


Availability, affordability, and quality of essential antiepileptic drugs in Lao PDR

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Abstract

Objective: Epilepsy is a chronic condition treatable by cost-effective antiepileptic drugs (AEDs), but limited access to treatment was documented. The availability and affordability of good quality of AEDs play a significant role in access to good health care. This study aimed to assess the availability, affordability, and quality of long-term AEDs in Lao PDR.

Method: A cross-sectional study was performed in both public and private drug supply chains in urban and rural areas in Lao PDR. Data on AEDs availability and price were obtained through drug suppliers. Affordability was estimated as the number of day wages the lowest-paid government employee must work to purchase a monthly treatment. Samples of AEDs were collected, and the quality of AEDs was assessed through Medicine Quality Assessment Reporting Guidelines.

Results: Out of 237 outlets visited, only 50 outlets (21.1% [95% CI 16.1-26.8]) had at least one AED available. The availability was significantly different between urban (24.9%) and rural areas (10.0%), $P = .017$. Phenobarbital 100 mg was the most available (14.3%); followed by sodium valproate 200 mg (9.7%), phenytoin 100 mg (9.7%), and carbamazepine 200 mg (8.9%). In provincial/district hospitals and health centers, AEDs were provided free of charge. In other healthcare facilities, phenytoin 100 mg and phenobarbital 100 mg showed the best affordability (1.0 and 1.2 day wages, respectively) compared to carbamazepine 200 mg (2.3 days) and other AEDs. No sample was identified as counterfeit, but 15.0% [95% CI 7.1-26.6] of samples were classified as of poor quality.

Significance: We quantified and qualified the various factors contributing to the high treatment gap in Lao PDR, adding to diagnostic issues (not assessed here). Availability remains very low and phenobarbital which is the most available and affordable AED was the worst in terms of quality. A drug policy addressing epilepsy treatment gap would reduce these barriers.

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KEYWORDS

epilepsy, treatment gap, accessibility, antiepileptic drugs, Asia

1 | INTRODUCTION

Epilepsy is one of the most common neurological disorders, and an important contributor to global neurological DALYs, ranked fifth worldwide and fourth in southeast Asia.¹⁻³ About 80% of people with epilepsy (PWE) live in low- and middle-income countries (LMICs).⁴ Epilepsy is a chronic condition that can be treated by cost-effective first-line antiepileptic drugs (AEDs).⁵ Despite that, several studies have documented low availability and low affordability of AEDs in many LMICs both in the public and private sectors.^{6,7} Besides, a recent study in African countries has reported a high proportion of poor-quality AEDs with 32.3% of substandard drugs.⁸ Few studies have addressed this topic in Southeast Asia.^{9,10}

Lao PDR has a population of 6.5 million people and is a landlocked LMIC in Southeast Asia. The population density is 27 people per km² (Lao population and 2015 housing census). The public healthcare institutions are classified into four tiers including 5 central hospitals, 13 provincial hospitals, 136 district hospitals, and 1055 health centers.¹¹ Concerning the private supply chain, there are 1028 private clinics/hospitals and 2132 private pharmacies including level I pharmacies (managed by a pharmacist with a 5-year diploma), level II pharmacies (run by a pharmacist assistant with a 3-year diploma), and level III pharmacies (managed by a health professional, most often nurses or midwives) in 2014. These private facilities are mostly located in the capital city and other provincial urban cities.¹²

The prevalence of epilepsy in Lao PDR was 7.7/1000 with a high treatment gap exceeding 90%.^{13,14} The management of epilepsy has improved in recent years to reduce the treatment gap, resulting in a greater number of neurologists (a rise from two in 2011 to nine in 2018). Electroencephalography (EEG) and brain imaging (CT), which are considered essential for accurate classification of seizure types and epilepsy syndromes, are currently available in many provinces.^{14,15} A three-day training program is conducted every two months in various provinces, aimed at pediatricians, physicians, and nurses.¹⁶ A daily broadcast time slot was also obtained from the local radio station and has been informing the public on epilepsy since 2010.¹⁵ Six AEDs (phenobarbital, clonazepam, diazepam, carbamazepine, phenytoin, and sodium valproate) are listed in the National Essential Drug List 8th edition 2015 of Lao PDR.

