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# Pharmaceutical Care Contributes to Tuberculosis Treatment Adherence and Drug Safety in Indonesia: A Systematic Review

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**ABSTRACT**

Tuberculosis (TB) remains a major public health challenge in Indonesia, where long-term therapy is complicated by non-adherence and adverse drug events. Patient-centered pharmaceutical care—encompassing counseling, education, monitoring, and medication review—aims to address these therapeutic obstacles. This systematic review evaluated how pharmaceutical care contributes to medication adherence and drug safety among TB patients in Indonesia. Guided by PRISMA 2020, comprehensive searches were conducted across PubMed and Google Scholar (January 2014–June 2026) using Medical Subject Headings (MeSH) and tailored keywords. Primary Indonesian studies investigating pharmacist interventions and reporting adherence, adverse drug reactions (ADRs), or drug-related problems (DRPs) were included. Methodological quality was appraised using Joanna Briggs Institute (JBI) tools. The synthesis included 15 studies across diverse healthcare settings. Ten studies (66.7%) showed that pharmacist-led counseling, education, and monitoring significantly improved medication adherence (e.g., proportion of days covered and MMAS scores). DRPs affected up to 84.34% of patients, predominantly involving drug interactions and hepatotoxicity, with ADRs identified as a primary driver of treatment default. Categorical analyses across quasi-experimental, cohort, and cross-sectional designs confirmed that structured pharmaceutical care enhances treatment compliance and safety surveillance. In conclusion, integrating pharmacists into national TB control programs (DOTS/Puskesmas) is essential to reduce preventable DRPs and optimize therapeutic success.



## INTRODUCTION

Tuberculosis (TB), owing to its prolonged therapeutic duration and infectious nature, places a heavy operational and financial burden on health systems worldwide. Recent epidemiological figures indicate that TB remains among the foremost contributors to morbidity and mortality globally, with Indonesia continuing to rank second worldwide in disease burden (World Health Organization, 2025). Indonesia's national TB control strategy emphasizes early case detection, sustained multi-drug treatment, and integrated health services as key ways to improve treatment success rates (Ministry of Health Republic Indonesia, 2020). Together, these priorities show that effective TB management requires comprehensive, patient-centered care models that extend beyond clinical diagnosis and basic drug dispensing.

Successful treatment outcomes depend largely on whether patients maintain consistent adherence to lengthy anti-tuberculosis drug regimens. Because standard anti-TB therapy extends over a minimum of six months, patients frequently experience severe treatment fatigue, difficulty managing complex pill burdens, and anxiety over unfavorable side effects—obstacles that are greatly magnified when patient education and counseling are insufficient. Consequently, erratic or non-adherent drug intake leads to treatment failure, disease relapse, community-wide transmission, and the rapid emergence of drug-resistant strains such as multidrug-resistant TB (Alipanah et al., 2018; Müller et al., 2018).

Ensuring medication safety is an equally vital component of effective TB therapy. First-line anti-tuberculosis agents—specifically isoniazid, rifampicin, pyrazinamide, and ethambutol—are intrinsically capable of producing severe adverse drug reactions (ADRs), including drug-induced liver injury (hepatotoxicity), gastrointestinal disturbances, and peripheral neuropathy. Such adverse reactions markedly diminish patient tolerance and drastically elevate the risk of therapy interruption or default. Early identification and structured management of ADRs, drug-related problems (DRPs), and drug therapy problems (DTPs) allow clinical teams to preserve therapeutic efficacy while safeguarding patient safety.

Pharmaceutical care is a patient-centered model of pharmacy practice in which pharmacists take direct responsibility for drug therapy outcomes to improve patient quality of life (Hepler & Strand, 1990). Within TB management, pharmaceutical care encompasses tailored medication counseling, patient education, adherence tracking, pharmacovigilance surveillance, medication reconciliation, and interprofessional coordination. Numerous primary studies across Indonesia have evaluated pharmacist-led interventions in TB care, demonstrating positive impacts on patient knowledge, adherence, and safety (Karuniawati et al., 2019; Priyandani et al., 2022). However, these studies exhibit considerable heterogeneity in study design, clinical settings, intervention protocols, and outcome metrics, leaving the national evidence base fragmented. Therefore, this systematic review synthesizes current evidence on the contribution of pharmaceutical care to medication adherence and drug safety among TB patients in Indonesia.

## METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement (Page et al., 2021). Although the review protocol was not formally registered in PROSPERO, the review strictly adhered to a pre-formulated methodology specifying research questions, explicit eligibility criteria, systematic search strategies, independent screening, structured data extraction, and formal methodological quality appraisal. Ethical approval was not required as the study relied exclusively on published secondary literature.

Eligibility criteria were defined based on the PICOS framework. Inclusion criteria comprised: (1) Population: Patients diagnosed with drug-sensitive or drug-resistant TB receiving anti-TB therapy in Indonesia; (2) Intervention/Exposure: Pharmaceutical care services, clinical pharmacy interventions, or pharmacist involvement (counseling, education, monitoring, DRP identification, reconciliation); (3) Comparators: Standard care or pre-intervention baseline; (4) Outcomes: Medication adherence, ADR incidence, DRP/DTP prevalence, or therapeutic success; (5) Study Designs: Primary empirical studies (quasi-experimental, cohort, cross-sectional, descriptive, database monitoring). Studies were excluded if they were conducted outside Indonesia, lacked primary data (reviews, editorials, opinions), did not evaluate pharmacist interventions, or lacked quantifiable adherence or safety outcomes.

Comprehensive literature searches were executed across PubMed and Google Scholar for articles published between January 2014 and June 2026. The search strategy incorporated Medical Subject Headings (MeSH) terms in PubMed (e.g., 'Tuberculosis'[Mesh], 'Pharmaceutical Services'[Mesh], 'Medication Adherence'[Mesh], 'Drug-Related Side Effects and Adverse Reactions'[Mesh]) alongside free-text keywords. The English search string was: (tuberculosis OR TB) AND (pharmaceutical care OR clinical pharmacy service OR pharmacist intervention) AND (medication adherence OR treatment compliance) AND (adverse drug reaction OR drug-related problems OR drug therapy problems OR medication safety). Equivalent Indonesian search terms were utilized to capture national journals. Full database search algorithms are provided in Supplementary Table S1.

Two reviewers independently screened titles, abstracts, and full texts and resolved discrepancies by consensus. Data extraction captured author/year, study design, participant characteristics (sample size N, age range, healthcare setting, TB type), pharmaceutical care components, outcome measures, adherence assessment instruments (Proportion of Days Covered [PDC], Morisky Medication Adherence Scale [MMAS-8], pill count, self-report), DRP/ADR

classification systems (Pharmaceutical Care Network Europe [PCNE v9.0], Cipolle DTP framework, Naranjo scale, WHO-UMC causality), and primary findings.

Methodological quality was appraised independently using the Joanna Briggs Institute (JBI) Critical Appraisal Tools tailored to each study design (Aromataris & Munn, 2020). Risk of bias was categorized as low, moderate, or high based on sample selection, validity of measurement tools, confounding control, and analytical appropriateness. Due to clinical and methodological heterogeneity across studies, data were synthesized narratively grouped into three distinct study design categories.

## RESULTS

### Study Selection

The initial database searches yielded 245 records (242 from Google Scholar and 3 from PubMed). After title and abstract screening, 201 records were excluded as irrelevant. Full-text assessment of 44 articles led to the exclusion of 29 studies because of ineligible populations, no pharmaceutical care evaluations, or incomplete outcome reporting. Ultimately, 15 primary studies met all criteria and were included in the synthesis.

### Characteristics of included studies

The 15 included studies (published 2014–2026) encompassed interventional quasi-experimental trials, prospective/retrospective cohorts, cross-sectional surveys, and database monitoring studies across primary care centers (Puskesmas), hospitals, and pharmacovigilance databases.

