2021

active Drug Safety Monitoring and Management (aDSM) in Indonesia

A SITUATIONAL ANALYSIS AND RECOMMENDATIONS FOR STRENGTHENING aDSM IMPLEMENTATION

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Technical Assistance Report

Country	Indonesia
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Report type	Final
Type of TA	Development of National Action Plan to strengthen implementation of aDSM for drug-resistant tuberculosis in Indonesia
Key deliverables	1. Report on the situational analysis of PV/aDSM in Indonesia 2. Identification of training needs for aDSM and workshop planning 3. Concept note for strengthening PV/aDSM implementation in Indonesia, including recommendations for future activities, timeline, lessons learned from aDSM implementation, human resources and financial gaps. 4. Presentation of results to NTP, BPOM, WHO/TDR
Purpose	A situational analysis was conducted to assess the progress towards implementation of Active Drug Safety Monitoring and Management (aDSM) within the programmatic management of drug-resistant tuberculosis (PMDT) in Indonesia. The information will be used to develop a Concept Note for strengthening pharmacovigilance within the national TB programme (NTP).
Method	Desktop situational analysis based on: - documents and information provided by the National TB Programme (Subdit Tuberkulosis) and the Indonesia Food and Drug Authority (BPOM) about the implementation of aDSM in Indonesia - a survey of healthcare professionals at DR-TB treatment facilities about aDSM implementation (Annexes 1&2) - virtual meetings with NTP and BPOM to discuss systems and processes for aDSM in Indonesia. - interviews of key people at the NTP, BPOM (conducted by a National Consultant)

Table of Contents

Abbreviations

aDSM	Active Drug Safety Monitoring and Management
BPOM	*Badan Pengawas Obat dan Makanan* (National Food and Drug Agency)
DG DPC	Directorate General of Disease Prevention & Control
DR-TB	drug-resistant tuberculosis
DS-TB	drug-sensitive tuberculosis
e-MESO	*elektronik - Monitoring Efek Samping Obat* (electronic - drug side effects monitoring)
ESO	*Efek Samping Obat* (Adverse Drug Reaction, ADR)
JEMM	Joint External Monitoring Mission for Tuberculosis
JKN	*Jaminan Kesehatan Nasional* (National Health Insurance)
Kemenkes	Ministry of Health
KTD	*Kejadian Tidak Diinginhan* (Adverse Event, AE)
MDR/RR-TB	Multidrug- or rifampicin-resistant TB
NADFC	National Agency of Drug and Food Control
NTP	National Tuberculosis Programme
PFM	*Pretugas Farmasi dan Makanan* (Pharmaceutical and Food Officer)
PMDT	Programmatic Management of Drug-resistant Tuberculosis
Poskesdes	*Pos Kesehatan desa* (village health post)
Puskesmas	*Pusat Kesehatan Masyarakat* (Public Health Centre)
SAE	serious adverse event
SITB	*Sistem Informasi Tuberkulosis* (Tuberculosis Information Systems)
Subdit TB	Sub-Directorate for Tuberculosis
YANKES	*Pelayanan Kesehatan* (Directorate General of Health Services)

Executive summary

Indonesia is implementing Active Drug Safety Monitoring and Management (aDSM) within the programmatic management of drug-resistant tuberculosis (PMDT). aDSM is a clinical safety monitoring method developed by WHO specifically for monitoring new and repurposed TB medicines and regimens within PMDT. The method involves active and systematic clinical and laboratory assessment of patients on DR-TB treatment to detect, manage and report suspected or confirmed drug toxicities. The NTP has chosen to implement the core aDSM package initially, which requires reporting only of serious adverse events.

A desktop situational analysis was conducted to review aDSM progress and to identify potential barriers to effective implementation. The review was conducted remotely and was based on documents and information provided by the National TB Programme (NTP) and the Indonesia Food and Drug Authority (BPOM), a survey of healthcare professionals at DR-TB treatment facilities and discussions with key people at the NTP and BPOM.

The *National Strategy for Tuberculosis Care and Prevention 2020-2024* (Ministry of Health of the Republic of Indonesia, 2020) is the guiding document for TB management in Indonesia. The strategy identifies BPOM as the agency responsible for strengthening pharmacovigilance of anti-TB drugs. The *National PMDT Technical Guideline* (Indonesia National TB Programme, 2020) recommends aDSM for all patients enrolled in treatment for DR-TB to ensure appropriate action and prompt response to adverse events.

aDSM was introduced in Indonesia in 2017. A series of trainings have been conducted to educate clinical staff at treatment facilities on why aDSM is needed and how to monitor, manage and report adverse events within the aDSM framework.

The NTP is responsible for overseeing the clinical monitoring, management and reporting of SAEs to DR-TB medicines. BPOM reviews the SAE reports and refers each report to the National Pharmacovigilance Committee for TB Medicines for causality assessment (a structured review of the information to assess the likelihood of a TB drug-related effect). After causality assessment, BPOM submits the SAE reports to the global adverse reactions database, VigiBase.

Adverse events are recorded in the Sistem Informasi Tuberkulosis (SITB), a purpose-built TB patient management software tool for Indonesia. SITB contains separate tabs for recording daily symptoms and for recording and reporting serious adverse events. An electronic bridge was constructed in 2020 to connect SITB to eMESO, the national adverse reaction reporting tool. The bridge enables reports that are entered into SITB to be submitted directly to BPOM.

Although the building blocks are in place and DR-TB treatment facilities have incorporated aDSM into their practice, there is considerable under-reporting of SAEs to DR-TB medicines in Indonesia. In 2020, there were 763 deaths in patients on DR-TB treatment, yet only 41 deaths were recorded as SAEs in SITB. In the same year, a total of 83 SAEs were reported in SITB for patients on DR-TB medicines, despite 4260 patients starting treatment for DR-TB. BPOM received 241 SAE reports associated with DR-TB treatment, but only 47 reports were submitted via the SITB-eMESO bridge, indicating that a significant proportion of the SAE reports entered into SITB are not being finalised and submitted to BPOM.

The National Pharmacovigilance Committee for TB Drugs is expected to meet every three months to conduct causality assessments. The meetings have taken place infrequently due to the limited availability of committee members, invited clinical experts and the treating physician (required at the meeting to provide further case details if needed). To date, only 36 SAE reports have been assessed and submitted to VigiBase.

Challenges and weaknesses identified in the implementation of aDSM are grouped into themes:

Theme 1: Insufficient awareness of aDSM in DR-TB treatment facilities

- Low visibility of aDSM in policy/guideline documents.
- There is no national guideline on aDSM for healthcare facilities
- Lack of knowledge about patient eligibility for aDSM and how to report SAEs was evident in the survey responses.
- SAEs are under-reported in SITB. In 2020, only 5.4% of deaths in patients on DR-TB treatment were recorded as SAEs in SITB.
- More training requested by majority of survey respondents

Theme 2: Difficulty observing or recognising SAEs

- Lack of awareness about what constitutes a 'serious' adverse event.
- Barriers to accessing healthcare may reduce the opportunity to detect or recognize adverse effects.
- Patients may be unwilling to travel to hospital for assessment and treatment of adverse effects.
- Family members sometimes collect the patient's medicine, so patient is not seen.

Theme 3: Communication

- Patients may be unwilling to disclose that they are experiencing side-effects to avoid additional medicines or referral to hospital
- Busy, over-crowded clinics, language barriers and hearing loss create barriers to effective communication.
- Difficulties contacting patients due to poor internet and cellular connectivity

Theme 4: Recording and reporting of SAEs

- Little information is available on patients who die at home.
- Transmission of reports to BPOM via eMESO requires a 'finalisation' step to be completed in SITB, which is often missed.
- SITB tool limitations
- Incomplete reports
- No report ID/reference provided when report submitted to BPOM.
- No mechanism for updating a report with additional information.
- Lack of familiarity on how to report SAEs in the SITB system.

Theme 5: Causality Assessment of SAE reports

- National Pharmacovigilance Committee for TB medicines meets infrequently
- Case information for review is often incomplete and inadequate for causality assessment.
- Long intervals between the SAE and the causality assessment.

Theme 6: Signal detection and communication

- Although individual case reports have been assessed, there has been no analysis of the reports to determine whether there are any potential safety signals.
- The NTP participates in the causality assessment meetings and the meeting minutes are shared with the NTP, but there is no formal mechanism for communicating aDSM outcomes directly with the NTP (such as a quarterly report of cases, assessed causality and reporting trends).
- There is no formal mechanism for providing feedback (in the form of summary statistics/aggregate data) to the reporters.

Theme 7: Human resources

- Roles and responsibilities for aDSM not well defined
- Training on aDSM and AE recording and reporting in SITB is needed for new staff.

The following recommendations are proposed for strengthening aDSM in Indonesia:

1. Compile/develop a simple aDSM guideline or SOP for use in hospitals and clinics. The guideline would include clear guidance on WHICH medicines/regimens are eligible for aDSM, WHAT constitutes a serious adverse event, HOW to report a SAE in SITB, WHO is responsible for submitting the report and WHEN (how soon) the report should be submitted.
2. Develop interactive self-paced training modules on aDSM for healthcare workers, including how to use SITB AE recording and SAE reporting pages. Link the learning modules to professional development requirements and/or workplace orientation to encourage uptake.
3. Provide training for healthcare workers on how to adopt a more patient-centred approach when discussing adverse effects with patients and family members/support person. The training would cover how to enquire about adverse effects at each patient encounter (real or virtual). For example, asking about how the patient is feeling in general, followed by more targeted questions about clinical symptoms of common AEs, and giving the patient time to raise concerns about their medicines may help to identify treatment-related adverse effects.
4. Optimise pharmacist involvement in DR-TB patient care, including educating patients on possible adverse effects to DR-TB medicines and what to do if they experience an adverse effect.
5. Strengthen use of the patient diary for recording adverse events/side-effects. Encourage family members to record the patient's symptoms if the patient is too unwell to do so.
6. Implement procedures for conducting a verbal autopsy when a patient dies at home.
7. Improve the quality of SAE reports by further developing SITB. For example:
    - use of auto-populated data fields to streamline date entry
    - mandatory fields to ensure essential data is collected
    - built-in guidance notes
    - pop-up alerts on opening a case file to notify the user that a SAE report has not been finalised and submitted to BPOM.
    - revise the daily symptom page so that it captures a wider range of symptoms (including free-text fields for symptoms that may not be on the list) and simplify the recording process.
    - reduce system 'crashes'.
8. Develop a mechanism acknowledging receipt of the SAE report in eMESO, which includes the report ID/reference. The reference could then be used to report further information about the case if it becomes available (eg, outcome information).
9. Increase the frequency of causality assessment meetings to monthly so that all cases can be reviewed and submitted to VigiBase in a timely manner. It may not be necessary to include all members at each meeting, but setting a quorum would require a certain number to be present for the meeting to go ahead.
10. Strengthen process for ensuring all necessary information is available to the committee prior to meeting. Consider whether members of the National Pharmacovigilance Committee for

TB Drugs members could have access to the SITB to check details in the patient's record directly, instead of needing to include the treating physician in the causality assessment meeting (given their limited availability to participate).