AEDs availability is unevenly distributed throughout the country, and newer AEDs are unavailable¹⁷. A shortage

Highlights of the findings

- Limited access to antiepileptic drugs was mainly due to both availability and affordability issues.
- A proportion of 15.0% of the sample was of poor quality and concerned only phenobarbital.
- Overall availability of AEDs in all supply chains was significantly (<15%) below the WHO recommended threshold
- Cross-border trade flows seem to interfere with official drug supply channels and raise questions about control of batches, traceability, and pharmacovigilance
- Health centers and level III pharmacies should be authorized to dispense AEDs by improving knowledge and qualification of healthcare workers

of phenobarbital was documented all over the country in 2009.¹⁸ Only 25 kg of phenobarbital (yearly quota controlled by the International Narcotic Board Committee in Vienna) was imported for local production in Lao PDR. This quota was estimated to allow to treat a maximum of 650 patients per year,¹⁶ while the total number of expected PWE was estimated at 50,000 (according to the prevalence of 7.7/1000 and total population reported in Lao PDR in 2015¹⁹). No study was done on the availability of other AEDs such as carbamazepine, phenytoin, and sodium valproate. These data showed a gap between supply and demand of AEDs in this country.²⁰ In addition, the population coverage for all prepayment health financing schemes remained low, at 19.6% in 2012.¹² Out-of-pocket payment for medicines remains high and represents a financial barrier for healthcare accessibility in Lao PDR where there is no medicine price regulation. The price of medicines is based on cost plus profit margins for imported or locally produced items.²¹

A high prevalence of low-quality drugs has been reported on different types of drugs in this country.^{22,23} Storage conditions have been deemed inappropriate as medicines were exposed to heat, light, and humidity. Such storage conditions could enhance chemical degradation and alter the biopharmaceutical properties of the drugs.^{9,24} Moreover, 60% of medicines were sold in bulk without any labels. The shortage of proper packaging and labeling may not only result in

poor information on drug use but may also cause a quality issue.²⁵ This study aimed to examine the availability, affordability, and quality of all major first-line AEDs in the whole supply chain in Lao PDR, twenty-two years after the launch of the “Out of the Shadows” campaign and eleven years after the launch of the Mental Health Gap Action Program.

2 | METHODOLOGY

2.1 | Study area

A cross-sectional study was performed from February to May 2018 in Lao PDR. This study was carried out in three main provinces (Figure 1): Vientiane capital (center), Luang Prabang (Northern), and Champasack (Southern), which account for 30% of the national population.¹⁹ The total number of expected PWE in the study areas was estimated to be 15,000 (prevalence of 7.7/1000). These provinces have shown the fastest development of city areas and were declared as the center of economic development in Lao PDR.²⁶ Then, in each province, the district with the highest population density was selected as the urban district and the district that had the lowest population density was selected as the rural one.

