guidelines on aDSM

Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

September 23, 2016

ADMINISTRATIVE ORDER
No. 2016 - 0040

Subject: Revised Policies and Guidelines on the Implementation of the Programmatic Management of Drug-Resistant TB (PMDT)

Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

JUN 02 2020

ADMINISTRATIVE ORDER
No. 2020 - 0025

SUBJECT: Policy and Guidelines on the Implementation of Active Drug Safety Monitoring and Management (aDSM) of the National Tuberculosis Control Program (NTP)

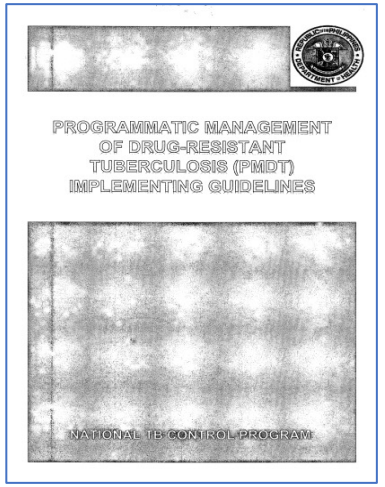
Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

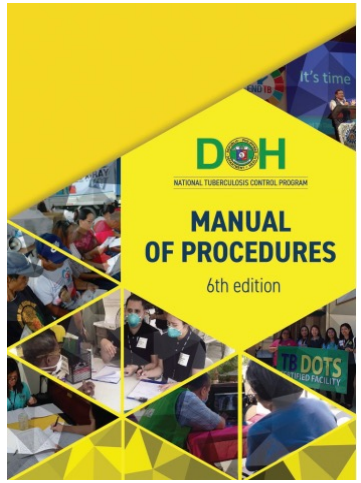
March 18, 2020

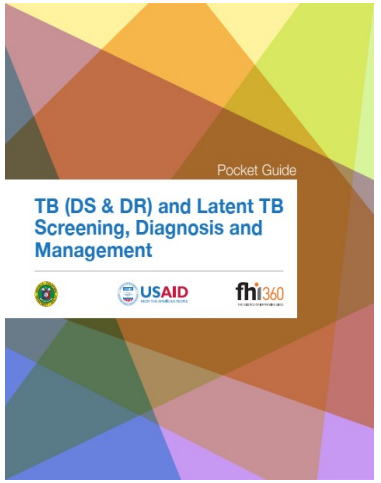
DEPARTMENT MEMORANDUM
No. 2020- 0177

TO : BANGSAMORO AUTONOMOUS REGION IN MUSLIM MINDANAO (BARMM) MINISTER OF HEALTH AND ALL DIRECTORS OF THE DEPARTMENT OF HEALTH CENTERS FOR HEALTH DEVELOPMENT (CHD), AND CHIEFS OF HOSPITALS WITH PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TB (PMDT) TREATMENT FACILITY

SUBJECT: Reiteration of Policy on the Implementation of Active TB drug-safety monitoring and management (aDSM)







aDSM Framework

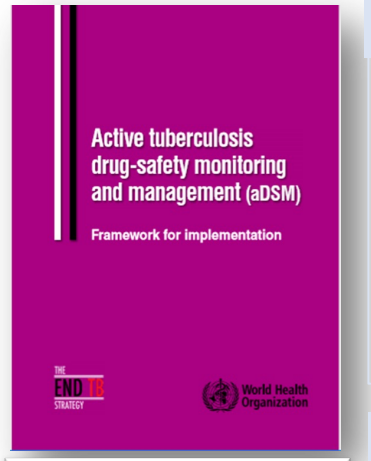
"**Active** and **systematic clinical** and **laboratory assessment** of patients while on treatment"

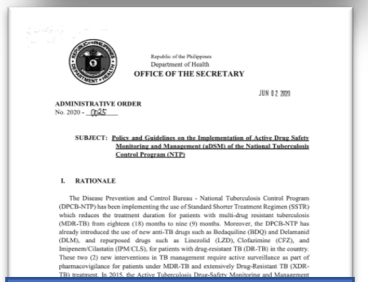
Objectives

- To **minimize the risks** associated with treatment
- To **inform future policy and guideline updates** on treatment of TB

Key Activities

- **Active and systematic clinical and laboratory assessment** during treatment to detect adverse events (AEs)
- **Management of AEs** in a timely manner
- **Systematic collection of standardized data** for AEs




Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY
ADMINISTRATIVE ORDER
SUBJECT: Policy and Guidelines on the Implementation of Active Drug Safety Monitoring and Management (aDSM) of the National Tuberculosis Control Program (NTP)
I. RATIONALE

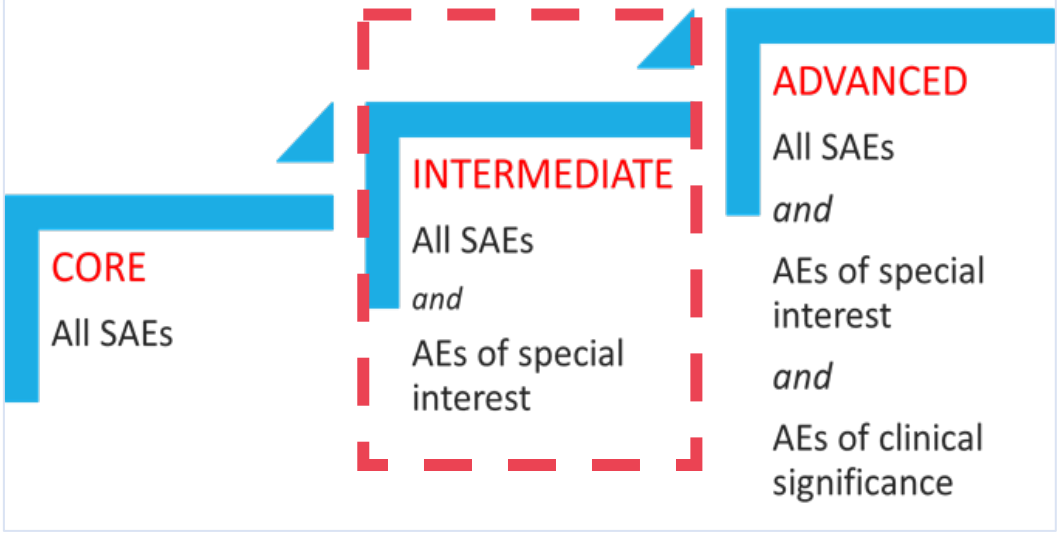
Policy and Guidelines on the Implementation of aDSM of the NTP