11. Conduct regular review of the cumulative SAE reports to identify potential safety signals as early as possible, so that the information may be used to inform clinical practice.
12. Establish mechanisms for communicating causality assessment conclusions on individual case reports, cumulative aDSM data reviews and potential safety signals between BPOM and NTP.
13. Establish a mechanism for providing feedback to DR-TB clinicians on the outcome of aDSM, including SAE reporting trends and any safety signals identified by the monitoring.

1 Introduction

1.1 Purpose

Indonesia is implementing Active Drug Safety Monitoring and Management (aDSM) within the programmatic management of drug-resistant tuberculosis (PMDT). A situational analysis was conducted to review progress and to identify potential barriers to effective implementation. This report describes the current status of aDSM in Indonesia and makes recommendations for strengthening the monitoring, reporting and evaluation of adverse events associated drug-resistant tuberculosis (DR-TB) treatment regimens in Indonesia.

1.2 Method

The situational analysis was conducted remotely as a desktop exercise based on:

1. Documents and information provided by the National TB Programme (Subdit Tuberkulosis) and the Indonesia Food and Drug Authority (BPOM) about the implementation of aDSM in Indonesia
2. A survey of healthcare professionals at DR-TB treatment facilities about aDSM implementation (Annexes 1-3)
3. Discussions with key people at the NTP and BPOM

1.3 Key resources for preparing report

- The Republic of Indonesia Joint External Monitoring Mission for Tuberculosis (JEMM) Report 2020 (JEMM Review Team, 2020)
- Regional Green Light Committee Country Support Mission Report 2020 (Chiang, 2020)
- The Republic of Indonesia Health System Review 2017 (Mahendradhata, et al., 2017)
- Resilient and people-centred health systems – Ch6 Indonesia 2018 (Mahendradhata, Y; Marthias, T; Trisnantoro, L, 2018)
- Presentations:

  NTP: aDSM of DR TB in Indonesia (26 Feb 2021)
  Implementation of aDSM in Indonesia (3 Mar 2021)
  aDSM reporting in SITB (17 Mar 2021)

  BPOM: PV in Indonesia (17 March 2021)
  PV system in Indonesia (3 Mar 2021)

2 Background

2.1 Health system structure and governance

Indonesia is the world's fourth most populous nation with a population of approximately 270.2 million people in 2020 (World Bank, 2021). Geographically, the country spans more than 17,500 islands of which approximately 6000 are inhabited, and is divided into 34 provinces with 513 districts/cities (JEMM Review Team, 2020). Indonesia is the world's 10th largest economy in terms of purchasing power parity and has the largest economy in Southeast Asia. Approximately 27.55 million people in Indonesia (10.19% or the population) are living in poverty. (World Bank, 2021)

The public health system in Indonesia is administered in line with the decentralised system of government, with responsibilities at central, provincial and district levels. (Mahendradhata, et al., 2017)

- The central Ministry of Health (*Kementerian Kesehatan, KEMENKES*) is responsible for the management of some tertiary and specialist hospitals, provision of strategic direction and

national guidelines, setting of standards, regulation, and ensuring availability of financial and human resources.

- Provincial governments are responsible for management of provincial-level hospitals, provide technical oversight and monitoring of district health services, and coordinate cross-district health issues within the province.
- District/municipal governments are responsible for management of district/city hospitals and the district public health network of community health centres (*puskesmas*) and associated subdistrict facilities.

Public health services are the responsibility of the Ministry of Health at national, provincial and district levels (Figure 1).

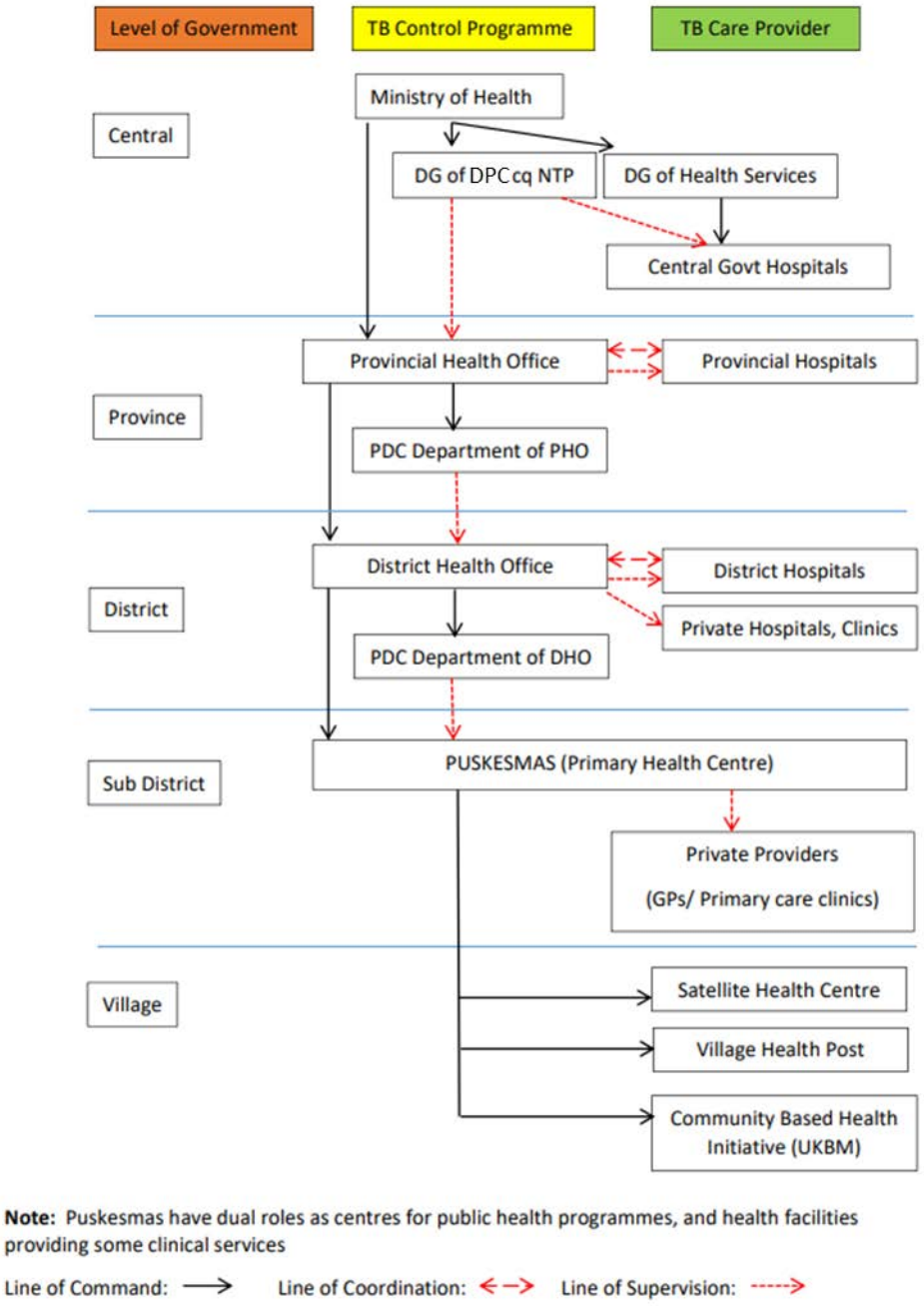


Figure 1. Structure and organisation of health service delivery in Indonesia. Source: JEMM Report 2020

As at 20 January 2020, there were 24,223 health facilities in Indonesia, including 10,158 sub-district public health centres (called *Pusat Kesehatan Masyarakat* or *puskesmas*). Forty-eight percent

(11,678) of the total public health facilities are actively engaged in TB control, of which 9656 (95%) are *puskesmas*. Below the *puskesmas* are satellite and mobile health centres, with 94 percent of the population living within 5 km of a facility. (JEMM Review Team, 2020)

Health governance is divided across several Ministry of Health directorates (Figure 2). Services for TB patients are included in the Directorate General of Disease Prevention and Control (DPC) at the Ministry of Health. The TB Sub-Directorate (Subdit TB), which sits under the Directorate of Communicable Disease Prevention and Control in the DPC, manages daily activities of TB control in Indonesia and serves as the National TB Programme (NTP). Public sector TB services are delivered through the *puskesmas* and hospitals, which are managed under the Directorate General of Health Services (called *Pelayanan Kesehatan* or *YANKES*). YANKES is also responsible for healthcare facility licensing and accreditation, laboratory services and infection control. Training and capacity building sit with the Agency for Health Human Resources Development and Empowerment, and responsibility for the health information system sits with the Secretariat General of Public Health. (JEMM Review Team, 2020).

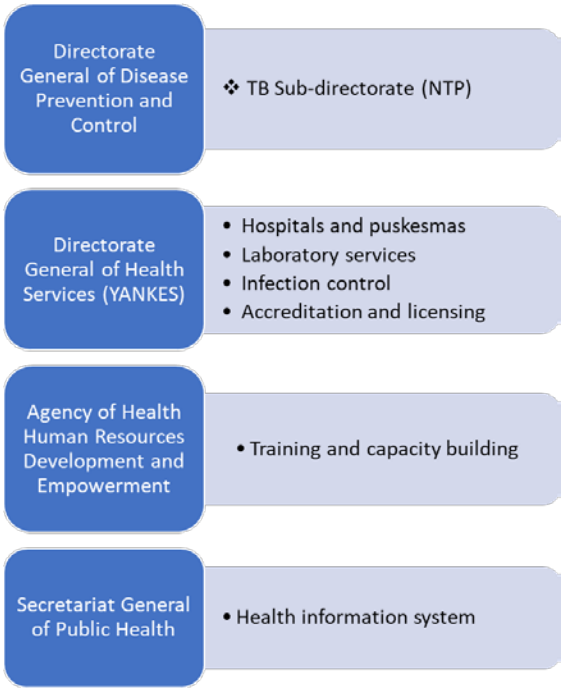


Figure 2. Ministry of Health of Republic of Indonesia divisions involved in TB public health service delivery

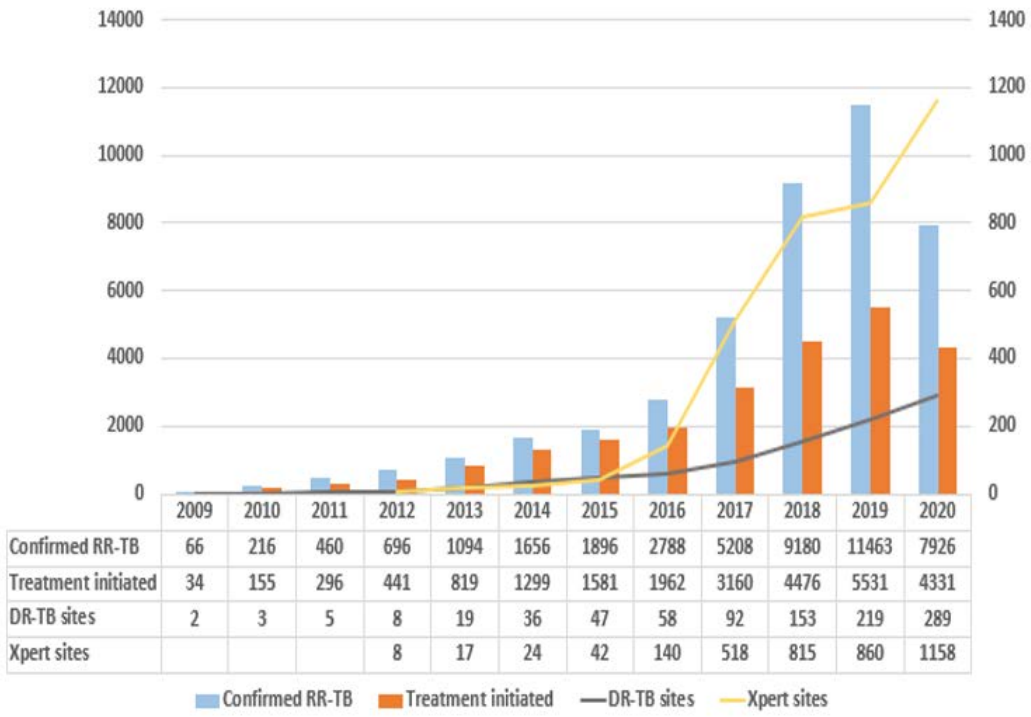
In addition to the public health system, the private sector has grown rapidly in recent years (JEMM Review Team, 2020). There is a range of private providers, including networks of hospitals and clinics managed by not-for-profit and charitable organizations, for-profit providers, and individual doctors and midwives who engage in both public and private practice.