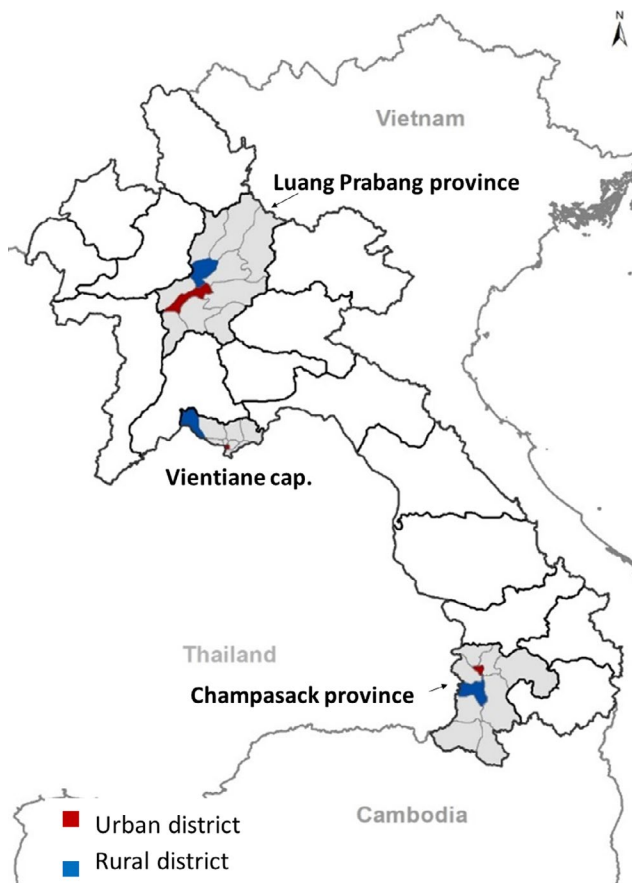


FIGURE 1 Study area

2.2 | Medicine inclusion criteria

The AEDs included were listed on the 20th WHO essential medicines list. Four AEDs were included: phenytoin, phenobarbital, carbamazepine, and sodium valproate. Only solid oral pharmaceutical forms (tablet/capsule) were investigated.

2.3 | Sample size

After communication with the district health officer in each district selected, we obtained the lists of registered public and private health facilities within the area. At the time of data collection, there were a total of 352 outlets registered in the 6 districts selected: 36 (10.2%) outlets were from the public sector (3 central hospitals, 2 provincial hospitals, 6 district hospitals, and 25 health centers) and 316 (89.7%) outlets were from the private sector (2 private hospitals, 99 private clinics, and 215 private pharmacies). Figure 2 presents the flowchart of the sampled outlets. Data on availability and price of AEDs were collected from all levels of public health facilities, and all private hospitals presented in both urban and rural districts. Random sampling was performed to select 50% of private pharmacies and private clinics in the urban district. In the rural district, all types of healthcare facilities were included.

2.4 | Data collection

In the public sector, AEDs availability, strength, cost, and country of manufacture were obtained from the head of the pharmacy service. In the private sector, the seller or owner of the outlet was not aware of the research study. Investigators of the study gathered information by acting as a patient, showing a handwritten prescription of AEDs with the International Non-proprietary Name (never the brand name) and then asking questions such as: “I would like to buy these drugs - Are these drugs available? If so, what strength? How much does it cost? And what is the country of manufacture?”.

2.5 | Availability and affordability endpoints

An AED was considered available if at least one strength of this AED was available in outlets, and its availability was expressed as a percentage, by molecule, and then by strength per molecule. To express the availability of medicines in the healthcare facilities, the following ranges were used: very low: < 30%; low: 30%-49%; fairly high: 50%-80%; high: >80%²⁷.

The customer price for purchasing AEDs was collected in Lao Kip (LAK) and converted in the international dollar,