Applicability

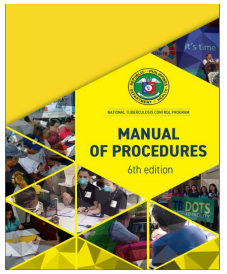
Patients with TB receiving:

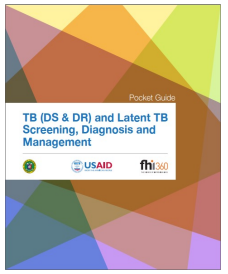
- **New anti-TB drugs**
- **Repurposed drugs**
- **Novel regimens**

Levels of Monitoring



Essential Activity 1:
Active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs





RR/MDR-TB Treatment Monitoring

1. Schedule of baseline and follow-up clinical, laboratory and bacteriologic examination for patients on standard short treatment regimen (SSOR/ SSTR)

		Intensive Phase: 4 months, may be extended up to 6 months				Continuation Phase: 5 months					Post-Treatment Follow-up	
Test/Examination	Baseline	M1	M2	M3	M4	M5	M6	M7	M8	M9	P6	P12
Clinical Evaluation by the PMDT Physician including weight for all and height for children	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mycobacteriological Tests												
Smear Microscopy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB Culture(TBC)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug Susceptibility Testing (DST)	✓	If culture remains positive at month 4 of treatment, in case of culture reversion or culture positive during post-treatment follow-up										
First-line and Second-line Line Probe Assay (LPA)	✓											
Diagnostic Tests												
Chest X-ray (CXR)	✓						✓				✓	✓
Electrocardiogram (ECG)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Visual Acuity and Color Vision	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Brief Peripheral Neuropathy Screening (BPNS)	✓	✓	✓	✓	✓							
Mental health screening	✓	Monthly if regimen contains Cycloserine (Patient Health Questionnaire-9 or short screening tool may be used)										
Audiometry	✓	Monthly while on injectable (SSTR)										
Blood Chemistry/Hematology/Immunological Tests												
Alanine and Aspartate Transaminase (ALT/AST) *	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Complete Blood Count (CBC)	✓	Monthly if regimen contains Linezolid										
Urea Nitrogen, Creatinine, Fasting Blood Sugar (FBS), Potassium (K),	✓											
Thyroid Stimulating Hormone (TSH)	✓						✓					
HIV Rapid Antibody Test	✓											
Pregnancy Test	✓											

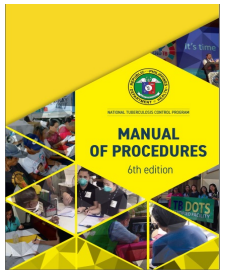
*If ALT and AST are higher than upper limit of normal value, consider doing total bilirubin test.

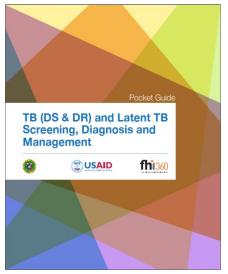
2. Schedule of baseline and follow-up Clinical, Laboratory and Bacteriologic Examinations for Patients on 18-20 months treatment regimens

		Intensive Phase: 6 months						Continuation Phase: 12-14 months														Post-Treatment Follow-up	
Test/ Examination	Base-line	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	P6	P12
Clinical Evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mycobacteriology Tests																							
Smear Microscopy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB Culture(TBC)	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓	✓
DST	✓	If culture remains positive at month 4 of treatment, in case of culture reversion or culture positive during post-treatment follow-up																					
LPA	✓																						
Diagnostic Tests																							
CXR	✓						✓						✓						✓			✓	✓
ECG	✓	Monthly if regimen contains Bedaquiline, Delamanid, Clofazimine and/or Moxifloxacin																					
Visual Acuity and Color Vision	✓	Monthly if regimen contains Linezolid and/or Ethambutol																					
BPNS	✓	Monthly if regimen contains Linezolid, Cycloserine and/or High Dose Isoniazid																					
Audiometry	Baseline and Monthly if regimen contains Amikacin or Streptomycin																						
Mental health screening	Baseline and Monthly if regimen contains Cycloserine (Patient Health Questionnaire-9 or short screening tool may be used)																						
Blood Chemistry/Hematology/Immunological Tests																							
ALT/AST*	✓	Monthly if regimen contains Bedaquiline and/or Pyrazinamide																					
CBC	✓	Monthly if regimen contains Linezolid																					
FBS,	✓																						
Urea Nitrogen, Creatinine, K	✓	Monthly if regimen contains Amikacin or Streptomycin																					
TSH	✓	Every 6 months if regimen contains Prothionamide or Para-aminosalicylic Acid (PAS) Every 3 months if regimen contains both Prothionamide and Para-aminosalicylic Acid (PAS)																					
Albumin	Baseline if regimen contains Delamanid																						
HIV Rapid Antibody Test	✓																						
Pregnancy Test	✓																						

* If ALT and AST are higher than upper limit of normal value, consider doing total bilirubin test. If regimen contain Bdq+Dlm and/ or Mfx+Cfz, more frequent ECG monitoring, every other week for initial 3 months is recommended.