**Table 1. Details participant characteristics, sample sizes, adherence tools, and DRP frameworks**

| Study (Author, Year) | Design | Setting & Sample (N, Age, TB Type) | Pharmaceutical Care Component | Instruments & Systems | Main Findings |
|---|---|---|---|---|---|
| Priyandani et al. (2022) | Quasi-experimental | Puskesmas Surabaya (N=68, Adult DS-TB) | Verification, education, monitoring model | PDC & Pill count | Significant adherence improvement in FDC therapy ($p < 0.05$). |
| Karuniawati et al. (2019) | Quasi-experimental | Lung Hospital (N=50, Adult Pulmonary TB) | Pharmacist counseling + educational leaflet | MMAS-8 score | Significant increase in adherence post-intervention ($p = 0.001$). |
| Noviyanto et al. (2024) | Cross-sectional | Puskesmas (N=45, Outpatient TB) | Drug information services (PIO) | Knowledge questionnaire | Enhanced patient understanding of dosing schedules. |
| Sari et al. (2014) | Monitoring study | Health Centers (N=112, Category-1 FDC) | ADR active monitoring | WHO-UMC scale | Mapped FDC side effect profile; GI and skin reactions most common. |

| Study (Author, Year) | Design | Setting & Sample (N, Age, TB Type) | Pharmaceutical Care Component | Instruments & Systems | Main Findings |
|---|---|---|---|---|---|
| Setiawan & Ascobat (2019) | Cross-sectional | Hospital Jakarta (N=140, Adult DS-TB) | ADR identification in medical records | Naranjo causality scale | ADR occurrence significantly linked to default risk (OR = 3.2, p < 0.05). |
| Lestari et al. (2025) | Descriptive | National Database (N=320 reports) | Pharmacovigilance monitoring | National MESO system | Hepatotoxicity and skin rash represented 62% of reported ADRs. |
| Perwitasari et al. (2025) | Prospective cohort | Hospitals (N=95, Adult TB) | Liver function & adherence monitoring | SGOT/SGPT logs & PDC | Early liver enzyme monitoring prevented severe hepatotoxicity interrupt. |
| Anggraeni et al. (2026) | Retrospective cohort | Hospital Jember (N=83, DS-TB) | DRP identification & review | PCNE Classification v9.0 | DRPs detected in 84.34% of patients; interactions and ADRs were the main causes. |
| Wijaya et al. (2024) | Cross-sectional | Puskesmas Surabaya (N=105, Outpatient TB) | DTP assessment | Cipolle DTP Framework | Polypharmacy is significantly associated with a higher DTP rate (p < 0.05). |
| Wardani (2025) | Retrospective cohort | Hospital (N=42, Outpatient TB) | Clinical pharmacy service monitoring | Medical record audit | High clinical monitoring correlated with treatment success. |
| Syafhan et al. (2025) | Cross-sectional | Puskesmas (N=118, Adult DS-TB) | Adherence evaluation via prescription refill | PDC metric (PDC >= 80%) | 82.2% achieved high adherence under structured pharmacy refills. |
| Hardianita & Nurlaeli (2025) | Cross-sectional | Puskesmas (N=55, Pulmonary TB) | Education & self-report adherence audit | Modified MMAS-4 | 78% showed good adherence following counseling. |

| Study (Author, Year) | Design | Setting & Sample (N, Age, TB Type) | Pharmaceutical Care Component | Instruments & Systems | Main Findings |
|---|---|---|---|---|---|
| Halim et al. (2023) | Descriptive | Outpatient Clinic (N=38, Pulmonary TB) | Refill & adherence evaluation | Pill count audit | Need for continuous ongoing education highlighted. |
| Perwitasari et al. (2022) | Cross-sectional | Banyumas (N=88, Outpatient TB) | Hepatotoxicity education & monitoring | Knowledge & MMAS-8 | Knowledge of hepatotoxicity was significantly linked to adherence ($p < 0.05$). |
| Yulia & Andrajati (2021) | Retrospective cross-sectional | Hospitals (N=150, Inpatient/Outpatient) | Medication reconciliation | Standard Reconciliation Form | Reconciliation identified medication discrepancies in 34.6% of patients. |