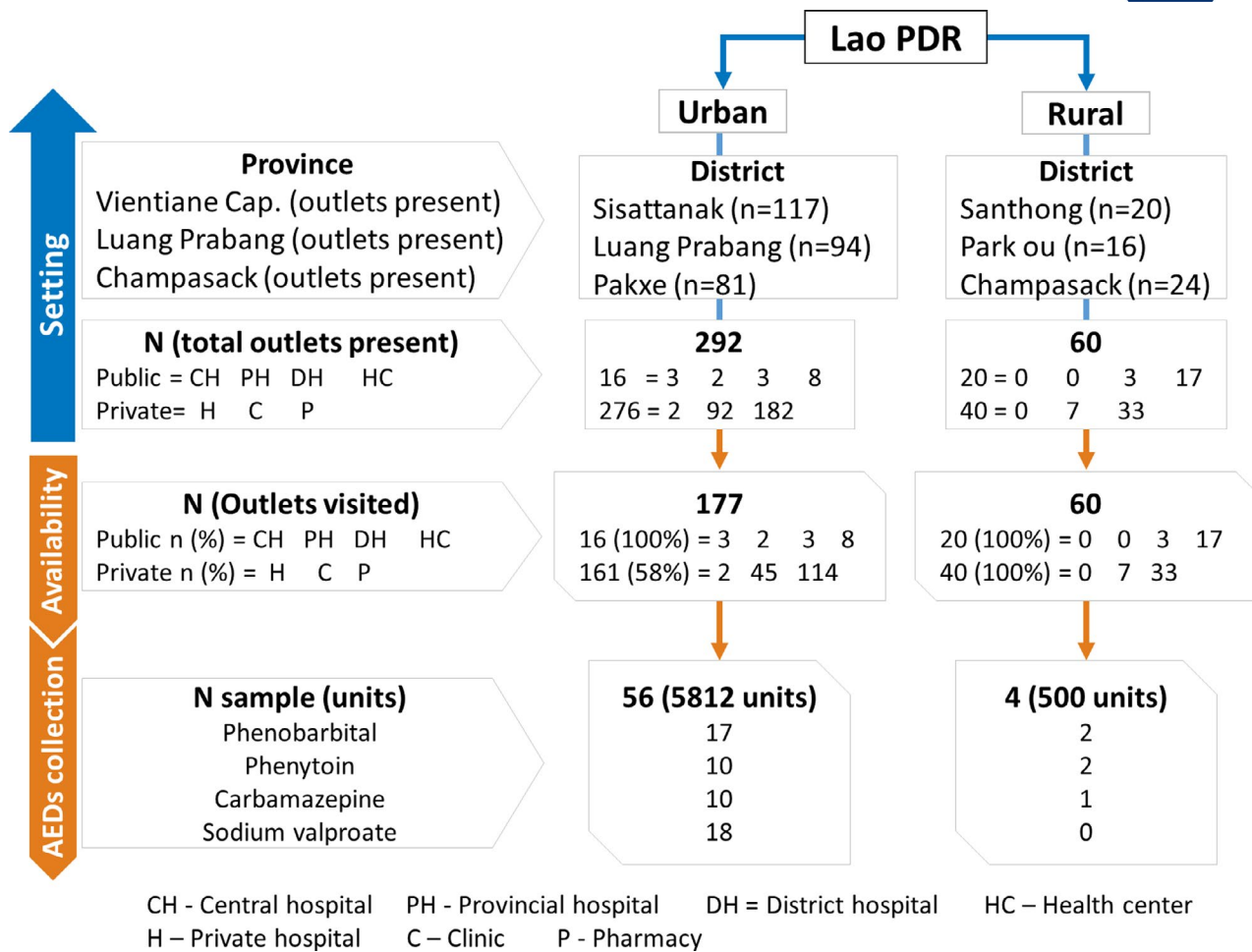


FIGURE 2 Sampling flowchart

using the exchange rate at the date of data collection, based on the WHO/HAI methodology²⁸. Pricing information was expressed as median price ratios (MPRs). The MPR was calculated by median unit price, compared with International Reference Prices (IRPs). The IRP used for this survey was taken from the International Medical Products Price Guide for 2014, and 2015^{29,30} then adjusted to the year of the study taking into account inflation/deflation of the currency. An MPR of 1.0 means that the local price is equivalent to the IRP.

Treatment affordability was estimated as the number of day wages the lowest-paid government employee needed to purchase a monthly treatment. The Defined Daily Dose (DDD) of individual medicines for the main indication in adults from ATC/DDD Index³¹ was used to estimate monthly treatment costs of AEDs. The daily minimum wage of lowest-paid government workers legislated by the Lao government in 2011 was 20 866.67 Kip (equivalent to 2.52 USD per day)³².

