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Research Article

Association of Vitamin B6 Administration with Adverse Events of Antituberculosis Drugs in Drug-Resistant Tuberculosis Patients

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Vitamin B6 (pyridoxine) is routinely co-administered with second-line antituberculosis drugs to prevent neurotoxicity, but its benefit in injection-free regimens for drug-resistant tuberculosis (DR-TB) remains unclear. This study aimed to analyze the association between vitamin B6 administration and the occurrence of antituberculosis drug adverse events in patients with MDR/RR-TB. A retrospective cohort study was conducted on 230 treatment episodes of the shorter treatment regimen (STR) and the longer treatment regimen (LTR) among 216 patients at dr. Soebandi Regional Hospital, Jember, in 2021–2023. Data were analyzed using chi-square/Fisher tests, Mantel-Haenszel stratification, binary logistic regression, and *generalized estimating equations* (GEE). Vitamin B6 was given in 100 episodes (43.5%), mainly with the LTR (66.7% vs. 8.7% with the STR). Adverse events occurred in 74.0% of episodes with B6 and in 41.5% of episodes without it ($p < 0.001$). After adjustment for regimen, age, and sex, B6 administration remained associated with any adverse event (aOR 3.56; 95% CI 1.79–7.07), gastrointestinal events (aOR 2.45; 1.26–4.78), and musculoskeletal events (aOR 2.83; 1.31–6.09), but not with skin events. Similar results were obtained in the LTR-only and GEE analyses. Vitamin B6 administration was not associated with fewer antituberculosis drug adverse events. The positive association observed likely reflects *confounding by indication* because the timing of B6 administration was not recorded; prospective studies recording the start date, dose, and reason for B6 administration are therefore needed.

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Indonesia accounted for 10% of global tuberculosis (TB) cases in 2024, the second highest after India, out of a total of 10.7 million people who fell ill with TB [1]. In the same year, an estimated 390,000 people worldwide developed rifampicin-resistant or *multidrug*-resistant TB (MDR/RR-TB) [1]. Treatment of drug-resistant TB (DR-TB) is longer, involves more drugs, and causes adverse events more often than treatment of drug-susceptible TB.

In 2025, the WHO consolidated all of its TB treatment recommendations into a single guideline that includes the 6-month all-oral BDLLfxC regimen and modified 9-month regimens for MDR/RR-TB [2]. In Indonesia, the management of DR-TB follows the Technical Guidelines of the Ministry of Health [3]. In practice, the two most widely used regimens are a 9-month all-oral bedaquiline-based regimen and an 18-month regimen containing linezolid and

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cycloserine[4]. Adverse events are a major problem of bedaquiline-based regimens. A 2026 systematic review reported adverse events in 41.8–72.8% of patients in implementation studies, with serious adverse events in 2.2–30.2% [5]. A cohort from three Indonesian referral hospitals recorded nausea or vomiting in 48.3% of patients, arthralgia in 38.3%, and QTcF interval prolongation in 30.0% during the first 4 months [4]. Linezolid has been associated with peripheral neuritis and gastrointestinal disturbances, whereas clofazimine has been associated with skin discoloration [6]. Linezolid-induced peripheral neuropathy depends on dose and duration, ranging from 13–38% in the ZeNix trial [7] to 3.5–91.9% across various studies [8].

Vitamin B6 (pyridoxine) is commonly given with cycloserine and isoniazid to prevent neurotoxicity [9]. However, evidence of its benefit in modern DR-TB regimens is inconsistent. A 2023 review found conflicting evidence for cycloserine and no protective effect in regimens without isoniazid; withdrawing the causative drug was more effective than pyridoxine [9]. A prospective cohort of patients receiving terizidone even found neuropathy to be more frequent with a pyridoxine dose of 200 mg than with 150 mg per day (aHR 2.79) [10]. Excess vitamin B6 is also known to cause neuropathy [11].