Essential Activity 2:
Management of AEs in a timely manner





Management of Hepatotoxicity

Possible Causative anti-TB Drugs: **Z, H, R, Pto/** Eto, PAS, Bdq, Ofz, Dlm

Presence of Hepatitis S/S:
(nausea,vomiting, abdominal pain, dark urine, jaundice, pale stool, anorexia)
and/ or
ALT/ AST done on regular follow up

Check AST, ALT

- **Normal** → Continue monthly monitoring
- **• >3x ULN • NO Hepatitis S/S** → Investigate for other causes[1] and DO Laboratory tests and diagnostics[2]
- **• >3x ULN • WITH Hepatitis S/S** → Investigate for other causes[1] and DO Laboratory tests and diagnostics[2]
- **• >5x ULN • WITH/NO Hepatitis S/S** → Investigate for other causes[1] and DO Laboratory tests and diagnostics[2]

PRESENCE of other liver disease → Refer to Gastroenterologist for co-management

- CONTINUE anti-TB drugs
- DO Weekly LFTs
- DO Total Bilirunin

Normal ALT/ AST → Continue monthly monitoring

AST/ALT >3x ULN • Total Bilirunin >2x ULN →
- STOP all anti TB drugs
- REPEAT LFTs after 1 week
- CONSULT TB MAC

Normal/decreasing ALT/ AST
- RESUME 3 not/ least hepatotoxic LED[3]s
- REPEAT AST/ALT after 1 week
- CONSULT with TB MAC

Normal/decreasing AST/ AST
- REINTRODUCE[4] possible culprit drugs if still vital in the regimen
- MONITOR ALT/AST q 3 days
- Discontinue culprit drug if AST/ ALT increases
- REFER to TB MAC

AST/ALT >3x ULN repeatedly after 2 weeks

AST/ALT >3x ULN
- REFER to TB MAC
- Refer to specialists for co-management

[1]Alcoholic and Non Alcoholic liver disease, viral hepatitis
[2]Serology tests for Hep A, Hep B (HbsAg, antiHBC) and Hep C, Hepatobiliary ultrasound, etc.
[3]LED - Likely Effective Drugs
[4]Most hepatotoxic (H,Z,R) drugs will be reintroduced using incremental dose starting with the least culprit drug for 3 days. Repeat AST/ALT q3 days prior to adding another drug.

Management of Myelosuppression

(Possible causative anti-TB Drug: **Lzd**)

Presence of any and combination of the following:
- ANEMIA
- LEUKOPENIA
- THROMBOCYTOPENIA

NO → Continue monthly CBC monitoring

YES →
- Investigate for other possible causes:
  - nutritional deficiencies
  - viral infections
  - advanced HIV/AIDS
  - chronic renal insufficiency
  - occult blood loss
  - intestinal parasitism
  - medications other than anti-TB medications (e.g. Azidothymidine, Zidovudine, cotrimoxazole)
  - other causes of myelosuppression
  → Manage Accordingly (clinical assessment and laboratory examinations such as BUN, Crea, Fecalysis with occult blood, etc)
- Determine the Grade of Myelosuppression

GRADE 1
- Hgb 9.5 to 10.5 g/dl
- ANC <1,500 mm3
- Platelet <100,000 mm3

→ • DECREASE Lzd to 300 mg daily • MONITOR CBC weekly

CBC improved or normalized?
- YES → • CONTINUE Lzd at 300 mg daily • MONITOR CBC monthly
- NO → REFER to TB MAC for further management and change in regimen

GRADE 2 and above
- Hgb <9.5.g/dl
- ANC <1,000 mm3
- Platelet <75,000 mm3

→ • STOP Lzd immediately • GIVE erythropoietin with caution (see page 68) • GIVE blood transfusion* • MONITOR CBC weekly

Severity reduced to Grade 1?
- YES → • REINTRODUCE Lzd at 300 mg daily • MONITOR CBC weekly for 2 weeks

CBC improved or normalized?
- NO → • STOP Lzd completely • REPLACE with any of the ff: Dlm, Cs, Pto, injectable
- YES → • CONTINUE Lzd at 300 mg daily • MONITOR CBC monthly

*Given to severity GRADE 4 (Hb of <6.5 g/dL, ANC <500/mm3 or and/or platelet count of <20,000/mm³)

Note: Absolute Neutrophilic Count (ANC) =10 x WBC count in 1000s x (% PMNs + bands)
The following web application may be used to compute for ANC: Calculate by QxMD; MDCalc Medical Calc; Medscape App

Management of Peripheral Neuropathy

(Possible causative anti-TB Drugs: Lzd, H, Cs, S, Am, Lfx, Mfx)

- burning sensation, "pins and needles?"
- numbness of both fingers and toes/feet; worse at night or when walking?
- leg weakness when walking?
- leg cramps or pain?

NO → Continue clinical surveillance

YES →
- Investigate for the following conditions:
  - Diabetes
  - Alcoholism
  - Vitamin Deficiencies
  - HIV
  - Hypothyroidism
  - Uremia
  - taking drugs other than anti-TB?
  → Manage Accordingly (clinical assessment and laboratory examinations such as fasting blood sugar, HbAIC, thyroid function tests, etc)
- Assess according to severity GRADING (using BPNS Tool, See page 40)

YES →

GRADE 1: BPNS Score 1-3 → STOP Lzd, Hhd, and Cs MONITOR BPNS weekly

Symptoms improved?
- YES → • Consider restarting Lzd (300 mg daily) , Cs and Hhd • INCREASE pyridoxine to 200 mg daily
- NO → REFER to TB MAC for further management and change in regimen

GRADES 2 and 3: BPNS Score ≥4 → STOP Lzd, Hhd, and Cs MONITOR BPNS weekly

Symptoms improved?
- YES → • Consider restarting Cs and Hhd • DO NOT reintroduce Lzd • INCREASE pyridoxine to 200 mg daily • May PROVIDE other ancillary drugs* with caution
- NO → REFER to TB MAC for further management and change in regimen

*Other ancillary drugs
- Gabapentin 300 mg daily
- Amitriptyline 25 mg at bedtime (for adult only; use with caution if with cardiac, hepatic, renal and thyroid pathology; avoid concomitant use with Lzd due to concern of Serotonin Syndrome)