2.6 | Quality of AEDs

Endpoints, sampling methodology, and analytical testing were adapted from those used in another project performed

in sub-Saharan Africa and published in 2018⁸. A degree of quality scale was designed based on type of issue(s) observed (active ingredient assay, impurities screening, pharmacotechnical features) (Figure S1).

2.7 | Data analysis and statistics

The database was secured at the University of Limoges. Statistical analyses were performed using SPSS version 23.0.

Proportion, means, standard deviations, and 95% confidence intervals (CIs) were used for the descriptive analysis. Comparative analysis was performed using chi-square and Fisher's exact tests. A multinomial logistic regression was performed to identify the association between the independent variables (storage conditions including presence or absence of air-conditioning, exposure to light or wind; presence or absence of packaging; healthcare sector; study area; local or imported AED) and the dependent variable (quality of AEDs). Only variables with a *P*-value < .25 after univariate analysis were entered into a multivariate logistic regression model using the backward stepwise exclusion method.

2.8 | Ethical approval

Ethical approval was obtained from the National Ethics committee for Health Research, Ministry of Health of Lao PDR (reference No.077/NECHR).

3 | RESULTS

3.1 | Sampling

A total of 237 outlets corresponding to a proportion of 67.3% of the total number of outlets present in the study area were included (60.6% of the total number of outlets in the urban area, and 100.0% in the rural area). All outlets in the public sector in both urban and rural areas were included. One private clinic was excluded because found closed after several visits. All private pharmacies within a half kilometer radius of central and provincial hospitals ($n = 23$) were added to the random sample ($n = 91$) of private pharmacies, due to their proximity to main epilepsy diagnostic centers. For the private

sector, 58.0% in the urban area and all the outlets in rural area were included.

3.2 | Availability

The overall AEDs availability was 21.1% (50/237 outlets) [95% Confidence Interval (CI) 16.1-26.8]. Availability in the public sector was 25.0% and 20.4% in the private sector, and no statistical difference was observed. Availability in the urban area was 24.9% and 10.0% in rural areas, $P = .017$. The availability of AEDs within healthcare facilities is detailed in Figure 3. Concerning level III pharmacies where AEDs are not allowed to be sold, the availability of AEDs was 5.7%.

3.2.1 | Choice of AEDs per outlet

The nature and number of molecules available varied. Among outlets where AEDs were available in the urban area ($n = 44$), 43.2% had only 1 type of AED, 15.9% had