2.2 DR-TB burden in Indonesia

Indonesia is included in the WHO list of high-burden countries for MDR-TB (World Health Organization, Global Tuberculosis Report, 2020)

In 2019, the burden of MDR/RR-TB in Indonesia was estimated to be 24,000 patients (8.8 per 100,000 population) (World Health Organization, 2020). The estimated proportion of RR-TB was 2.4 percent among new TB cases and 13 percent of previously treated TB cases. In the same year, 11,463 cases of RR-TB were laboratory-confirmed and 5531 patients commenced treatment for DR-TB (Figure 3).

Fewer patients with RR-TB were diagnosed (7926) and initiated on treatment (4331) in 2020 due to disruption caused by the Covid-19 pandemic.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Confirmed RR-TB	66	216	460	696	1094	1656	1896	2788	5208	9180	11463	7926
Treatment initiated	34	155	296	441	819	1299	1581	1962	3160	4476	5531	4331
DR-TB sites	2	3	5	8	19	36	47	58	92	153	219	289
Xpert sites				8	17	24	42	140	518	815	860	1158

Figure 3. Availability of DR-TB diagnostic and treatment centres in Indonesia, 2009-2020
Source: Presentation provided for situational analysis by NTP, 26 Feb 2021 (Data current to 29 Jan 2021)

As at 28 April 2021, there are 308 DR-TB treatment centres in Indonesia, including 8 private clinics with capacity to treat DR-TB (Indonesia National TB Programme, 2021).

In January 2020, the Joint External Monitoring Mission for Tuberculosis (JEMM) noted that nearly 60 percent of MDR/RR-TB cases remain undetected. Of those that are diagnosed, only half start treatment and of these, only half have successful outcomes[1], with high rates of loss-to-follow-up (LTFU) and death. Programmatic reasons identified in the report for the poor detection and cure rates included: insufficient treatment sites, access difficulties due to the hospital-based treatment model, limited counselling and support, and stigma and discrimination. Medicine-related causes for suboptimal treatment outcomes included fear and misinformation about side-effects, and access to falsified therapies via the internet. (JEMM Review Team, 2020).

2.3 MDR-TB treatment

PMDT started in Indonesia in 2009 with two DR-TB treatment centres. The programme has extended over the years to now include 1098 DR-TB diagnostic centres and 308 DR-TB treatment centres (as at 28 April 2021). DR-TB treatment is initiated at hospital level facilities, but ongoing care is managed at the primary health care (puskesmas) level.

In December 2020, the NTP released a new national PMDT guideline to align with the WHO 2020 DR-TB guidance, including the all-oral shorter TB regimen (STR) and preventive treatment for DR-TB contacts (Indonesia National TB Programme, 2020). Transition to the new treatment guidelines is now underway (Table 1). The NTP advised that in 2020, a total 4260 patients started treatment for

[1] Of 2997 patients with MDR/RR-TB who started on second-line treatment in 2017, 45 percent were successfully treated (World Health Organization, 2020).

DR-TB and a further 102 household contacts started preventive treatment. Table 3. Use of DR-TB regimens in Indonesia 2019-2021

Table 1. Transition of DR-TB regimen use in Indonesia 2019-2021

Regimen	Criteria	Number of patients		
		2019	2020†	2021‡
Oral STR	MDR/RR-TB (introduced Aug 2020)	0	565	3853
Oral LTR	MDR/RR-TB previously treated >1 month, Pre-/XDR TB, STR intolerant (introduced in Oct 2019)	1393	1992	2012
STR with injectable*	MDR/RR-TB	3085	1159	0
LTR with injectable*	MDR/RR-TB previously treated >1 month, Pre-/XDR TB, STR intolerant	1172	544	150
Preventive treatment for contacts	Household contacts (all ages) of DR-TB patients where TB/DR-TB is excluded	NA	102	844

LTR longer MDR-TB regimen, STR shorter MDR-TB regimen
** kanamycin, † data as at 29 January 2021, ‡ projected data*
Source: Presentation by NTP (Indonesia National TB Programme, 2021)

In 2021, the new guidelines are being distributed to all existing DR-TB treatment centres across Indonesia and to new treatment centres as they are established. Training on the new guidelines was conducted in April 2021 for clinicians in established DR-TB treatment centres. A national workshop for paediatricians on DR-TB treatment in children is planned. (Indonesia National TB Programme, 2021)

Treatment for DR-TB is started at district hospital level facilities. The patient is then followed-up at the puskesmas nearest to the patient's home. The hospital contacts the puskesmas and provides advice/training on how to manage the patient, with support from district health office. The clinic doctor will review the patient if they are experiencing adverse effects, and may refer the patient to hospital if the side effects are severe.

Due to the Covid-19 pandemic, daily follow-up visits at the puskesmas have been replaced with weekly visits during the initiation phase and fortnightly visits during the continuation phase. Patients are given their medicines to take at home between visits.

2.4 Pharmacovigilance in Indonesia

The Indonesian Food and Drug Agency (called *Badan Pengawas Obat dan Makanan* or *BPOM*) is the national regulatory authority for foods, cosmetics, health supplements, traditional medicines and therapeutic products. Pharmacovigilance is undertaken by the 'Directorate for Safety, Quality, and Export-Import of Drug, Narcotic, Psychotropic, Precursor, Addictive Substance Control', which sits in the 'Division of Drug, Narcotic, Psychotropic, Precursor, Addictive Substance Control'.

Indonesia became a full member of the WHO Programme for International Drug Monitoring in 1990. (Uppsala Monitoring Centre, 2021). BPOM achieved maturity level 4 for the Vigilance Function in the WHO Global Benchmarking Tool for National Regulatory Authorities in July 2018 (Indonesia Food & Drug Agency (BPOM), 2021). Pharmacovigilance activities undertaken by the BPOM include

medicine safety surveillance, pharmacovigilance inspections, monitoring adverse drug reactions (ADRs) and adverse events following immunisation (AEFIs).

Ministry of Health regulations require the pharmaceutical industry to report all suspected ADRs and AEFIs (ie, mandatory reporting). Reporting by healthcare providers is not mandatory. (Indonesia Food & Drug Agency (BPOM), 2021)

Information provided by BPOM on ADR reporting in 2020 indicated that 1798 reports came from industry and 4315 reports came from healthcare professionals. No reports came from patients.

Patients can contact BPOM via the BPOM mobile app or Halo BPOM telephone service if they are concerned about their medicines. However, if an adverse reaction is suspected, the patient is advised to see their healthcare provider so that they can report it to BPOM. Healthcare facilities and the pharmaceutical industry can enter reports directly into e-MESO through a web-based application. Figure 4

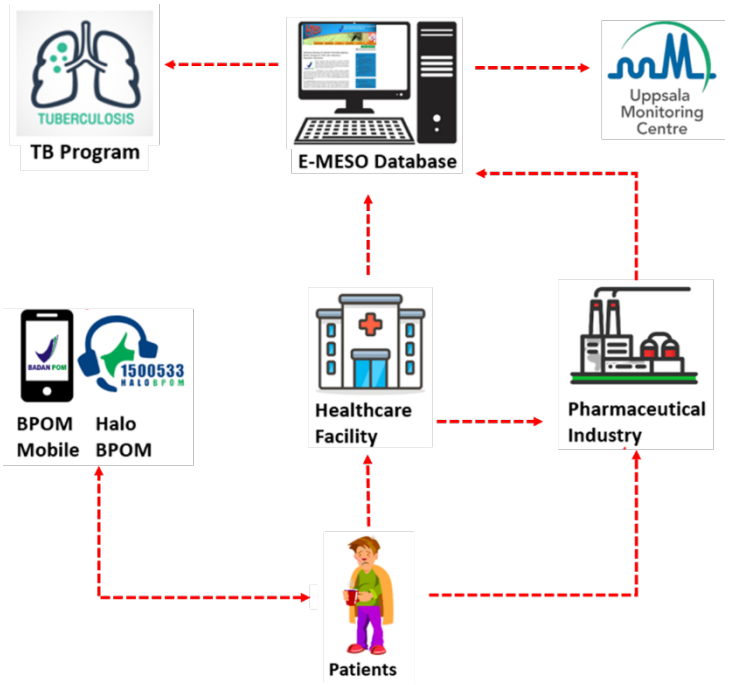


Figure 4. ADR and AEFI reporting pathways in Indonesia (adapted from BPOM presentation)

On receipt of the report in e-MESO, pharmacovigilance officers check the completeness of the report (data verification) and conduct an initial review of the information to assess the likelihood of a causal association (referred to as ADR manifestation validation). Formal causality assessment is subsequently performed on a monthly basis by the **National Pharmacovigilance Committee**. The Committee has 13 members, with expertise across clinical pharmacology, internal medicine, epidemiology, immunology and neurology. Additional experts from other fields may be invited as necessary. A separate **National Pharmacovigilance Committee for TB Medicines** was established in 2019 to assess the causality of SAE reports from aDSM.

Following causality assessment, the ADR/SAE reports are submitted to the Uppsala Monitoring Centre (UMC) every three months via VigiFlow[2]. Figure 5

[2] VigiFlow is a web-based system for individual case safety reports (ICSRs). It was developed and is maintained by the Uppsala Monitoring Centre for use by national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring.