Previous studies on pyridoxine in drug-resistant TB (DR-TB) have focused on neuropathy or neurotoxicity as a single outcome, mostly in regimens containing cycloserine/terizidone or isoniazid, and their findings are inconsistent [9, 10]. In a Georgian cohort of 100 patients receiving linezolid with pyridoxine prophylaxis of at least 50 mg/day, linezolid-attributed peripheral neuropathy still occurred, and it was associated with the 50 mg/day dose rather than 100–200 mg/day [12]. Conversely, long-term or high-dose pyridoxine can itself cause sensory neuropathy [13, 14], and the European Food Safety Authority used peripheral neuropathy as the critical effect when it set a tolerable upper intake level of 12 mg/day for adults [15]. Evidence on vitamin B6 in modern bedaquiline-based regimens that include linezolid is limited. It is also unknown whether vitamin B6, which in routine practice is recorded as part of the regimen, is related to other categories of adverse events.

At dr. Soebandi Regional Hospital, Jember, vitamin B6 50 mg is recorded as part of the regimen for some DR-TB patients. Although the established benefit of pyridoxine is the prevention of neurotoxicity, adverse events in this study were grouped by organ system as documented in the medical records. Gastrointestinal, musculoskeletal, and skin events were analyzed because they were the most frequent categories in this cohort (44.3%, 29.1%, and 16.5%, respectively) and are the categories linked to linezolid, cycloserine, and clofazimine in earlier reports [4, 6, 8]. Hepatic and renal events were too rare (3 and 1 episodes) to be analyzed. Numbness/tingling of the hands or feet and peripheral neuropathy are recorded as separate items in the Indonesian Tuberculosis Information System (SITB), but in this study they were grouped with musculoskeletal events and were not assessed with a standardized neuropathy tool. This study therefore aimed to evaluate, as an exploratory real-world analysis, the association between vitamin B6 administration and the occurrence of antituberculosis drug adverse events in patients with MDR/RR-TB at dr. Soebandi Regional Hospital, Jember, in 2021-2023.

Results and Discussion

Characteristics of the subjects

Of the 230 treatment episodes, vitamin B6 was given in 100 (43.5%). The median age of the subjects was 46.5 years (range 19–83); 119 episodes (51.7%) involved men, and 138 (60.0%) used the LTR. Vitamin B6 was given in 92 of 138 LTR episodes (66.7%) and in only 8 of 92 STR episodes (8.7%). The B6 group included more men and more often received linezolid and cycloserine (Table 1).

Table 1. Characteristics of treatment episodes by vitamin B6 administration

Characteristic	Vitamin B6 (n = 100)	No vitamin B6 (n = 130)	p-value
Age, years, median (range)	43 (20–75)	47 (19–83)	0.582[a]
Male, n (%)	60 (60.0)	59 (45.4)	0.028[b]
Resistance category[c], n (%)			0.067[d]
RR	66 (76.7)	87 (70.7)	
MDR	16 (18.6)	35 (28.5)	
Pre-XDR	4 (4.7)	1 (0.8)	
LTR regimen, n (%)	92 (92.0)	46 (35.4)	< 0.001[b]
Linezolid 600 mg, n (%)	89 (89.0)	44 (33.8)	< 0.001[b]
Cycloserine, n (%)	84 (84.0)	40 (30.8)	< 0.001[b]
Bedaquiline, n (%)	95 (95.0)	116 (89.2)	0.115[b]
Delamanid, n (%)	5 (5.0)	10 (7.7)	0.412[b]

[a] Mann-Whitney; [b] Pearson chi-square; [c] percentages of episodes with category data (21 episodes not recorded); [d] Fisher-Freeman-Halton. RR: rifampicin-resistant; MDR: *multidrug-resistant*; XDR: *extensively drug-resistant*; LTR: longer treatment regimen.

Adverse events by vitamin B6 administration

Overall, 128 episodes (55.7%) had at least one adverse event: gastrointestinal in 102 (44.3%), musculoskeletal in 67 (29.1%), skin in 38 (16.5%), hepatic in 3 (1.3%), and renal in 1 (0.4%). Gastrointestinal and musculoskeletal events were more frequent in the B6 group, whereas skin events did not differ significantly (Table 2). Episodes with B6 also more often had two or more types of adverse events (38.0% vs. 22.3%; 3-category chi-square $p < 0.001$).