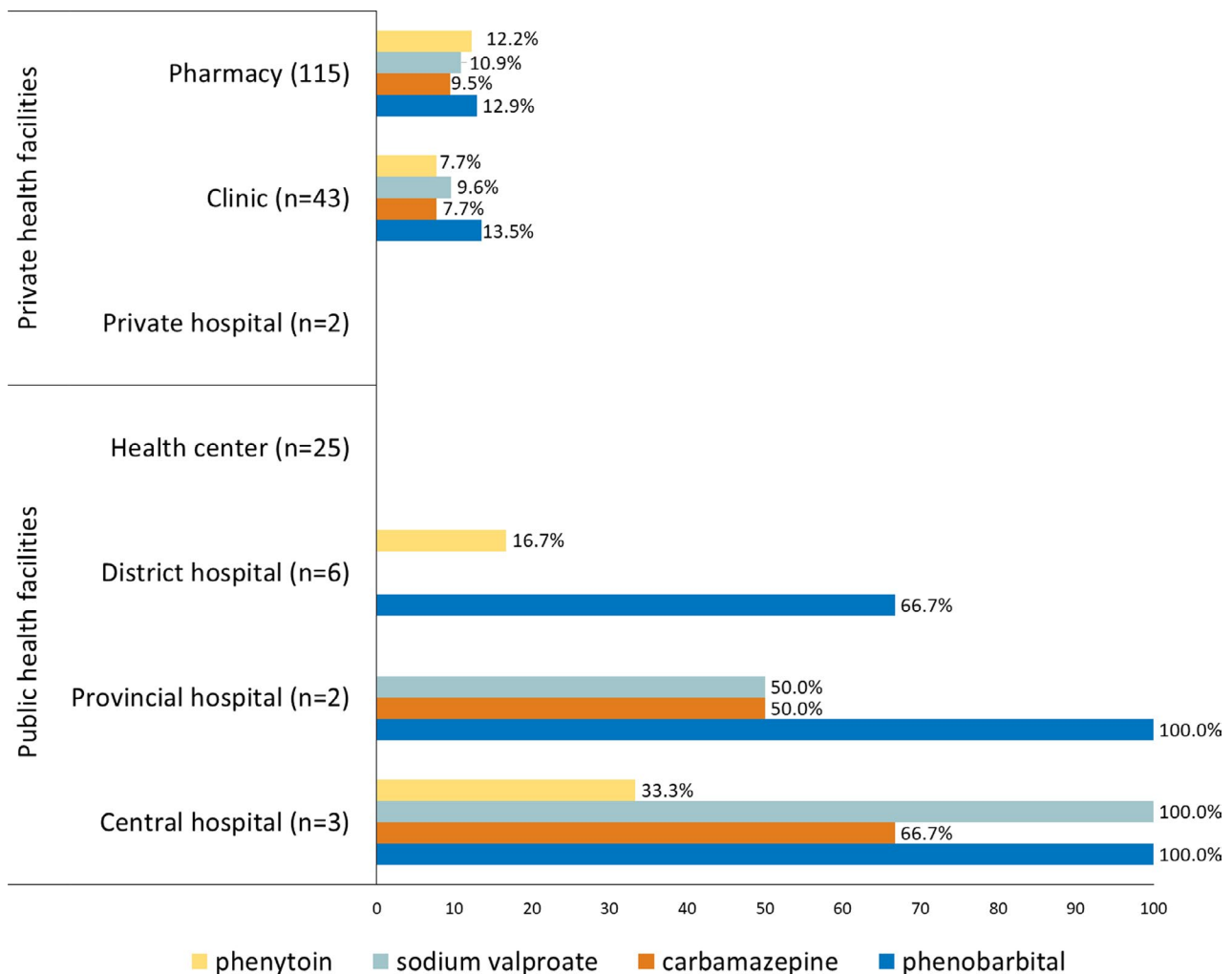


FIGURE 3 Availability of each AED within healthcare facilities

two different AEDs, 18.1% had three different AEDs and 22.7% had the four AEDs considered in this study. Among outlets where AEDs were available in the urban area ($n = 6$), 66.6% had only 1 type of AED, 16.6% had two different AEDs, 16.6% had three different AEDs and no outlet had the four AEDs.

3.2.2 | Availability per AED

In the 237 outlets investigated, phenobarbital 100 mg was the most available in 34 outlets (14.3% [95% CI 10.1-19.5]), followed by sodium valproate 200 mg in 23 outlets (9.7% [95% CI 6.3-14.2]), phenytoin 100 mg in 23 outlets (9.7% [95% CI 6.3-14.2]), and carbamazepine 200 mg in 21 outlets (8.9% [95% CI 5.6-13.2]). Other strengths of sodium valproate (500 mg), phenobarbital (60 mg), and phenytoin (50 mg) were available respectively in 18 outlets (7.6% [95% CI 4.6-11.7]), 2 outlets (0.8% [95% CI 0.1-3.0]), and 1 outlet (0.4% [95% CI 0.01-2.3]). The availability of carbamazepine 200 mg was higher in the urban area than the rural area (11.2% vs. 1.7%, $P = .031$). In contrast, the availability of phenobarbital 100 mg and phenytoin 100 mg was not significantly different between urban and rural area. Another important finding was the absence of sodium valproate (any strength), phenobarbital 60 mg, and phenytoin 50 mg in the rural area. Moreover, the majority of pharmacies, where AEDs were available in both urban and rural areas, were located in front of the public hospital (<50 m). These public hospitals included mainly central hospitals and provincial hospitals where epilepsy can be diagnosed.