Note: Peripheral neuropathy may be irreversible. However, many patients experience **improvement when offending drugs are suspended, especially if the symptoms are mild.**

Essential Activity 3:
Systematic collection and reporting of standardized data for SAE and AESI

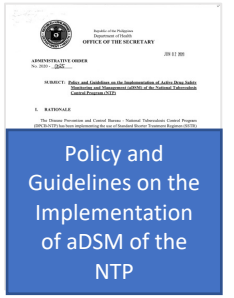
What to Report

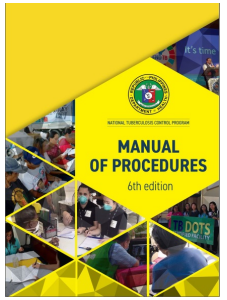
Serious AE – Any untoward medical occurrence that at any dose:

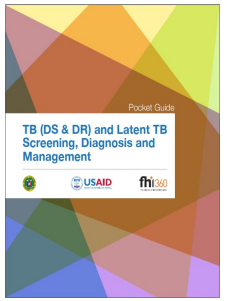
- Results in death
- Is life threatening
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- AEs that do not immediately result in one of these outcomes, but which require an intervention to prevent a serious outcome are included

AEs of Special Interest

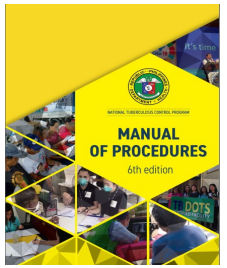
- Acute kidney injury
- Hepatitis
- Hypokalemia
- Myelosuppression
- Optic Nerve Disorder
- Ototoxicity
- Pancreatitis
- Peripheral Neuropathy
- Prolonged QT interval (using Fridericia Formula)
- Psychiatric Disorders and CNS toxicity

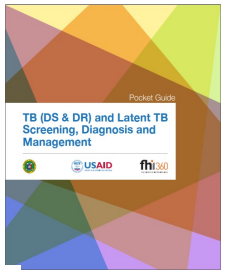




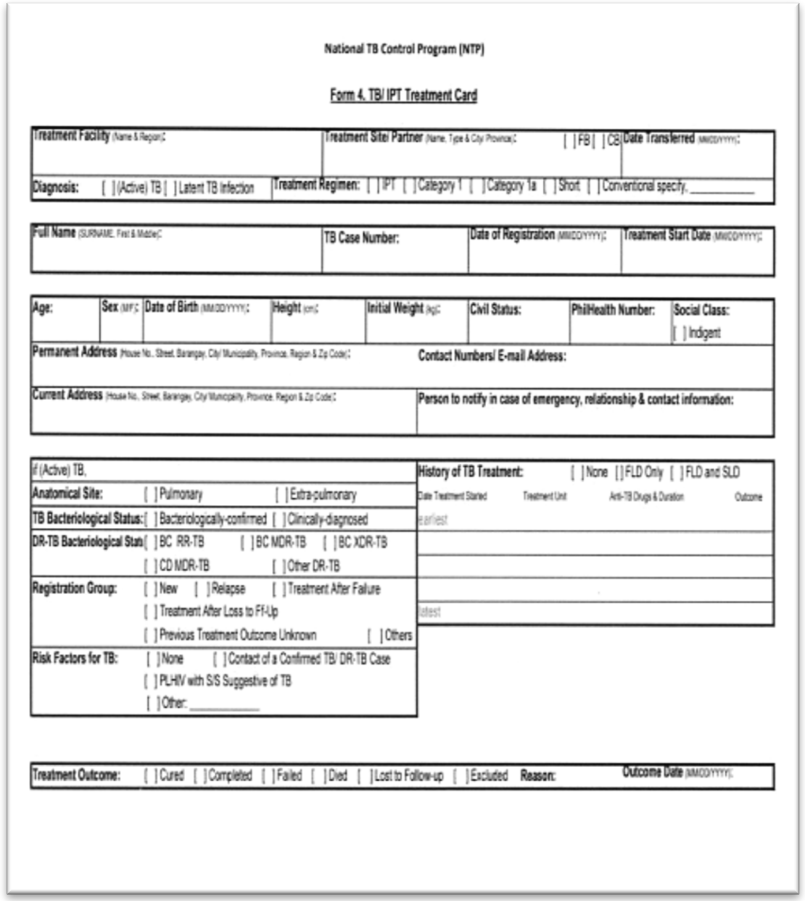


Essential Activity 3:
Systematic collection and reporting of standardized data for SAE and AESI





How to Report



National TB Control Program (NTP)

Form 4. TBI IPT Treatment Card

Treatment Facility (Name & Region): | Treatment Site/ Partner (Name, Type & City/ Province): [ ] FB [ ] CB | Date Transferred (MM/DD/YYYY):

Diagnosis: [ ] (Active) TB [ ] Latent TB Infection | Treatment Regimen: [ ] IPT [ ] Category I [ ] Category Ia [ ] Short [ ] Conventional specify: _____

Full Name (SURNAME, First & Middle): | TB Case Number: | Date of Registration (MM/DD/YYYY): | Treatment Start Date (MM/DD/YYYY):

Age:	Sex (M/F):	Date of Birth (MM/DD/YYYY):	Height (cm):	Initial Weight (kg):	Civil Status:	PhilHealth Number:	Social Class: [ ] Indigent

Permanent Address (House No., Street, Barangay, City/ Municipality, Province, Region & Zip Code): | Contact Numbers/ E-mail Address:

Current Address (House No., Street, Barangay, City/ Municipality, Province, Region & Zip Code): | Person to notify in case of emergency, relationship & contact information:

If (Active) TB,

Anatomical Site: [ ] Pulmonary [ ] Extra-pulmonary

TB Bacteriological Status: [ ] Bacteriologically-confirmed [ ] Clinically-diagnosed

DR-TB Bacteriological Stat: [ ] BC RR-TB [ ] BC MDR-TB [ ] BC XDR-TB [ ] CD MDR-TB [ ] Other DR-TB