**Categorized analysis: contribution to treatment adherence**

Ten of the 15 studies (66.7%) demonstrated a positive contribution of pharmaceutical care to medication adherence. Grouping by study design revealed distinct levels of evidenc:

1. First, interventional and quasi-experimental studies with control or pre-post groups showed statistically significant adherence gains. Karuniawati et al. (2019) observed a significant increase in MMAS-8 scores ($p = 0.001$) following structured pharmacist counseling paired with educational leaflets. Similarly, Priyandani et al. (2022) confirmed that a structured pharmaceutical care verification and monitoring model significantly enhanced PDC adherence rates for fixed-dose combination (FDC) regimens ($p < 0.05$).
2. Observational & Cohort Studies: Wardani (2025) and Perwitasari et al. (2025) showed that continuous clinical monitoring by pharmacists maintained high adherence, which strongly correlated with therapeutic success and prevented premature treatment default.
3. Cross-sectional and descriptive surveys using objective refill metrics (Syafhan et al., 2025) reported that 82.2% of patients receiving structured pharmaceutical care achieved PDC >= 80%. Educational interventions directly correlated with higher patient knowledge regarding hepatotoxicity and adherence (Perwitasari et al., 2022).

**Categorized analysis: contribution to medication safety and DRP management**

Pharmaceutical care substantially fortified medication safety through systematic DRP detection, ADR surveillance, and medication reconciliation:

1. DRP and DTP Identification: Utilizing the PCNE v9.0 classification, Anggraeni et al. (2026) identified DRPs in 84.34% of TB patients, driven primarily by drug-drug interactions and adverse events. Wijaya et al. (2024), applying Cipolle's framework, established that polypharmacy significantly increased DTP incidence ($p < 0.05$).
2. ADR Surveillance & Default Risk: Setiawan and Ascobat (2019) confirmed using Naranjo causality scoring that ADR occurrence was an independent risk factor for treatment default (OR = 3.2, $p < 0.05$). Pharmacist-led monitoring (Sari et al., 2014; Lestari et al., 2025) enabled early detection of FDC-induced hepatotoxicity and dermatological reactions.
3. Medication Reconciliation: Yulia and Andrajati (2021) showed that pharmacist reconciliation at hospital admission/discharge intercepted medication discrepancies in 34.6% of TB patients, preventing unintended therapy cessation.

### Risk of bias assessment

Quality appraisal using JBI tools classified 2 studies as low risk of bias, 10 as moderate risk, and 3 as high risk (Table 2).

**Table 2. Risk of bias assessment**

| Study | Design | Risk of Bias | Main Methodological Limitation |
|---|---|---|---|
| Priyandani et al. (2022) | Quasi-experimental | Moderate | Lack of full randomization across healthcare centers |
| Karuniawati et al. (2019) | Quasi-experimental | Moderate | Uncontrolled confounding patient socio-economic variables |
| Noviyanto et al. (2024) | Cross-sectional | Moderate | Cross-sectional design limits causal inference |
| Sari et al. (2014) | Monitoring study | Moderate | Observational design without parallel control cohort |
| Setiawan & Ascobat (2019) | Cross-sectional | Moderate | Retrospective medical record extraction limitations |
| Lestari et al. (2025) | Descriptive | Moderate | Spontaneous reporting database prone to underreporting |
| Perwitasari et al. (2025) | Prospective cohort | Low | Prospective design with standardized biomarker laboratory tracking |
| Anggraeni et al. (2026) | Retrospective cohort | Moderate | Single-center retrospective chart audit |
| Wijaya et al. (2024) | Cross-sectional | Moderate | Inability to establish temporal directionality |
| Wardani (2025) | Retrospective cohort | High | Small sample size (N=42) limiting statistical power |
| Syafhan et al. (2025) | Cross-sectional | Low | Objective refill PDC metric applied across a representative sample |
| Hardianita & Nurlaeli (2025) | Cross-sectional | Moderate | Self-reported adherence metric subject to recall bias |
| Halim et al. (2023) | Descriptive | High | Small sample size (N=38) at a single outpatient facility |
| Perwitasari et al. (2022) | Cross-sectional | Moderate | Self-administered survey tool without long-term follow-up |
| Yulia & Andrajati (2021) | Retrospective cross-sectional | High | Incomplete documentation in hospital archive records |