3.2.3 | The characteristics of AEDs available

Among outlets where phenobarbital was available ($n = 34$), a proportion of 73.5% of them (25 outlets) sold phenobarbital manufactured in Cambodia, 17.6% (6 outlets) from local production and 8.8% (3 outlets) from Vietnam. All phenobarbital 60 mg and carbamazepine 200 mg were imported from Thailand. All strengths of sodium valproate were imported from Spain and France. Out of 23 outlets where phenytoin 100 mg was available, 86.9% (20 outlets) was imported from Thailand. While 8.6% (2 outlets), and 4.3% (1 outlet) were imported from the United States of America (USA), and Germany respectively.

3.2.4 | AEDs registered

According to the medicine registration list obtained from Department of Food and Drugs of the Ministry of Health

(FDD) of Lao PDR, only phenobarbital 100 mg from local production, phenobarbital 60 mg (imported from Thailand), and phenytoin 50 mg (imported from USA) were authorized.

3.3 | Price and affordability of each AED

Affordability was estimated only in central hospitals, private clinics, and private pharmacies (86.1% from the total of outlets visited) because in provincial hospitals, district hospitals and health centers, AEDs were provided free of charge. All AEDs were sold at higher prices than the IRP. The lowest MPR was observed for phenytoin 100 mg with MPR of 1.9 times higher. The highest MPRs were observed for phenobarbital 100 mg with MPRs of 20.6 times higher. Overall, affordability for phenytoin 100 mg and phenobarbital 100 mg was the best, with respectively 1.0 and 1.2 days for a month of treatment, compared to carbamazepine 200 mg (2.3 days) and sodium valproate 500 and 200 mg (15.6 and 17.5 days). Results of affordability across the study area (urban vs rural) and outlet types are detailed in Table 1.

3.4 | Quality of AEDs

A total of 60 samples of AEDs, representing 6312 units, were analyzed: 31.6% of phenobarbital, 20.0% of carbamazepine, 30.0% of sodium valproate, 18.3% of phenytoin. These AED samples were collected from 27 outlets (24 outlets from urban and 3 outlets from rural areas). The information on all samples collected is detailed in Table 2.

3.4.1 | Packaging and leaflet

Fifty-five percent (33/60) of samples were sold with their primary and secondary packaging and the medicine leaflet. A proportion of 18.3% (11/60) of samples was sold with packaging but without a leaflet, and 26.6% (16/60), without any packaging and leaflet. A leaflet written in the Lao language was found only for local production of phenobarbital 100 mg. For all other AEDs, the leaflet language was the same as that of the country of manufacture.

3.4.2 | Drug quality

No sample was identified as counterfeit, and 15.0% [95% CI 7.1-26.6] were of poor quality (Table S1-S4). Poor quality was only found in phenobarbital samples. Of all the poor-quality samples, 8.3% of them were substandard (meaning