Registration Group: [ ] New [ ] Relapse [ ] Treatment After Failure [ ] Treatment After Loss to F/-Up [ ] Previous Treatment Outcome Unknown [ ] Others

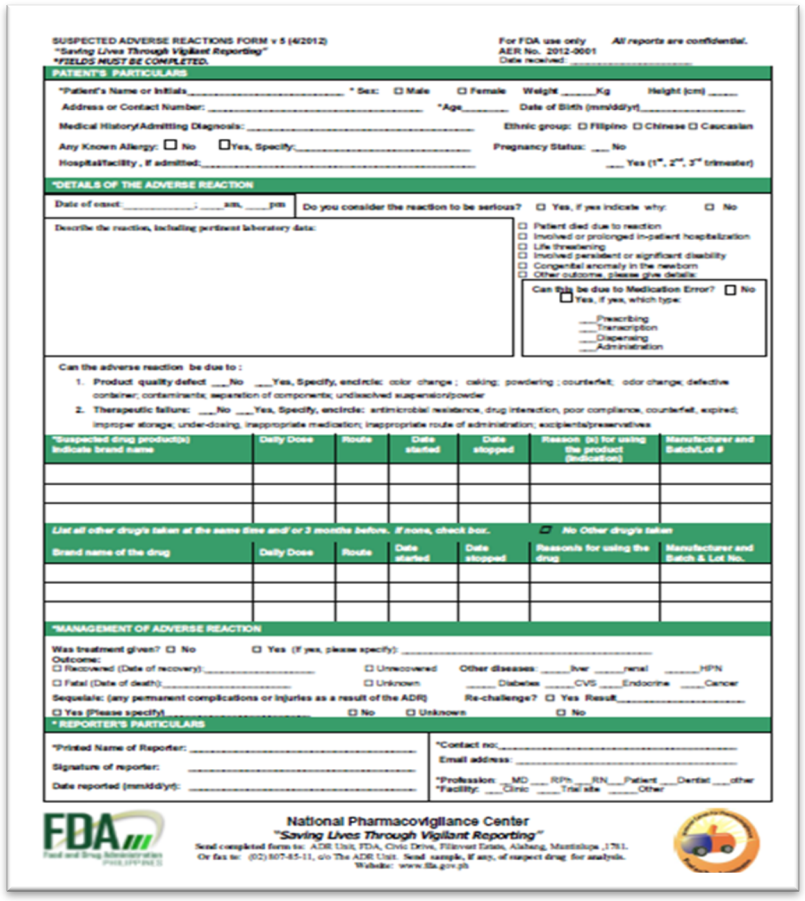
Risk Factors for TB: [ ] None [ ] Contact of a Confirmed TB/ DR-TB Case [ ] PLHIV with S/S Suggestive of TB [ ] Other: _____

History of TB Treatment: [ ] None [ ] FLD Only [ ] FLD and SLD

Date Treatment Started	Treatment Unit	Anti-TB Drugs & Duration	Outcome
earliest			
latest			

Treatment Outcome: [ ] Cured [ ] Completed [ ] Failed [ ] Died [ ] Lost to Follow-up [ ] Excluded Reason: Outcome Date (MM/DD/YYYY):

NTP TB Treatment Card



SUSPECTED ADVERSE REACTIONS FORM v 5 (4/2012)
"Saving Lives Through Vigilant Reporting"
*FIELDS MUST BE COMPLETED.

For FDA use only. All reports are confidential.
AER No. 2012-0001
Date received: _____

PATIENT'S PARTICULARS

*Patient's Name or Initials _____ * Sex: ☐ Male ☐ Female Weight _____Kg Height (cm) _____
Address or Contact Number: _____ *Age_____ Date of Birth (mm/dd/yr)_____
Medical History/Admitting Diagnosis: _____ Ethnic group: ☐ Filipino ☐ Chinese ☐ Caucasian
Any Known Allergy: ☐ No ☐ Yes, Specify: _____ Pregnancy Status: ___ No
Hospital/Facility , if admitted: _____ ___ Yes (1st, 2nd, 3rd trimester)

*DETAILS OF THE ADVERSE REACTION

Date of onset: _____; ____ am, ____ pm | Do you consider the reaction to be serious? ☐ Yes, if yes indicate why: ☐ No

Describe the reaction, including pertinent laboratory data:

☐ Patient died due to reaction
☐ Involved or prolonged in-patient hospitalization
☐ Life threatening
☐ Involved persistent or significant disability
☐ Congenital anomaly in the newborn
☐ Other outcome, please give details:

Can this be due to Medication Error? ☐ No ☐ Yes, if yes, which type:
___Prescribing
___Transcription
___Dispensing
___Administration

Can the adverse reaction be due to :
1. Product quality defect ___No ___Yes, Specify, encircle: color change ; caking; powdering ; counterfeit; odor change; defective container; contaminants; separation of components; undissolved suspension/powder
2. Therapeutic failure: ___No ___Yes, Specify, encircle: antimicrobial resistance, drug interaction, poor compliance, counterfeit, expired; improper storage; under-dosing, inappropriate medication; inappropriate route of administration; excipients/preservatives

*Suspected drug product(s) indicate brand name	Daily Dose	Route	Date started	Date stopped	Reason (s) for using the product (indication)	Manufacturer and Batch/Lot #

List all other drug/s taken at the same time and/ or 3 months before. If none, check box. ☐ No Other drug/s taken

Brand name of the drug	Daily Dose	Route	Date started	Date stopped	Reason/s for using the drug	Manufacturer and Batch & Lot No.