Table 2. Adverse events by vitamin B6 administration (*crude* analysis)

Adverse event	Vitamin B6 (n = 100), n (%)	No vitamin B6 (n = 130), n (%)	p	OR (95% CI)
At least one type	74 (74.0)	54 (41.5)	< 0.001	4.01 (2.27–7.06)
Gastrointestinal	58 (58.0)	44 (33.8)	< 0.001	2.70 (1.58–4.62)
Musculoskeletal	40 (40.0)	27 (20.8)	0.001	2.54 (1.42–4.55)
Skin	20 (20.0)	18 (13.8)	0.213	1.56 (0.77–3.13)
Hepatic	0	3 (2.3)	0.260[a]	–
Renal	1 (1.0)	0	0.435[a]	–

Pearson chi-square test unless otherwise stated. [a] Fisher. OR: *odds ratio*; 95% CI: 95% confidence interval.

Stratification by regimen

Without vitamin B6, the frequency of adverse events was almost the same with the STR (40.5%) and the LTR (43.5%). With both regimens, adverse events were more frequent in episodes with B6, and the strength of the association was homogeneous across regimens (Table 3).

Table 3. Adverse events by vitamin B6 administration within each regimen, n (%)

Adverse event	STR + B6 (n = 8)	STR without B6 (n = 84)	LTR + B6 (n = 92)	LTR without B6 (n = 46)	Mantel-Haenszel OR (95% CI)	Breslow-Day p
At least one type	6 (75.0)	34 (40.5)	68 (73.9)	20 (43.5)	3.81 (1.93–7.52)	0.845
Gastrointestinal	4 (50.0)	28 (33.3)	54 (58.7)	16 (34.8)	2.52 (1.31–4.85)	0.730
Musculoskeletal	4 (50.0)	18 (21.4)	36 (39.1)	9 (19.6)	2.82 (1.35–5.90)	0.704
Skin	1 (12.5)	15 (17.9)	19 (20.7)	3 (6.5)	2.44 (0.92–6.53)	0.156

STR: shorter treatment regimen; LTR: longer treatment regimen; B6: vitamin B6; 95% CI: 95% confidence interval.

Multivariable and sensitivity analyses

In model A, vitamin B6 remained associated with any, gastrointestinal, and musculoskeletal adverse events, but not with skin events (aOR 2.15; 95% CI 0.81–5.72). After B6 was entered into the model, the LTR was no longer associated with adverse events (aOR 1.18; 0.60–2.32; p = 0.630). Younger age was associated with skin events (aOR 0.968 per year; p = 0.017). Model B, the LTR-only analysis, and GEE did not change the direction or magnitude of the association (Figure 1). Model calibration was good (Hosmer-Lemeshow p > 0.05), except for model A for musculoskeletal events (p = 0.048).