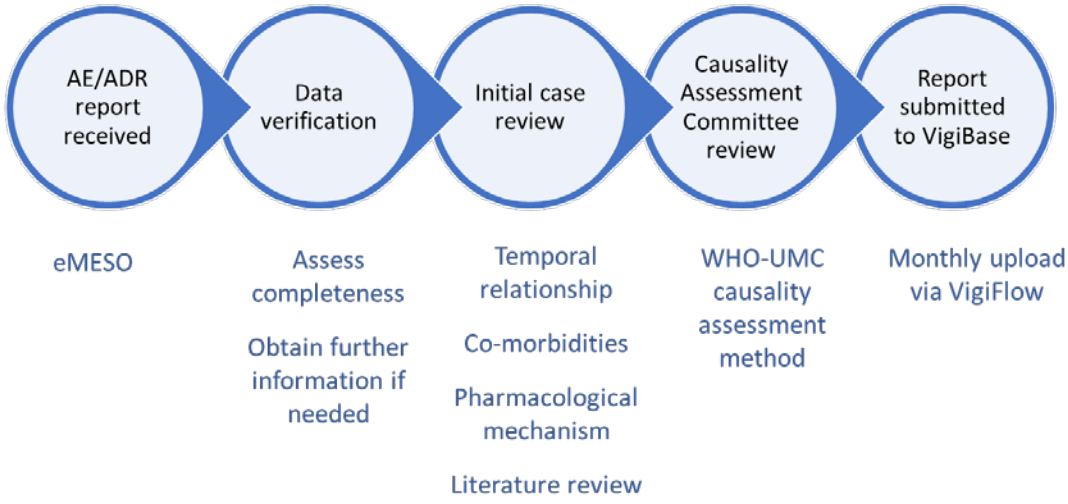


Figure 5. ADR report evaluation process (Indonesia Food & Drug Agency (BPOM), 2021)

2.5 Active Drug Safety Monitoring and Management (aDSM)

The WHO developed active drug safety monitoring and management (aDSM) to strengthen pharmacovigilance within the programmatic management of drug-resistant TB (PMDT). aDSM involves the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities (World Health Organization, 2015).

Countries may choose to implement the core, intermediate or advanced aDSM package, depending on their capacity to undertake the reporting requirements, which increase with each level (Figure 6).

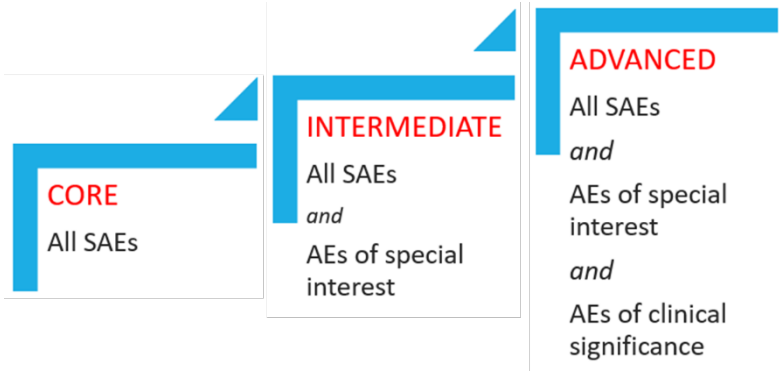


Figure 6. Reporting requirements for the core, intermediate and advanced aDSM packages. AE adverse event, SAE serious adverse event

The core package requires the reporting of serious adverse events (SAEs) [3]. A SAE is an undesirable event that occurs during or after treatment with a medicine that results in death or is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Other important medical events that

[3] SAEs are defined in the ICH **E2A** guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org).

may jeopardise the patient or require intervention prevent one of the outcomes listed above may also be considered serious. Box 1

In addition to SAEs, the intermediate package requires reporting of adverse events of special interest (AESI) and the advanced package further requires reporting of adverse events of clinical significance (AECS). (See Box 1 for definitions of AE types).

With the introduction of the shorter TB regimen (STR) in 2017, Indonesia began implementing the core aDSM package in all DR-TB treatment facilities. Capacity building was conducted in 2017-2018 for DR-TB treatment centers.

Box 1. Definitions of adverse event types for aDSM

Serious adverse event (SAE)

An adverse event that:

- ☐ Results in death *or*
- ☐ Is life-threatening (ie, the patient was at risk of death at the time of the event, not just a hypothetical risk of death if the event was more severe) *or*
- ☐ Requires inpatient hospitalisation or prolongation of existing hospitalisation *or*
- ☐ Results in persistent or significant disability or incapacity *or*
- ☐ Is a congenital anomaly/birth defect *or*
- ☐ Is an important medical event that is not immediately life-threatening but may jeopardise the patient or require timely intervention to prevent one of the other outcomes listed above

Adverse events of special interest (AESI)

- ☐ Specified list of events for the particular medicine or class of medicine being monitored
- ☐ Serious or non-serious
- ☐ Identified during clinical development of medicine or a theoretical risk based on disease being treated or related to the class of medicine

Adverse events of clinical significance (AECS)

An adverse event that:

- ☐ Results in a change or discontinuation of treatment *or*
- ☐ Is judged as otherwise clinically significant by the clinician

Note: AESIs for aDSM are defined in the WHO aDSM implementation handbook (World Health Organization, 2015)

3 Policy framework for aDSM implementation in Indonesia

3.1 National Strategy for TB Care and Prevention 2020-2024

The *National Strategy for TB Care and Prevention 2020-2024* (Ministry of Health of the Republic of Indonesia, 2020) is the guiding document for TB management in Indonesia.

The strategy notes that the National Agency of Drug and Food Control (ie BPOM) is responsible for

- Ensuring the availability of anti-TB drugs by
    - guiding and providing solutions related to barriers in the development of anti-TB drugs and
    - facilitating fast-track registration for TB programme drugs
- Monitoring the quality of anti-TB drugs
- Strengthening pharmacovigilance of anti-TB drugs.

Specifically, the plan includes strengthening the Pharmacovigilance National Committee with an annual coordination meeting and workplan. The strategy does not mention aDSM implementation within PMDT.

3.2 National PMDT Guideline

The NTP released an updated national PMDT technical guideline in December 2020 (Indonesia National TB Programme, 2020). The national guideline aligns with the 2020 WHO consolidated guidelines on tuberculosis (World Health Organization, 2020). Accordingly, the national guideline recommends that NTPs implement aDSM for all patients enrolled on treatment for DR-TB to ensure appropriate action and prompt response to adverse events.

Figure 7. Technical Guideline – Management of DR-TB in Indonesia

3.3 Pharmaceutical and Therapeutics Committee

The Minister of Health Decree 72/2016 requires hospitals to establish a Pharmaceutical and Therapeutics Committee (Komite Farmasi dan Therapy, KFT) to oversee the standard of pharmaceutical services in the hospital. Committee members include doctors from each specialty in the hospital, pharmacist, and other health workers if needed. The Committee's terms of reference are to:

- Develop a policy on the use of drugs in the hospital
- Evaluate and select drugs to be included in the hospital formulary;
- Develop standard therapy
- Identify problems in medicine use
- Ensure the rational use of medicines
- Coordinate the management of adverse events
- Coordinate the management of medication errors
- Disseminate information related to drug use policies in the hospital.

4 Practical Implementation of aDSM

4.1 Training on pharmacovigilance in PMDT

Pharmacovigilance training for PMDT in Indonesia began in 2015 with workshops on Cohort Event Monitoring (CEM) for bedaquiline.

Starting in 2017, a series of training workshops have taken place to support the introduction of aDSM in Indonesia. These workshops include:

- 2017-2019: Workshops to support the implementation of aDSM at provincial and district levels, focusing on the recording and reporting of AEs in DR-TB care. The workshops involved clinicians from 49 DR-TB hospitals across 16 districts and 6 provinces of Indonesia.
- March 2019: Follow-up training on aDSM for clinicians from DR-TB treatment centres in 13 provinces.
- May 2019: Workshop on the role of pharmacists in DR-TB treatment, supported by KNCV, WHO, NTP and BPOM.
- August 2019: Workshop for Provincial Technical Officers on DR-TB treatment updates and aDSM.
- October 2020: Pharmacovigilance workshop for provincial hospital TB clinicians. The training covered TB treatment updates, aDSM and causality assessment.
- 2020: Three workshops on how to report SAEs using the paper MESO form. Participants included clinical experts and nurses from 88 DR-TB Treatment centres in 34 provinces.
- April 2021: Update on DR-TB national guideline, treatment and aDSM.
- May 2021: Refresher workshop on recording and reporting of SAEs in SITB. Participants included TB officers and DR-TB technical officers from Provincial Health Officer and clinical experts, pharmacists, data officers and nurses from DR-TB treatment centres.

4.2 Coordination between NTP and BPOM

The NTP and BPOM are working together to implement aDSM in Indonesia (Figure 8). The NTP is responsible for overseeing the clinical monitoring and management of adverse events and reporting of SAEs for patients on DR-TB treatment. BPOM is responsible for reviewing the reports to assess the likelihood of a causal association between the SAE and the DR-TB medicines, and for submitting reports to the global adverse reactions database – VigiBase.

The NTP and BPOM collaborate on data collection. Clinical staff record SAEs in the TB patient information system (Sistem Informasi Tuberkulosis, SITB). SITB is linked to the BPOM's electronic adverse drug reaction reporting tool (eMESO), which enables direct transfer of individual SAE reports into the BPOM data management system.

The NTP and BPOM also collaborate on the causality assessment of SAE reports. The National Pharmacovigilance Committee for DR-TB includes clinical experts from the NTP and BPOM.

Collaboration between the NTP and BPOM to strengthen pharmacovigilance for TB medicines started in 2012. The agencies worked together to conduct a Cohort Event Monitoring (CEM) study of bedaquiline in 2015-2017.

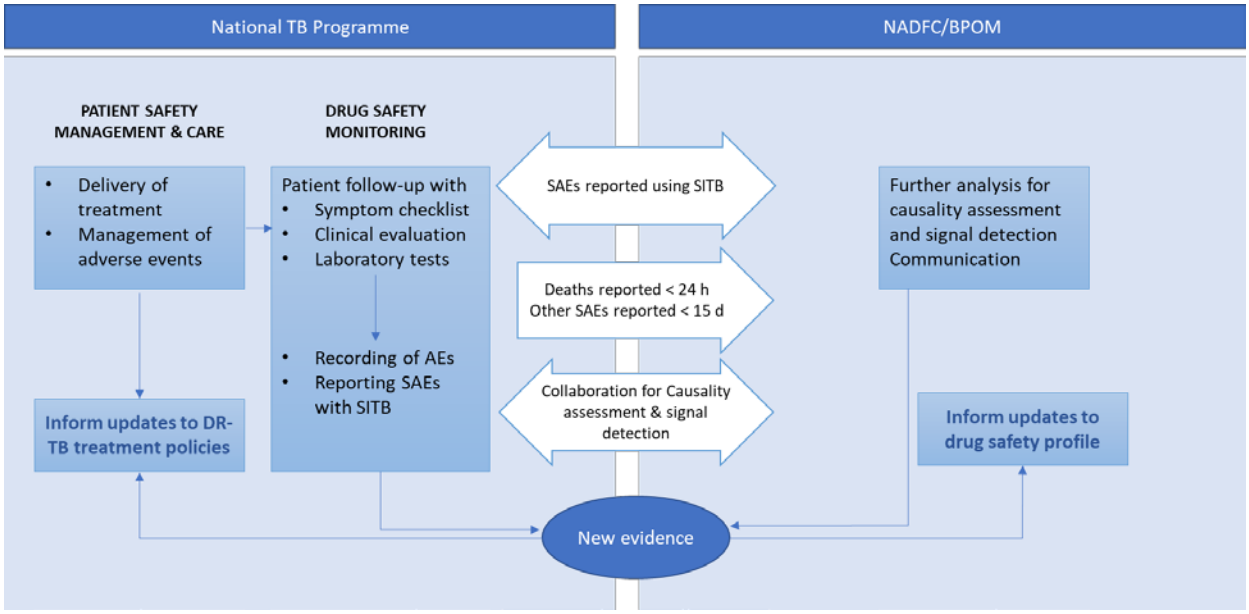


Figure 8. aDSM information sharing between NTP and BPOM

4.3 Clinical and laboratory monitoring

DR-TB treatment must be initiated at the district hospital level. Throughout Indonesia there are currently 308 hospitals with capacity to initiate DR-TB treatment. Ongoing care is managed by the local primary care facility (puskesmas), with monthly follow-up visits at the district hospital clinic.