*MANAGEMENT OF ADVERSE REACTION

Was treatment given? ☐ No ☐ Yes (If yes, please specify): _____
Outcome:
☐ Recovered (Date of recovery): _____ ☐ Unrecovered Other diseases: _____liver _____renal _____HPN
☐ Fatal (Date of death): _____ ☐ Unknown _____Diabetes _____CVS _____Endocrine _____Cancer
Sequela/e: (any permanent complications or injuries as a result of the ADR) Re-challenge? ☐ Yes Result _____
☐ Yes (Please specify) _____ ☐ No ☐ Unknown ☐ No

* REPORTER'S PARTICULARS

*Printed Name of Reporter: _____ *Contact no: _____
Signature of reporter: _____ Email address: _____
Date reported (mm/dd/yr): _____ *Profession: ___MD ___RPh ___RN ___Patient ___Dentist ___other
*Facility: ___Clinic ___Trial site ___Other

FDA Food and Drug Administration PHILIPPINES

National Pharmacovigilance Center
"Saving Lives Through Vigilant Reporting"
Send completed form to: ADR Unit, FDA, Civic Drive, Filinvest Estate, Alabang, Muntinlupa ,1781.
Or fax to: (02) 807-85-11, c/o The ADR Unit. Send sample, if any, of suspect drug for analysis.
Website: www.fda.gov.ph

NATIONAL PHARMACOVIGILANCE CENTER

FDA Suspected Adverse Drug Reactions Form

Pharmacovigilance Monitoring System

Essential Activity 3:
Systematic collection and reporting of standardized data for SAE and AESI

When and Where to Report

Within 2 working days from receipt of information of SAE or AESI

Submit accomplished ADR reports to:

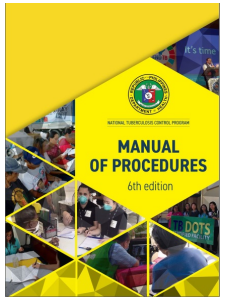
Subject : SAE and AESI Reporting

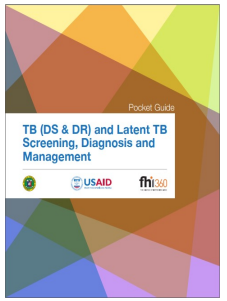
pharmacovigilance@fda.gov.ph
ntp.pharmacovigilance@gmail.com
dohpdpimu@gmail.com

NOTE:

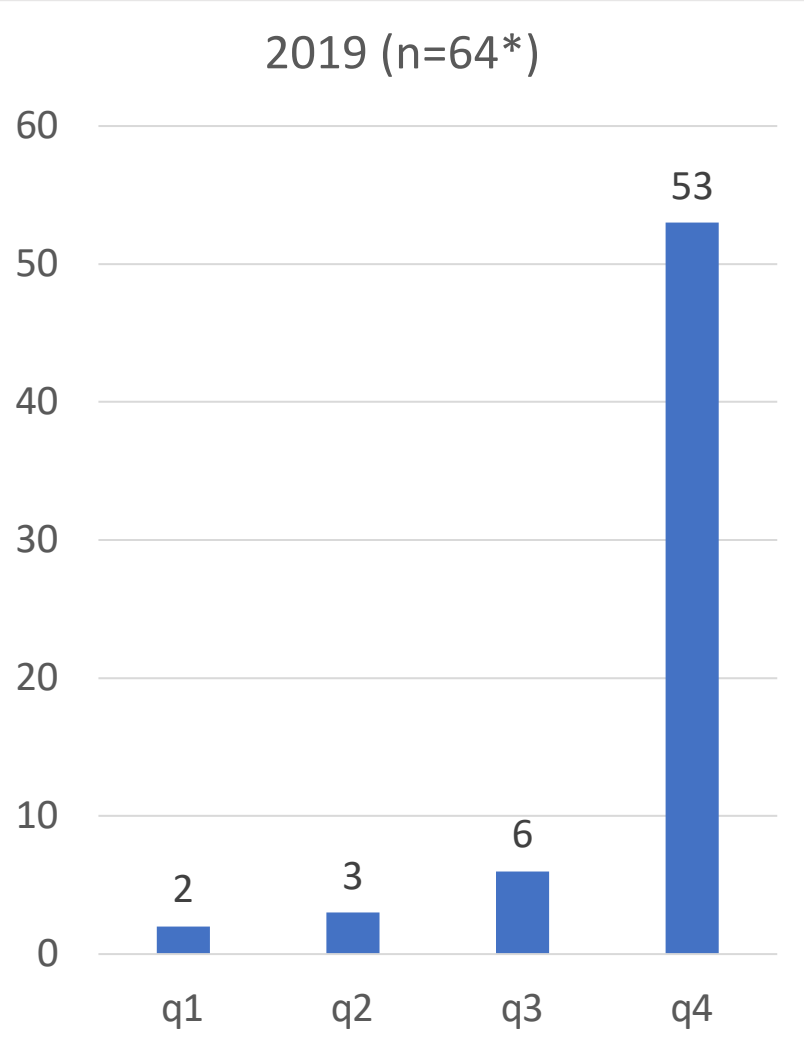
*For updating of cases: Please submit on the same email thread or indicate **Document Tracking Number** provided by FDA.*