## DISCUSSION

### Methodological justification of search discrepancy

A notable finding in the search process was the stark discrepancy between records retrieved from Google Scholar (n=242) and PubMed (n=3). This discrepancy reflects the structure

of the publishing landscape for pharmacy research in Indonesia. Most Indonesian clinical pharmacy and pharmaceutical care evaluations are published in national, accredited university journals (indexed in SINTA and GARUDA). Google Scholar crawls these national journals comprehensively, but MEDLINE/PubMed largely omits them because of indexing constraints. While Google Scholar yields a broader record set that requires rigorous manual screening to remove duplicates and grey literature, relying solely on PubMed would have introduced severe geographical selection bias by omitting over 90% of locally conducted empirical studies.

### Impact on adherence, safety, and clinical practice

The synthesized evidence confirms that pharmaceutical care plays a pivotal role in strengthening TB management in Indonesia. Interventional studies established statistically significant improvements in adherence metrics (PDC and MMAS scores, $p < 0.05$) when pharmacists provided structured counseling paired with visual educational leaflets (Karuniawati et al., 2019; Priyandani et al., 2022). Education directly mitigated patient anxieties regarding drug toxicity, thereby directly addressing key behavioral drivers of default. From a safety perspective, detecting DRPs in up to 84.34% of patients (Anggraeni et al., 2026) and establishing ADRs as a primary predictor of default (OR = 3.2; Setiawan & Ascobat, 2019) underscores that clinical pharmacists are indispensable for early pharmacovigilance and therapeutic optimization within the national Directly Observed Treatment Short-course (DOTS) framework.

### Strengths, limitations, and PROSPERO disclosure

This review possesses key strengths, including strict adherence to PRISMA 2020 guidelines, rigorous JBI appraisal, and a specific focus on Indonesian health system dynamics. Limitations include the lack of PROSPERO registration, the exclusion of Scopus/Web of Science databases, and the predominance of observational study designs, which precludes formal meta-analytical pooling.

## CONCLUSION

Pharmaceutical care significantly contributes to improving treatment adherence and medication safety among TB patients in Indonesia. Pharmacist-led counseling, educational leaflets, structured refill monitoring, PCNE-based DRP identification, and medication reconciliation collectively mitigate therapeutic barriers and intercept drug toxicity.

Based on these findings, the following actionable recommendations are proposed at the policy and programmatic level (The Ministry of Health of the Republic of Indonesia and local health offices) to formally incorporate clinical pharmacists into multidisciplinary DOTS teams across all Puskesmas and hospitals and establish standardized pharmaceutical care performance indicators. Healthcare facilities should mandate standardized DRP documentation using PCNE v9.0, routine PDC refill tracking, and routine liver enzyme surveillance for patients on FDC regimens. Future studies should employ multi-center randomized controlled trials (RCTs) utilizing objective adherence measures (PDC) and standardized clinical outcome endpoints.

## AUTHOR'S DECLARATION

### Authors' contributions and responsibilities

**RW:** conducted conceptualization, data curation, analysis, and draft writing; **EYS:** provided methodology supervision, validation, and manuscript editing.

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**Availability of data and materials**
Data examined in this review are derived from published literature cited in this manuscript and supplementary files.

**Competing interests**
The authors declare no competing financial or personal interests.

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