The clinical monitoring schedule includes baseline examinations, monthly follow-up checks and an end-of treatment assessment. Patients are followed-up for a further 2 years after completion of treatment (Table 2). (Indonesia National TB Programme, 2021)

Table 2. Clinical monitoring schedule for DR-TB treatment (source: Indonesia National TB Programme)

Investigation	Baseline	Week 2	Week 4 & monthly	End of treatment	6m/ 2yrs post treatment
Clinical tests					
physical examination	√		√	√	√
counselling and evaluation of psychosocial conditions	√		√	√	√
body weight (BMI)	√		√	√	√
peripheral neuropathy screen	√		√	√	
visual function screen	√		√	√	
drug side-effects			√	√	
treatment outcome			√	√	
Microbiological tests					
sputum smear	√		√	√	√
sputum culture	√		√	√	√
second line LPA	√				
phenotypic sensitivity test	√				
Laboratory, Radiology, ECG					
Chest x-ray	√			√	√
ECG	√	√	√	√	
complete blood count	√		√	√	

liver function (AST, ALT, total bilirubin)	√		√	√	
electrolytes (Na, K, Ca, Mg)	√		√		
kidney function (urea, serum creatinine)	√		√	√	
uric acid	√		√		
fasting blood sugar & 2h post-prandial	√				
TSH	√				
Pregnancy test	√				
HIV test	√				

The NTP provided audiometry equipment and 250 ECG machines to district hospitals to support the clinical monitoring of DR-TB patients. (Indonesia National TB Programme, 2021)

Patients are encouraged to keep a daily record of symptoms. District hospital treatment centres and satellite clinics (puskesmas) have access to *Sistem Informasi Tuberkulosis* (SITB), an online TB patient management software tool (see 4.4.1). Health workers at the puskesmas record the presence or absence of adverse events in the SITB *MESO Harian* (daily drug side-effects monitoring) tab.

4.4 Recording and reporting of SAEs

Nurses or data officers at the DR-TB treatment facilities (including hospitals and puskesmas) record SAEs in the SITB *Laporan KDT Serius* tab. When complete, the case report is submitted to BPOM via an electronic bridge between SITB and eMESO. SAEs should be reported to BPOM as soon as possible: fatal cases within 24 hours of the patient's death and non-fatal cases within 15 calendar days of the event (Chiang, 2020).

BPOM reviews the SAE case reports and refer them to the Pharmacovigilance National Committee for TB medicines for causality assessment. BPOM submits the assessed SAE reports to VigiBase, the WHO global database of individual case safety reports. The feedback pathway from BPOM to NTP is via the Pharmacovigilance National Committee for TB medicines, which includes members from the NTP. (Figure 9).

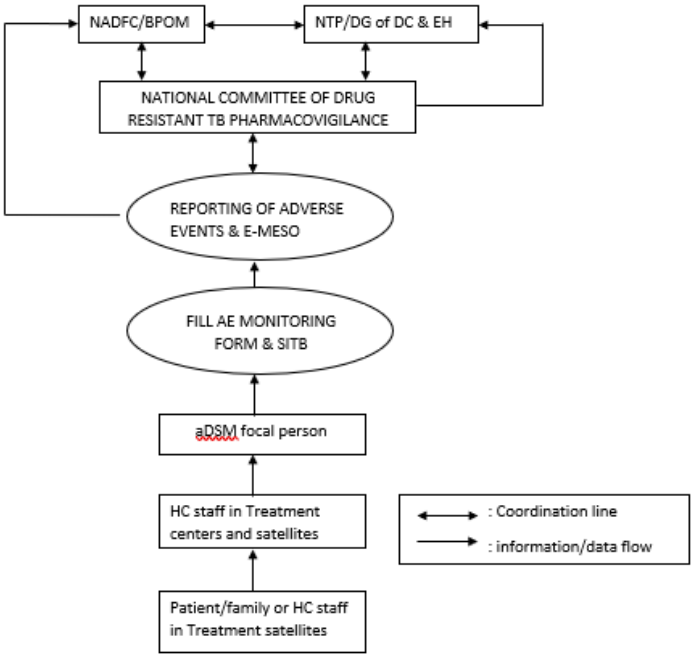


Figure 9. Flow of SAE information for DR-TB medicines (National TB Programme Indonesia, 2021)

4.4.1 Sistem Informasi Tuberkulosis (SITB)

SITB is a web-based application for recording and reporting TB case information in Indonesia (Image 1). The software was developed by Subdit-TB with the support of KNCV through the Challenge TB project, funded by USAID (Ministry of Health Rupublic of Indonesia, 2021).

Image 1. SITB login page

SITB replaces two previous systems: eTB Manager for DR-TB and SITT for DS-TB. The new system was implemented on 1 January 2020, and all new DR- and DS-TB cases since then have been entered into SITB. Due to the cohort nature of the data, SITT will be maintained until the end of 2021 and eTB Manager will be maintained until the end of 2022.

Healthcare facilities (including puskesmas, hospitals, independent practitioners, clinics, laboratories and pharmacies) can enter case information into the system. The data can be accessed by the Ministry of Health at the city/regency, provincial and central levels.

The SITB user-interface includes separate tabs for recording patient information, treatment details, laboratory data and adverse events. The *MESO Harian* tab is for active monitoring of adverse effects to the TB medicines (Image 2).

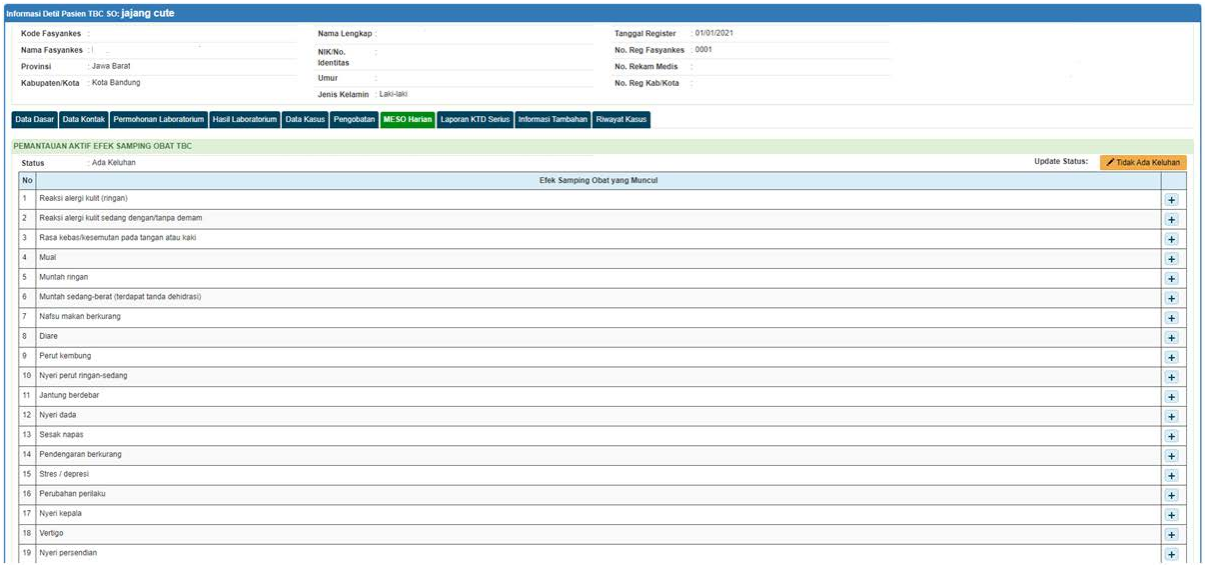


Image 2. Screen shot of SITB MESO Harian page showing list of adverse events that may be recorded

The daily events page includes a list of 24 adverse effects (see Table 4).

The dates on which the adverse events occurred can be recorded by clicking on the + symbol next to the event to open a new dialogue box where the reporter can select either 'complaint' or 'no complaint' against each date (Image 3).

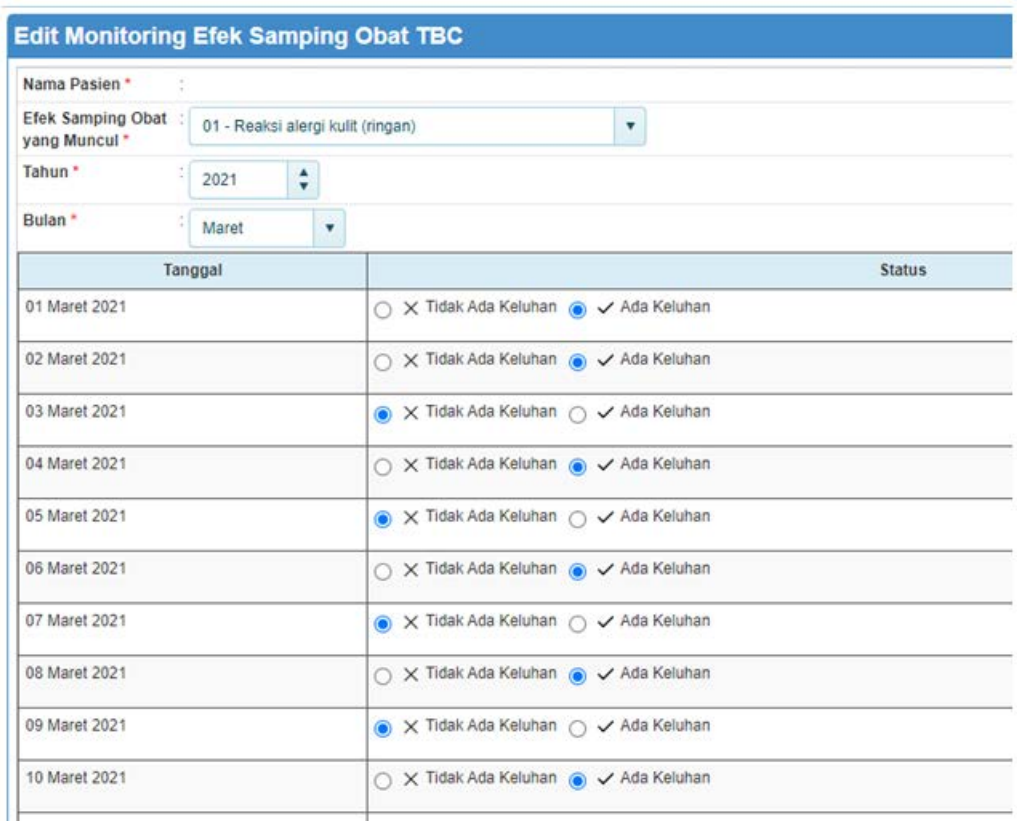


Image 3. SITB daily adverse effect recording page. For the selected adverse event, the reporter selects either 'complaint' or 'no complaint' next to the date to record the dates when the event occurred.