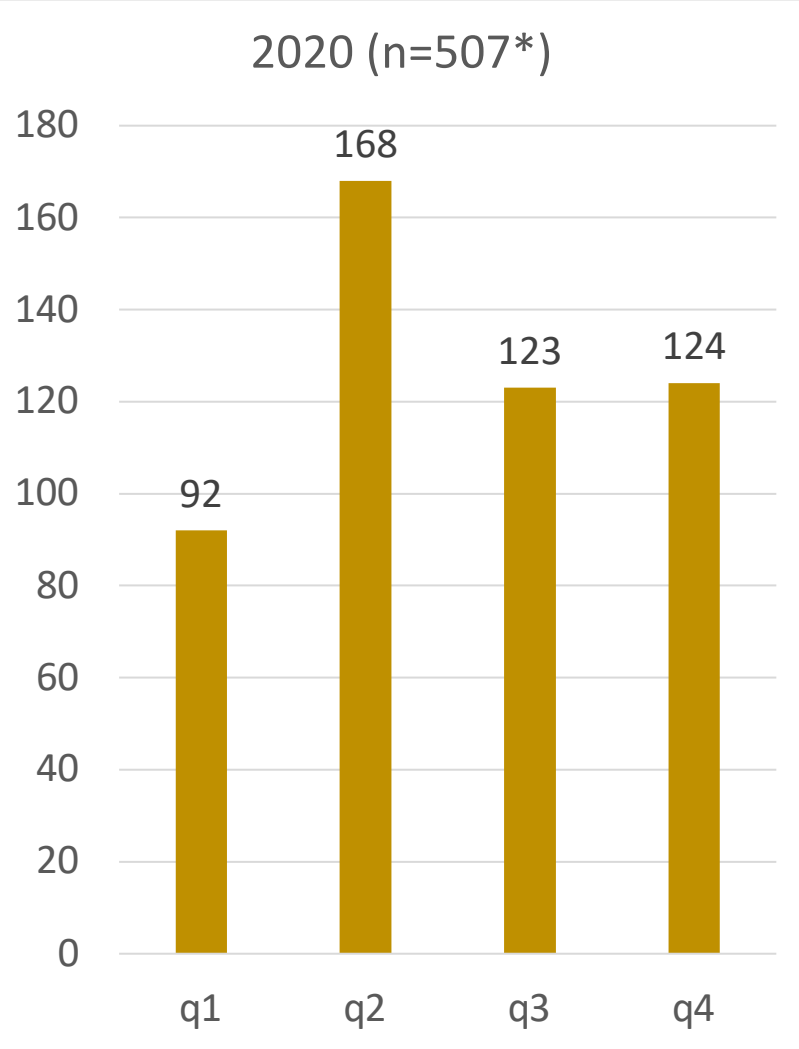
Policy and Guidelines on the Implementation of aDSM of the NTP





Report Submission per Quarter, 2019-2020





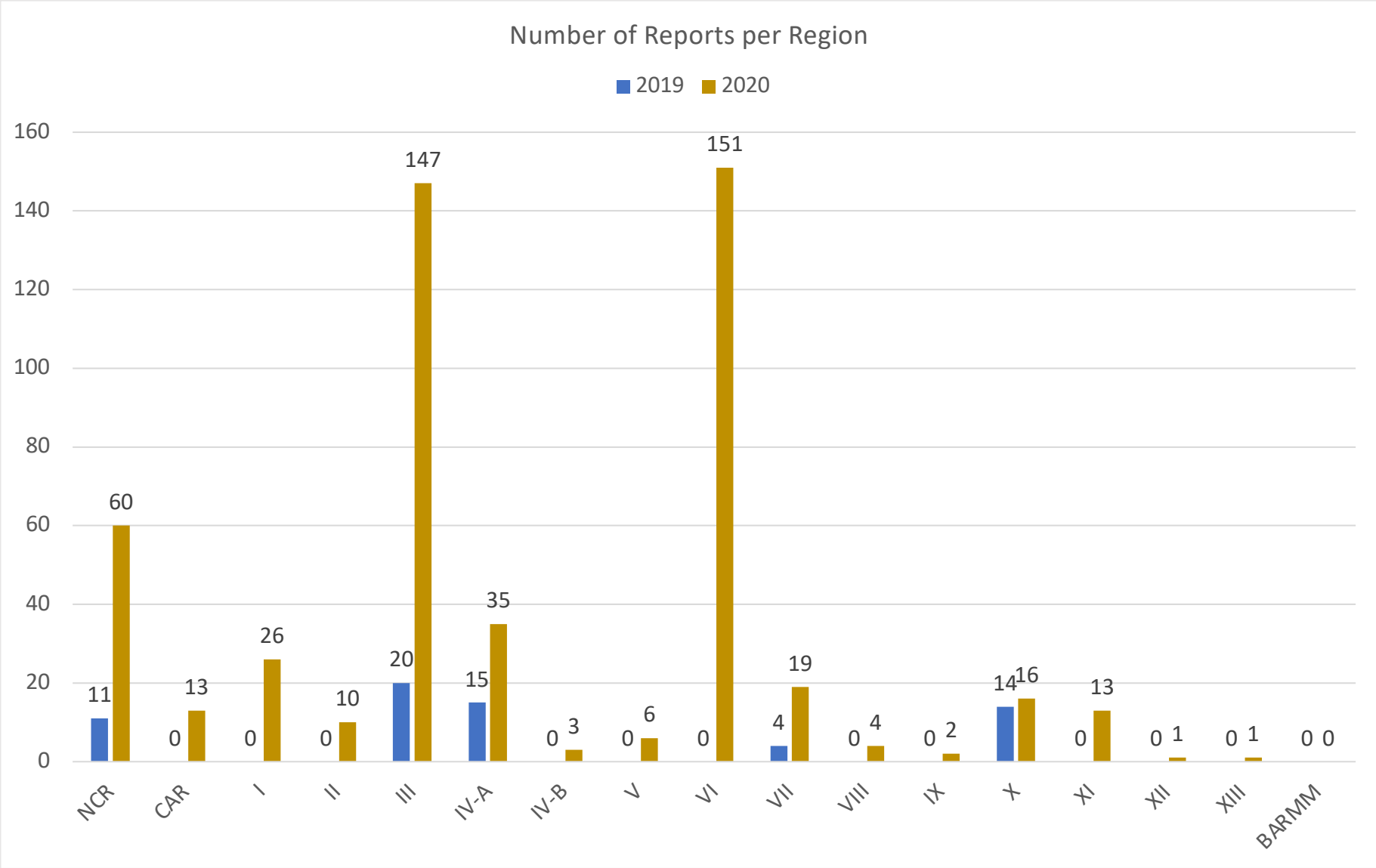
Key Findings:

- Individual cases reported during year 2019 and 2020 show **substantial increase of reported cases**
- Total individual case report forms submitted
  - **2019: 64**
  - **2020: 507**