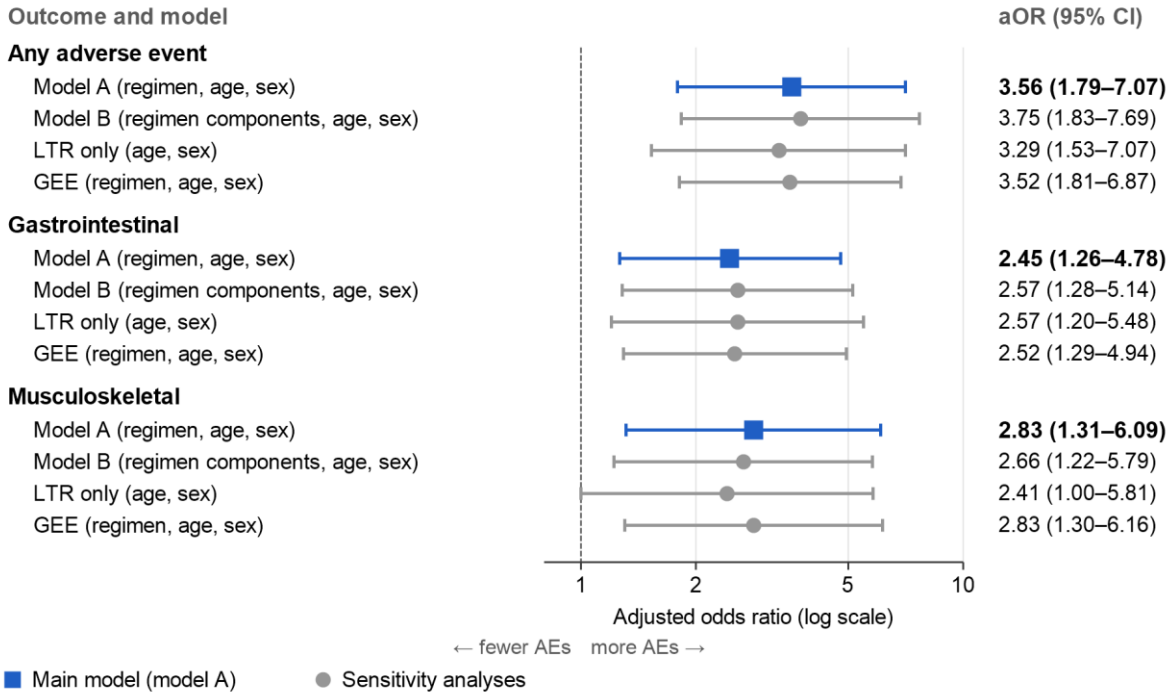


Figure 1. *Adjusted odds ratios* (aOR) of adverse events (AEs) in episodes with vs. without vitamin B6. Model A: regimen, age, sex; model B: linezolid, cycloserine, bedaquiline, delamanid, age, sex; LTR only (n = 138): age, sex; GEE: model A covariates with robust standard errors clustered by patient. Dashed line: OR = 1.

Interpretation of the main findings

This study found no association between vitamin B6 administration and fewer antituberculosis drug adverse events. Episodes with B6 instead had approximately 3.6-fold higher odds of adverse events after adjustment, and this association was consistent across stratification by regimen, the regimen-component model, the LTR-only analysis, and GEE.

The most likely explanation is *confounding by indication*, which occurs when a therapy is given because of a condition that also affects the outcome [16]. The data recorded only whether B6 was part of the regimen, not when or why it was given. If B6 was added after patients complained of tingling, muscle pain, or nausea, B6 would be a marker of adverse events rather than their cause. The data pattern supports this hypothesis: without B6, the frequency of adverse events with the STR and the LTR was almost the same (40.5% vs. 43.5%), and the association between the LTR and adverse events disappeared after B6 was entered into the model.

Vitamin B6 as a marker of neurotoxic drugs

The B6 group received linezolid (89.0% vs. 33.8%) and cycloserine (84.0% vs. 30.8%) much more often. However, adjustment for linezolid, cycloserine, bedaquiline, and delamanid did not weaken the association (model B). Residual confounding remains possible, for example from the dose and duration of linezolid, the treatment period, or closer monitoring that led to more adverse events being recorded in patients receiving B6.

Consistency with pharmacological evidence

A protective effect of B6 against gastrointestinal and skin adverse events would not be expected, because B6 is intended to prevent neurotoxicity. Even for neuropathy, a 2023 review found no protective effect of pyridoxine in regimens without isoniazid [9]. Even with pyridoxine prophylaxis of at least 50 mg/day, linezolid-attributed neuropathy occurred in a Georgian cohort and was associated with the 50 mg/day dose rather than 100–200 mg/day [12]. Linezolid-induced neuropathy is managed mainly by dose adjustment; a target trial emulation of 303 patients in the endTB cohort showed that an immediate change of linezolid did not reduce treatment success [17]. In a rat model, pyridoxine only partially relieved linezolid-induced neuropathic pain [18]. Higher pyridoxine doses were even associated with neuropathy in patients receiving terizidone [10], and excess B6 is known to be neurotoxic [11, 13, 14]. The 50 mg dose in this study is low, but it equals the reference point from which the European Food Safety Authority derived a tolerable upper intake level of 12 mg/day [15], and a cumulative effect over an 18-month regimen cannot be ruled out.