SAEs can be reported in SITB via the *Laporan KTD Serius* tab (Image 4). This page includes the same data fields as the paper-based SAE reporting form (Annex 4). Information in the SAE report is automatically copied from SITB to e-MESO for reporting to BPOM when the report is 'finalised'. The bridge from SITB to e-MESO was developed in 2020.

When the status is changed from ‘Draft’ to ‘Final’, a confirmation pop-up message is displayed, which includes a statement that finalised data cannot be changed, the report date, and a Yes/No button choice for finalising the report (Image 5). Finalised reports are submitted automatically to eMESO.

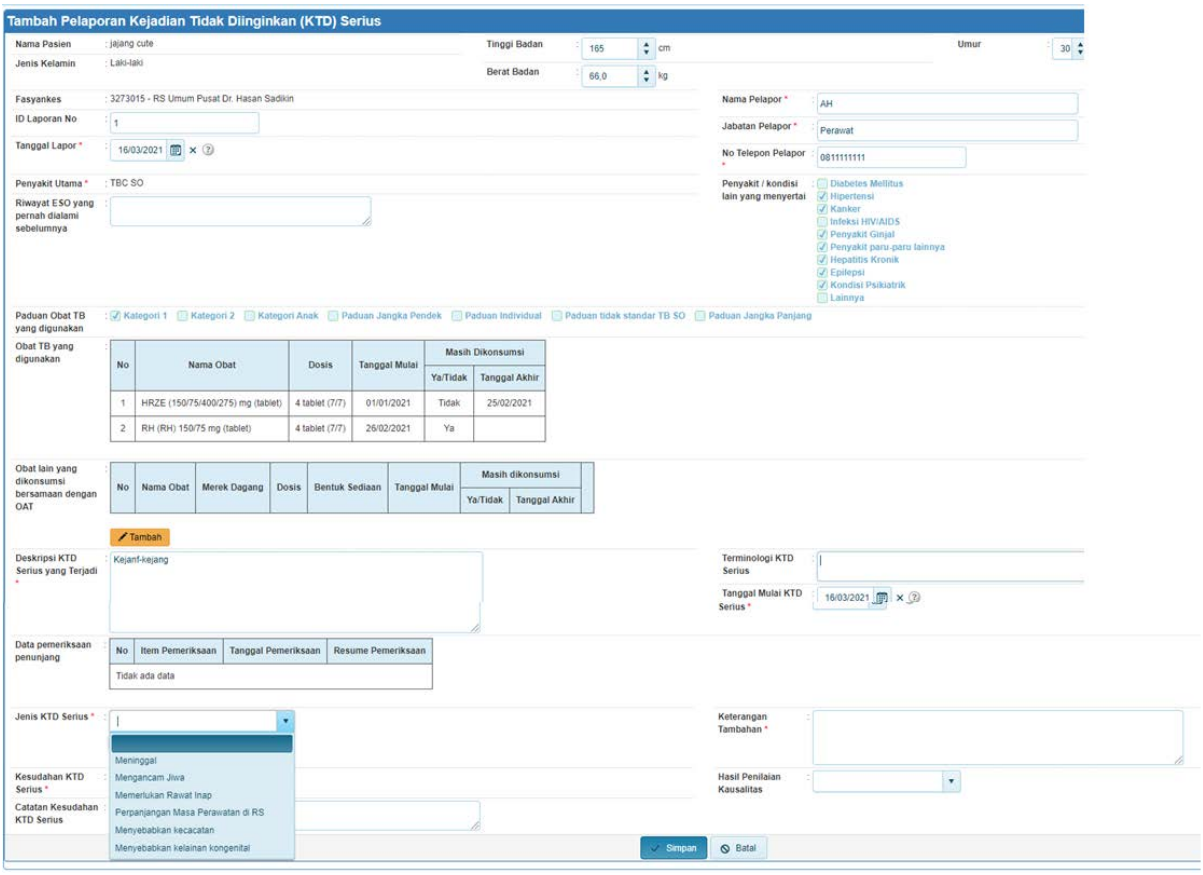


Image 4. SITB SAE reporting page

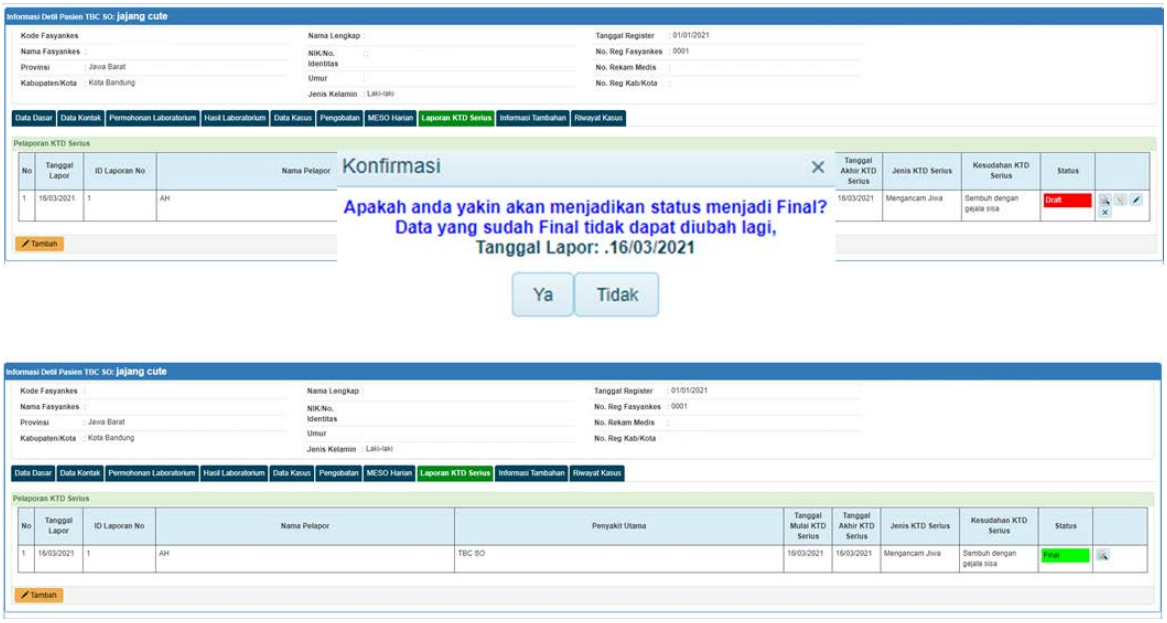


Image 5. SITB SAE report finalisation step. The top image shows the status as ‘draft’ (red). Clicking on the red status button opens a confirmation box. By selecting Ya (yes), the status will change to ‘final’ (green) as shown in the lower image. Finalised reports are automatically submitted to eMESO.

4.4.2 SAE reporting form

The paper-based SAE Form (Annex 4) continues to be used for patients who were registered in eTB Manager (patients who start DR-TB treatment before 2020). The form is either emailed to BPOM (with copy to the NTP) or entered into the eMESO via the BPOM website.

4.4.3 e-MESO

e-MESO (*e-Monitoring Efek Samping Obat* or electronic Drug Side Effects Monitoring) is the national adverse drug reaction (ADR) reporting tool and database. The web-application facilitates adverse event reporting from healthcare facilities and pharmaceutical companies. SAE reports that have been finalised in the SITB are submitted to BPOM via the eMESO bridge.

e-MESO does not conform to the ICH E2B data format. To submit reports to VigiBase, BPOM generates an xml file from eMESO so that the data can be transferred to VigiFlow and then uploaded to VigiBase.

4.5 Data management and analysis

4.5.1 BPOM

BPOM manages the SAE reports from DR-TB treatment facilities in the same way as all other ADR reports. BPOM officers[4] check the completeness of the report (data verification) and conduct an initial review of the information to assess the likelihood of a causal association (referred to as 'ADR manifestation validation'). This review takes into consideration the timing of the event in relation to starting the TB medicine, the patient's underlying health conditions, the effect of dechallenge and rechallenge (if applicable), and the known ADR profile of the medicines concerned. A Summary of Technical Information is compiled for review by the Pharmacovigilance National Committee for TB drugs. (Figure 10)

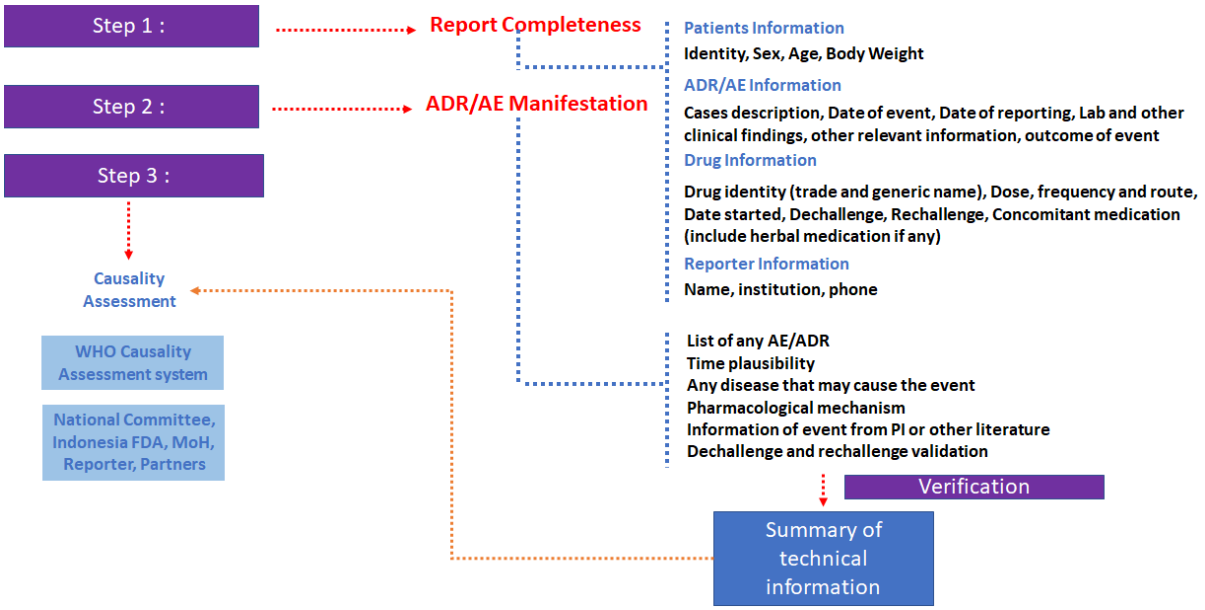


Figure 10. Data validation and verification process at BPOM

BPOM submits the causality assessed reports to UMC each month. However, as the Pharmacovigilance National Committee for TB drugs meets quarterly, SAE reports for DR-TB medicines are submitted to UMC less frequently.