*Individual Case Report Forms

Source of Data: NTP Excel File of Reports Received

Regional Coverage of Reported Cases, 2019-2020

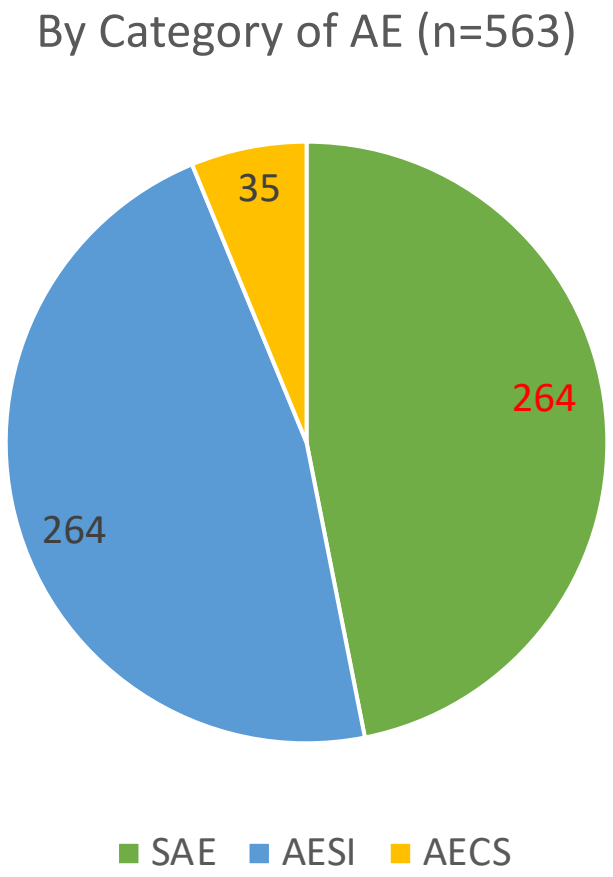


Key Findings:

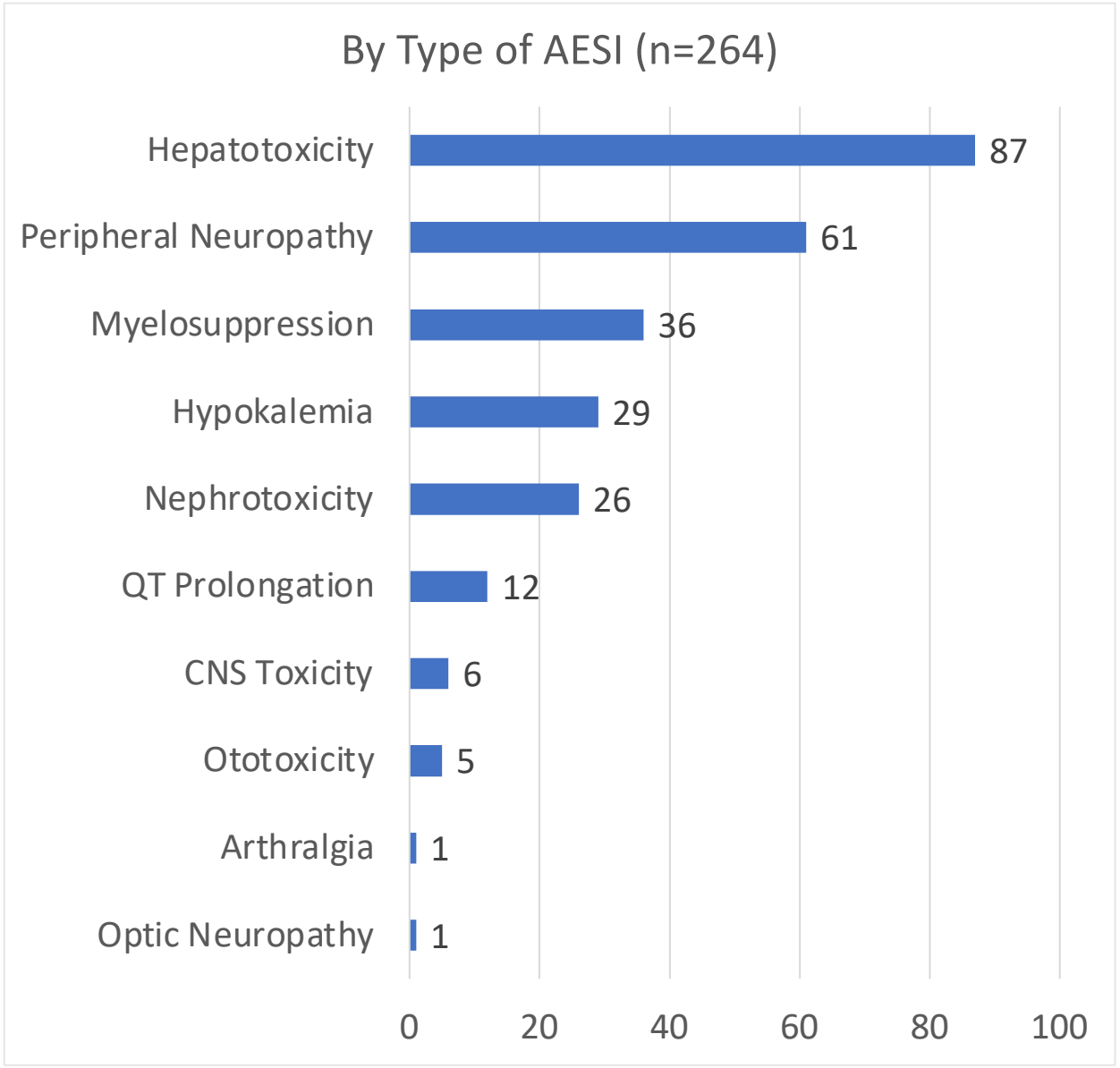
- **Increasing regional trend** of reported cases
- **Regional coverage increased** from 5 (2019) to 16 (2020) regions
- Regions VI, III NCR, and IV-A constituted majority of the reported cases

Source of Data: NTP Excel File of Reports Received

Breakdown of Adverse Events, 2020



Note: May change after initial causality assessment exercise



Source of Data: NTP Excel File of Reports Received


THANK YOU