Comparison with other studies

The adverse event frequency of 55.7% of episodes falls within the range of 41.8–72.8% reported in implementation studies of bedaquiline-based regimens [5]. The frequencies of gastrointestinal (44.3%) and musculoskeletal (29.1%) events are close to the rates of nausea or vomiting (48.3%) and arthralgia (38.3%) in an Indonesian cohort [4]. Hepatic and renal events were rare (< 2%), so their association with B6 could not be assessed. Younger age was associated with skin events; this may be related to clofazimine-induced skin discoloration [6], which younger patients may complain about more often, but this hypothesis needs to be confirmed. Cycloserine-associated neuropsychiatric adverse events, whose risk increases with anemia and hypoalbuminemia [19], were not recorded in these data.

Clinical implications and limitations

Vitamin B6 cannot be considered protective against gastrointestinal or musculoskeletal adverse events. Structured active drug safety monitoring remains key [20], including linezolid dose adjustment when neuropathy develops [17]. Hospitals need to record the start date, dose, and reason for B6 administration so that its benefit can be evaluated.

This study has several limitations. First, the records did not document the start date or indication of vitamin B6; therefore, the temporal sequence between B6 administration and adverse event onset could not be determined, confounding by indication and reverse causation cannot be excluded, and a causal relationship cannot be inferred. Second, adverse events were grouped by organ system without severity grading, and numbness/tingling and peripheral neuropathy recorded in SITB were grouped with musculoskeletal events and were not assessed with a standardized neuropathy tool. Third, data on comorbidities (diabetes mellitus, HIV), nutritional status, and hemoglobin levels were not available, although these may affect the risk of adverse events [19, 21]. Fourth, the study was conducted in a single hospital, and the STR group receiving B6 was very small (n = 8).

Conclusion

Vitamin B6 administration was not associated with fewer antituberculosis drug adverse events in patients with MDR/RR-TB. Episodes with B6 instead more often had any, gastrointestinal, and musculoskeletal adverse events, independent of regimen, age, sex, and regimen components. This finding most likely reflects *confounding by indication* and does not indicate that B6 causes adverse events. Recording the start date, dose, and indication of B6, together with prospective studies using standardized neuropathy assessment, is needed to evaluate the benefit of B6 in regimens containing linezolid and cycloserine.

Materials and Methods

Design, setting, and subjects

This was an analytical observational study with a retrospective cohort design using the medical records of DR-TB patients at dr. Soebandi Regional Hospital, Jember, who started treatment in 2021–2023. All recorded treatment episodes were included (*total sampling*), comprising 235 episodes from 216 patients. A total of 19 patients had two episodes because of a regimen change, mostly from the STR to the LTR. The treatment episode was used as the unit of analysis because the regimen, and therefore exposure to vitamin B6 and to other drugs, changed between episodes; in this way, each adverse event was linked to the regimen in which it occurred. Five episodes of individualized or isoniazid-monoresistant regimens were excluded because they were not standardized and none of them included vitamin B6; the main analysis therefore included 230 episodes.

Variables and operational definitions

The exposure variable was the administration of vitamin B6 50 mg (yes/no), as recorded in the regimen details. The records documented whether vitamin B6 was part of the regimen, but not its start date or indication. The outcome variable was antituberculosis drug adverse events recorded in the medical records, grouped as gastrointestinal, skin, musculoskeletal, renal, and hepatic; the composite outcome was at least one type of adverse event. An adverse event was defined as any event documented by the treating clinician during the treatment episode in the medical record and in the Indonesian Tuberculosis Information System (Sistem Informasi Tuberkulosis, SITB), in which non-serious events are entered in the daily drug side-effect monitoring (MESO harian) form and serious adverse events are reported separately as KTD/ESO serius [3], and the recorded items were grouped by organ system (Table 4); severity was not graded in this study, and numbness/tingling and peripheral neuropathy, although recorded as separate SITB items, were grouped with musculoskeletal events and were not assessed with a standardized neuropathy tool. Covariates included regimen, age, sex, resistance category (RR, MDR, pre-XDR), and regimen components.