[4] Petugas Farmasi dan Makanan (PFM) – Pharmaceutical and Food Officer: Pertama (junior) and Muda (senior)

4.5.2 National Pharmacovigilance Committee for TB drugs

The National Pharmacovigilance Committee for TB drugs was established in 2019. The Committee currently has 19 members from various medical specialties including Pulmonology, Clinical Pharmacology, Internal Medicine, Epidemiology, Dermatology, Otolaryngology, Gynaecology and Psychiatry.

In May 2019, the Head of the National Agency for Drug and Food Control (BPOM) issued a decree stating the Terms of Reference for the Committee, which include:

- Causality assessment of SAE reports for DR-TB drugs
- Conduct analysis of SAE reports for BPOM and NTP
- Make recommendations based on the analysis
- Regularly report to BPOM and NTP

The Committee is expected to meet four times per year to conduct a formal causality assessment of SAE reports for DR-TB medicines. BPOM schedules and organises the meetings. No specific quorum is required, but the meetings cannot go ahead unless there is adequate representation from relevant specialties, such as a pulmonologist, internist, pharmacologist. Additional experts with relevant expertise can be invited to meetings if needed. The NTP and the treating physician also participate in these meetings to provide further case details as necessary.

To date, the Committee has met eight times to conduct causality assessments: once in 2018, twice in 2019, four times in 2020 and once in 2021. Usually, approximately 7-10 members are available to participate in the meeting. The meeting schedule has been disrupted by the Covid-19 pandemic, with limited availability of committee members and the treating physicians to participate in meetings.

BPOM selects the cases for causality assessment and sends the case information to the committee members to review before the meeting. Fatal cases are prioritised for review by the Committee, and cases from regions or healthcare facilities with the highest number of fatal SAEs are reviewed first.

The causality assessment is added to the report in eMESO before it is submitted to UMC.

There is no formal mechanism for sharing the causality assessment outcome with the NTP, but the NTP is present at the causality assessment meetings and BPOM shares the meeting minutes with the NTP.

5 aDSM reporting in 2020

A total of 4351 DR-TB cases were recorded in SITB in 2020. Of these, 1122 patients had at least one AE recorded (25.8%). Table 3

Table 3. AE reporting in SITB for DR-TB patients in 2020 (Indonesia National TB Programme, 2021)

Adverse Events reported	Number of patients
No adverse event	45 (1%)
Any adverse event	1122 (25.8%)
Not reported	3184 (73.2%)
Total	4351

For the 1122 patients with any recorded event, there were 3514 events recorded in the *MESO Harian* tab of SITB. Nausea (23.4%) and mild vomiting (14.2%) were the most frequently reported

adverse events, followed by decreased appetite (7.8%), joint pain (7.6%) and headache 7.5%). (Table 4)

Table 4. Frequency of adverse events recorded in MESO Harian tab of SITB for DR-TB patients in 2020 (Indonesia National TB Programme, 2021)

Adverse Event	number	percent
1. Allergic skin reactions (mild)	134	3.8%
2. Moderate allergic skin reactions with / without fever	25	0.7%
3. Numbness / tingling sensation in the hands or feet	113	3.2%
4. Nausea	821	23.4%
5. Mild vomiting	499	14.2%
6. Moderate-severe vomiting (there are signs of dehydration)	84	2.4%
7. Decreased appetite	273	7.8%
8. Diarrhoea	28	0.8%
9. Flatulence	57	1.6%
10. Mild-moderate abdominal pain	70	2.0%
11. Heart palpitations	58	1.7%
12. Chest pain	93	2.6%
13. Shortness of breath	176	5.0%
14. Hearing loss	122	3.5%
15. Stress / depression	32	0.9%
16. Changes in behaviour	21	0.6%
17. Headache	265	7.5%
18. Vertigo	113	3.2%
19. Joint pain	267	7.6%
20. Seizure	7	0.2%
21. Injection site pain	76	2.2%
22. Changes in skin colour	90	2.6%
23. Ankle pain	59	1.7%
24. Swelling or redness of the joints	31	0.9%
	3514	**100%**

In 2020, there were 763 deaths in patients on DR-TB treatment. However, only 41 deaths (5.4%) were reported as SAEs (Indonesia National TB Programme, 2021). Some of the deaths may have occurred in patients from earlier cohorts that were registered in the previous system (eTB Manager) and therefore not be picked up in the SITB statistics. However, data from BPOM suggests that under-reporting of serious AEs (including deaths) is significant, regardless of the data management system being used. In 2020, DR-TB treatment facilities submitted 241 SAE reports to BPOM (47 were

submitted via eMESO), which is much lower than would be expected if all deaths had been reported as SAEs.

BPOM has submitted 38 of these reports to UMC (following causality assessment by the National Pharmacovigilance Committee for TB drugs).

VigiBase shows 51 serious cases were reported from Indonesia during the period 1 January 2017 to 11 July 2021 for DR-TB medicines[5]. Of these, 33 reports were fatal. (Table 5) [6]

Table 5. VigiBase serious reports and serious reports with fatal outcome from Indonesia, 2017-2021, for DR-TB medicines

Year	Total	Serious	Fatal
2021	77	25	22
2020	187	23	10
2019	103	3	1
2018	76	0	0
2017	74	0	0
Total	**517**	**51**	**33**

6 Survey responses

To understand the practical reality of monitoring and reporting adverse events in DR-TB treatment facilities in Indonesia, healthcare workers at hospitals and puskesmas across the 34 provinces were asked to complete a survey. The full survey results are presented in Annex 3.

In total, 620 healthcare workers agreed to participate in the survey. The majority (68.1%) were nurses, followed by pharmacists (13.5%), and more than half of the respondents were from puskesmas (52.3%). Almost half (45.9%) of the responses were from the Java region, and just over a quarter (27.7%) were from the Sumatera region. Respondents represented 504 unique healthcare facilities. (Questions 1-6)

Nearly a quarter of the respondents indicated that their healthcare facility had treated DR-TB patients for at least five years, and 11.3% responded that their facility had less than 12-months experience of treating DR-TB. The mean (range) number of patients that started treatment for DR-TB in the respondent's healthcare facility was 12 (0-476) in 2019 and 10 (0-283) in 2020. The lower number in 2020 is likely to reflect disruption due to the global Covid-19 pandemic. (Questions, 7, 11 &12)

Respondents from puskesmas indicated that GPs, nurses and pharmacists are the main clinical staff involved in DR-TB treatment at their facility. The majority of hospital respondents indicated that a range of specialists (including pulmonologists, internists and other specialists), GPs, nurses and pharmacists are involved in DR-TB care at their facility, with approximately 70% also having a data manager. (Questions 8-9)

[5] VigiBase search included the following medicines used to treat DR-TB: bedaquiline, clofazimine, cycloserine, delamanid, levofloxacin, linezolid and moxifloxacin. Medicines that are also used to treat DS-TB were excluded to identify only DR-TB cases.

[6] The number of reports found in VigiBase for DR-TB medicines is lower than the number BPOM advised they have submitted. The difference may be a result of the search strategy and the dates on which the data was reported.

Pharmaceutical and Therapeutics Committees were either not well publicised or are yet to be implemented in hospitals, with only 61.6% of hospital respondents (doctors, nurses and pharmacists only) aware of such a committee in their facility. (Question 10)

Respondents generally agreed or strongly agreed that aDSM is an essential component of DR-TB patient management and that it is important to report serious adverse events that occur during DR-TB treatment. (Question 14a-b)

Among the hospital respondents, 14.3% of doctors and 19.4% of nurses were not confident in their knowledge of how to manage serious adverse events in patients on DR-TB treatment. Almost two-thirds of hospital doctors and pharmacist and one-fifth of hospital nurses were not aware of which patients are eligible for aDSM. Similarly, more than a quarter of doctors and pharmacists, and one fifth of nurses were not familiar with how to report a SAE.

Among the puskesmas respondents, 26.7% of doctors and 22.2% of nurses were not confident in their knowledge of how to manage serious adverse events. More than a quarter of doctors, nurses and pharmacists did not know which patients are eligible for aDSM and approximately 20 percent did not know how to monitor patients for adverse events. Some puskesmas respondents indicated that they were not familiar with how to report a SAE (doctors 33.3%, nurses 16.0% and pharmacists 24.1%). (Question 14c-f)

Approximately one-third of hospital doctors and nearly one-half of puskesmas doctors were not familiar with the term 'causality assessment'. (Question 14g)

The majority of respondents (90.2%) had not received training on aDSM. Most of the 61 respondents who had received aDSM training did so as part of an MDR-TB workshop within the past two years. (Questions 15-17)

Approximately 60-70% of respondents were able to correctly assess the seriousness of four case scenarios. The remaining 30-40% were either incorrect or did not know whether the scenario described a serious AE. (Questions 18-21)

Respondents indicated that tools needed for physical examination are not available at all treatment facilities. Weight scales, hight measures and stethoscopes are widely available in the hospital clinics and puskesmas. There is less availability of tendon hammers, tuning forks, Snellen charts, Ishihara cards, and audiometry in both settings. ECG and CXR are rarely available in puskesmas, but usually available in the hospital clinics. (Question 25)

Overall, the most common challenge identified for performing physical examinations were the lack of equipment, (including unavailability, insufficient number and broken/uncalibrated equipment). Other issues suggested a lack of qualified staff to examine patients. (Question 26)

The most common challenge in obtaining laboratory and other diagnostic tests was unavailability of the test (30.3%). Other key issues identified were a lack of test reagent, lack of expertise to perform the test and budget constraints. (Question 27)

Nearly 92% of the doctor, nurse and pharmacist respondents at hospitals and puskesmas indicated that they routinely enquire about adverse effects at patient follow-up visits. Approximately half of these respondents also check the patient's symptom diary. (Question 28)

Challenges in ascertaining whether a patient has experienced adverse effects to DR-TB medicines included: (Question 29)

- **Communication**: difficulty contacting patients due to poor internet and cellular network connectivity in some areas, language barriers (including hearing loss in some patients), over-crowding in clinics and limited consultation skills prevent effective communication

- **Service provision**: limited access to afterhours health care and laboratory services for patients who experience adverse effects at home
- **Healthcare facilities**: lack of diagnostic equipment and space for physical examination in some clinics
- **Knowledge**: lack of awareness about adverse effects to DR-TB medicines among patients and healthcare workers

Approximately half of the clinical respondents (doctors, nurses and pharmacists) indicated that their healthcare facility has a guideline or SOP for reporting SAEs. (Question 30).

Approximately 70% of respondents are using SITB to report SAEs in their healthcare facility (Question 31)

Nurses and doctors are mainly responsible for filling in the AE reporting form in both hospitals and puskesmas. Approximately one-third of hospital respondents and one-quarter of puskesmas respondents indicated that pharmacists are also responsible for completing the forms. The focal person for aDSM is also responsible for reporting SAEs in some facilities (indicated by approximately one-quarter of puskesmas and hospital respondents). (Question 32)

Pharmacists, doctors, nurses and the focal person for aDSM are all responsible for submitting SAE reports to BPOM (Question 33).

In total, 177 (28.5%) of the 620 respondents (88 puskesmas, 89 hospital) indicated that they had reported a SAE. Of these, nurses were the main group at both puskesmas (74/88, 84.1%) and hospitals (53/89, 59.6%). Hospital pharmacists were the next largest group to have reported an SAE (16/89, 18%). SAEs were more likely to be reported on the same day or within one week of the patient consultation. Approximately 43% indicated that they encountered some difficulty when trying to report a SAE. The difficulties reported were mainly due to not knowing how to report and what information to include in the report. The reporting form (paper or SITB) was not available in some locations, so SAE reported via WhatsApp or phone instead. Internet and cellular connectivity issues were also noted. (Questions 34-37)

Among 427 respondents who had not reported a SAE, the majority stated that it was because their patients had not experienced any SAEs. Other key reasons for not reporting were not knowing how to report or which events should be reported. (Question 38)

Overall, 571 (92.1%) of respondents indicated that they would like to receive training on aDSM. The majority (75.3%) indicated that they would like to receive training in all aspects of aDSM, including how to monitor patients for AEs, how to identify SAEs, how to report SAEs and how to manage AEs. Other aDSM training topics suggested by respondents were:

- Side effects of TB drugs
- Referral process
- Benefits (of aDSM) for patients in particular and society in general
- How to differentiate SAE to TB medicines from progression of underlying comorbidities
- Roles and responsibilities of the different types of healthcare professionals for reporting SAEs.

The preferred training method for most respondents is a mix of online training workshop and self-paced online training modules. (Questions 39-41)

The final survey question solicited further comments or suggestions for how to improve aDSM in their health facility. Responses can be grouped as follows:

- **Training**: More training is needed. SAE form is too complicated.

- **Guideline**: More guidance on how to conduct aDSM is needed, including roles and responsibilities for aDSM
- **Human resources**: There is a need for more human resources to conduct aDSM effectively and improve reporting. Greater use of pharmacists for monitoring patient medication.
- **Equipment and facilities**: IT equipment such as laptops for entering data information into SITB so that staff do not need to use their own devices. Poor internet is a problem. Build capacity for clinical resources such as examination and laboratory equipment.
- **Coordination**: Better coordination between doctors, nurses, pharmacists and other team members. Improve coordination between puskesmas and hospital level facilities
- **Communication**: Improve patient consultation skills for healthcare staff. Involve family members in patient's treatment. Ask patients about adverse effects to medicines at each encounter.

7 Challenges and weaknesses in aDSM implementation

Challenges and weaknesses noted in the presentations, discussions and survey responses are grouped below by theme.

Theme 1: Insufficient awareness of aDSM in DR-TB treatment facilities

- Low visibility of aDSM in policy/guideline documents.
    - Strengthening pharmacovigilance of anti-TB drugs is mentioned briefly in the National Strategy for Tuberculosis Care and Prevention 2020-2024.
    - The National PMDT Guideline recommends that NTPs implement aDSM for all patients enrolled on DR-TB treatment, without further detail.
- There is no national guideline on aDSM for healthcare facilities.
- Lack of knowledge about patient eligibility for aDSM and how to report SAEs was evident in the survey responses.
- SAEs are under-reported in SITB. In 2020, only 5.4% of deaths in patients on DR-TB treatment were recorded as SAEs in SITB.
- More training requested by majority of survey respondents

Theme 2: Difficulty observing or recognising SAEs

- Lack of awareness about what constitutes a 'serious' adverse event. The survey found that approximately 60-70% of respondents were able to correctly assess the seriousness of four case scenarios. The remaining 30-40% were either incorrect or did not know whether the scenario described a serious AE.
- Barriers to accessing healthcare, such as limited availability of afterhours services or healthcare services that are located a long way from the patient's home, may reduce the opportunity to detect or recognise adverse effects.
- Patients are sometimes unwilling to travel to hospital for further assessment and treatment of AEs
- Family members sometimes collect the patient's medicine, so patient is not seen.

Theme 3: Communication

- Patients are sometimes unwilling to disclose that they are experiencing side-effects to a DR-TB medicine, to avoid additional medicines or referral to hospital

- Busy, over-crowded clinics, language barriers and hearing loss create barriers to effective communication.
- There are difficulties contacting patients due to poor internet and cellular connectivity

Theme 4: Recording and reporting of SAEs

- Little information is available on patients who die at home. There are often delays between the death and the puskesmas or hospital being notified, which lead to delays in reporting (deaths should be reported to BPOM/NTP within 24 hours).
- Reports entered into SIBT are not submitted to BPOM until the report status is changed from 'draft' to 'final'. The finalisation step is often not completed. It is not clear who is responsible for ensuring the report is finalised and submitted to BPOM. In 2020, just over half of the SAEs recorded in SITB were submitted to BPOM via the eMESO bridge.
- SITB tool limitations:
    - SITB allows information on a predetermined list of AEs to be recorded in the daily monitoring page. Other types of AE cannot be recorded here.
    - The list of AE terms is not optimised. For example, there is some overlap in the terms 'joint pain', 'ankle pain', and 'swelling and redness in the joints'.
    - The process of recording the presence or absence of each of the symptoms in the list on a daily basis appears to be quite onerous. For it to work as designed, each of the 24 symptoms on the list would need to be opened each day to report its presence or absence.
    - The SAE page is not auto-populated with data from elsewhere in the SITB system. For example, medicines start and stop dates and dose could be pre-loaded into the SAE form.
    - The STIB system often 'crashes' and health centre staff are unable to enter data.
- SAE reports entered into SITB are not always complete, and can lack important information needed for causality assessment. For example, laboratory results, onset dates, pre-existing conditions, action taken and effect of intervention may be missing from the report.
- eMESO does not send an automatic acknowledgement when the SAE report has been submitted and no report ID/reference is provided.
- The outcome of the SAE is not always known at the time of reporting. In this situation the outcome should be recorded as 'not yet recovered' and a follow-up report submitted when the outcome is known.
- There is no mechanism for updating a report with additional information if it becomes available, such as the outcome of an adverse event.
- Many healthcare workers are not yet familiar with how to report SAEs in the SITB system.

Theme 5: Causality Assessment of SAE reports

- The National Pharmacovigilance Committee for TB medicines meets infrequently due to limited availability of members. SAE reports are not submitted to VigiBase until they have been assessed by the Committee.
- The treating physician is invited to participate in the causality assessment meeting to provide additional clinical details from the patient's record. However, the physician who

attends the meeting may not have been directly involved in the patient's care. Case information for review is often incomplete and inadequate for causality assessment.

- The interval between the SAE and the causality assessment may be quite long (in some cases more than a year) and it may be difficult to obtain further information about the case from the clinical team if needed.

Theme 6: Signal detection and communication

- Although individual case reports have been assessed, there has been no analysis of the reports to determine whether there are any potential safety signals.
- The NTP participates in the causality assessment meetings and the meeting minutes are shared with the NTP, but there is no formal mechanism for communicating aDSM outcomes directly with the NTP (such as a quarterly report of cases, assessed causality and reporting trends).
- There is no formal mechanism for providing feedback (in the form of summary statistics/aggregate data) to the reporters.

Theme 7: Human resources

- Roles and responsibilities for aDSM not well defined
- Training on aDSM and AE recording and reporting in SITB is needed for new staff.

8 Recommendations

1. Compile/develop a simple aDSM guideline for use in hospitals and clinics. The guideline would include clear guidance on WHICH medicines/regimens are eligible for aDSM, WHAT constitutes a serious adverse event, HOW to report a SAE in SITB, WHO is responsible for submitting the report and WHEN the report should be submitted.
2. Develop interactive self-paced training modules on aDSM for healthcare workers, including how to use SITB AE recording and SAE reporting pages. Link the learning modules to professional development requirements and/or workplace orientation to encourage uptake.
3. Provide training for healthcare workers on how to adopt a more patient-centred approach when discussing adverse effects with patients and family members/support person. The training would cover how to enquire about adverse effects at each patient encounter (real or virtual). For example, asking about how the patient is feeling in general, followed by more targeted questions about clinical symptoms of common AEs, and giving the patient time to raise concerns about their medicines may help to identify treatment-related adverse effects.
4. Optimise pharmacist involvement in DR-TB patient care, including educating patients on possible adverse effects to DR-TB medicines and what to do if they experience an adverse effect.
5. Strengthen use of the patient diary for recording adverse events/side-effects. Encourage family members to record the patient's symptoms if the patient is too unwell to do so.
6. Implement procedures for conducting a verbal autopsy[7]when a patient dies at home.
7. Improve the quality of SAE reports by further developing SITB. For example:

[7] See: www.who.int/standards/classifications/other-classifications/verbal-autopsy-standards-ascertaining-and-attributing-causes-of-death-tool

- use of auto-populated data fields to streamline date entry
- mandatory fields to ensure essential data is collected
- built-in guidance notes
- pop-up alerts on opening a case file to notify the user that a SAE report has not been finalised and submitted to BPOM.
- revise the daily symptom page so that it captures a wider range of symptoms (including free-text fields for symptoms that may not be on the list) and simplify the recording process.
- reduce system 'crashes'.

8. Develop a mechanism acknowledging receipt of the SAE report in eMESO, which includes the report ID/reference. The reference could then be used to report further information about the case if it becomes available (eg, outcome information).
9. Increase the frequency of causality assessment meetings to monthly so that all cases can be reviewed and submitted to VigiBase in a timely manner. It may not be necessary to include all members at each meeting, but setting a quorum would require a certain number to be present for the meeting to go ahead.
10. Strengthen process for ensuring all necessary information is available to the committee prior to meeting. Consider whether members of the National Pharmacovigilance Committee for TB Drugs members could have access to the SITB to check details in the patient's record directly, instead of needing to include the treating physician in the causality assessment meeting (given their limited availability to participate).
11. Conduct regular review of the cumulative SAE reports to identify potential safety signals as early as possible, so that the information may be used to inform clinical practice.
12. Establish mechanisms for communicating causality assessment conclusions on individual case reports, cumulative aDSM data reviews and potential safety signals between BPOM and NTP.
13. Establish a mechanism for providing feedback to DR-TB clinicians on the outcome of aDSM, including SAE reporting trends and any safety signals identified by the monitoring.

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