Table 4. Classification of adverse event items recorded in SITB into organ-system categories

Category	Adverse event items recorded in SITB (MESO harian)
Gastrointestinal	Nausea, including moderate–severe nausea with signs of dehydration (*mual*); mild vomiting (*muntah ringan*); moderate–severe vomiting (*muntah sedang-berat*); acute dyspepsia (*dispepsia akut*); mild–moderate abdominal pain (*nyeri perut ringan-sedang*); bloating (*perut kembung*); decreased appetite (*nafsu makan berkurang*)
Musculoskeletal	Joint pain (*nyeri persendian*); joint disorder (*gangguan sendi*); arthritis; joint swelling/redness (*bengkak/kemerahan pada sendi*); ankle pain (*nyeri pergelangan kaki*); numbness/tingling of the hands or feet (*rasa kebas/kesemutan pada tangan/kaki*)[a]; peripheral neuropathy (*neuropati perifer*)[a]
Skin	Skin discoloration (*perubahan warna kulit*); mild skin allergic reaction (*reaksi alergi kulit ringan*); moderate skin allergic reaction with/without fever (*reaksi alergi kulit sedang dengan/tanpa demam*); severe rash (*ruam berat*)
Hepatic	Liver disorder (*gangguan hati*); elevated SGOT and SGPT during treatment[b]
Renal	Elevated serum creatinine during treatment[b]
Not analyzed	Anemia; sleep disturbance, behavioral change, and depression/stress; visual disturbance and optic neuritis; chest pain, palpitations, and QTc prolongation; headache; tinnitus; cough; weakness with dyspnea; tendinopathy

SITB: Sistem Informasi Tuberkulosis (Indonesian Tuberculosis Information System); MESO: monitoring efek samping obat (drug side-effect monitoring). Serious adverse events (KTD/ESO serius) are reported in a separate SITB menu. Item names are given as written in SITB; spelling variants were merged. [a] Recorded as separate SITB items but grouped with musculoskeletal events; not assessed with a standardized neuropathy tool. [b] Laboratory values recorded during treatment; a hepatic event required elevation of both SGOT and SGPT, and a renal event required an elevated serum creatinine. SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase.

The STR consisted of bedaquiline, levofloxacin, ethionamide, ethambutol, pyrazinamide, isoniazid, and clofazimine, whereas the LTR generally consisted of bedaquiline, levofloxacin, linezolid, clofazimine, and cycloserine. Unrecorded resistance categories (21 episodes) were treated as missing data, and data on diabetes mellitus comorbidity were not analyzed because their recording was invalid.

Statistical analysis

Analyses were performed using IBM SPSS Statistics 27. Categorical data are presented as n (%). Age was not normally distributed (Shapiro-Wilk $p < 0.001$); it is therefore presented as median (range) and was compared using the Mann-Whitney test. Proportions were compared using Pearson's chi-square test, or Fisher's exact test when any cell had an expected frequency < 5 (Fisher-Freeman-Halton for tables larger than 2×2). The strength of association is expressed as the *odds ratio* (OR) with its 95% confidence interval (95% CI).

The role of regimen as a confounder was assessed using Mantel-Haenszel stratification and the Breslow-Day test of homogeneity. Multivariable analysis used binary logistic regression with the *enter* method: model A included vitamin B6, regimen, age, and sex, whereas model B replaced regimen with its component drugs (linezolid, cycloserine, bedaquiline, delamanid). Model calibration was assessed using the Hosmer-Lemeshow test. Sensitivity analyses included an LTR-only model and *generalized estimating equations* (GEE; binomial logit, *exchangeable* correlation, robust standard errors) to account for the non-independence of episodes from the same patient (19 patients contributed two episodes), with standard errors clustered by patient. A p-value < 0.05 was considered significant.

Research ethics

This study was approved by the Health Research Ethics Committee, Faculty of Dentistry, Universitas Jember (approval number 2746/UN25.8/KEPK/DL/2024, dated 5 August 2024) as part of the research protocol "Study of the Effect of Side Effects of Anti-tuberculosis Drugs on Adherence to Taking Medication for DR-TB Patients at RSD dr. Soebandi Jember". Patient identities were anonymized before analysis.

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