TABLE 1 Price (median price ratios) and affordability of AEDs

	Area				Healthcare facility type							
	Urban		Rural		Central hospital		Private clinic		Private pharmacy		Total	
	MPR (n)	Day wages	MPR (n)	Day wages	MPR (n)	Day wages	MPR (n)	Day wages	MPR (n)	Day wages	MPR (n)	Day wages
Phenobarbital												
60 mg	6.2 (2)	2.0	NA	NA	NA	NA	7.2 (1)	2.4	5.0 (1)	1.7	6.2 (2)	2.0
100 mg	19.4 (25)	1.1	21.8 (3)	1.3	14.5 (3)	0.9	36.4 (7)	2.2	21.8 (18)	1.3	20.6 (28)	1.2
Carbamazepine												
200 mg	6.8 (18)	2.3	16.9 (2)	5.7	12.4 (2)	4.2	8.5 (3)	2.9	6.8 (15)	2.3	6.7 (20)	2.3
Sodium valproate												
200 mg	7.3 (23)	17.5	NA	NA	12.6 (3)	30.2	7.3 (5)	17.5	6.2 (15)	14.8	7.3 (23)	17.5
500 mg	7.3 (17)	15.6	NA	NA	9.2 (3)	19.8	NA	NA	7.1 (14)	15.3	7.3 (17)	15.6
Phenytoin												
50 mg	2.3 (1)	9.1	NA	NA	NA	NA	NA	NA	2.3 (1)	9.1	2.3 (1)	9.1
100 mg	1.9 (20)	1.1	6.4 (2)	3.7	NA	NA	7.6 (4)	4.3	1.7 (18)	1.0	1.9 (22)	1.0

Note: The median price ratios (MPR) was calculated by median unit price, compared with international reference prices.

Abbreviation: NA: Not applicable because AEDs were not available.

that only one test failed) and 6.7% were of bad quality (meaning that a minimum of two tests failed). No statistical difference was observed across study areas (urban vs. rural) and healthcare sectors (public vs. private). Figure 4 shows details of the quality in terms of authorized and unlicensed AEDs samples.

Samples with a marketing authorization represented 11.6% (7/60 samples). According to The United States Pharmacopeia (USP), within 45 minutes in the dissolution test, the tablet should release more than 75% of active ingredient (AI) amount but all samples of phenobarbital (local production) release less than 20% of AI. For unlicensed AEDs, 9.4% [95% CI 3.1-20.7] were identified as substandard.

A proportion of 44.4% (12/27) of outlets had air-conditioning in the storage location, but turned-on only in 75.0% of them (9/12) and only during the opening period. AEDs were exposed to direct sunlight in 55.6% (15/27), to the wind in 25.9% (7/27). Four variables were found to be significantly correlated with the quality of medicine in the univariate analysis. In the final multivariate logistic regression analysis, no significant associated factors were found. These factors were: (i) samples collected in urban areas (univariate, OR = 0.21, 95%CI [0.03-1.54], $P = .1$; multivariate, aOR = 0.40, 95%CI [0.02-5.77], $P = .5$); (ii) the public sector (OR = 2.60, 95%CI [0.55-13.02], $P = .2$; aOR = 2.70, 95%CI [1.02-7.09], $P = .6$); (iii) absence of packaging (OR = 2.87, 95%CI [0.54-15.2], $P = .2$; aOR = 0.214, 95%CI [0.46-22.15], $P = .2$); (iv) exposure to light or wind (OR = 0.19, 95%CI [0.44-0.86], $P = .03$; aOR = 0.18, 95%CI [0.01-2.62], $P = .2$).

4 | DISCUSSION

Epilepsy is a non-communicable disease (NCD), which has received little attention in health development agendas, especially in developing countries. Hence, medicines to treat NCDs were significantly less available than those for acute conditions in these countries.^{33,34} In three main provinces of Lao PDR, availability (21.1% of outlets had at least one AED available) and quality issues (15.0%) for AEDs were observed. The low availability may be the result of several factors: strict regulatory control of psychotropic and narcotic substances at the national and international levels, lack of regular assessment of the current need for AEDs in the country, and low rates of diagnosis.³⁵⁻³⁷ Despite a higher prevalence of epilepsy in rural areas than in urban areas,³⁸ and although a proportion of 67.1% of Lao population resided in rural zone, lower availability and higher price of AEDs were reported in the rural area. Furthermore, the uneven distribution of delivery structures might reduce the availability of AEDs for PWE residing in a rural area.

This study highlights a worse situation than described in a previous study on the same subject carried out in 2007 in Lao PDR. The availability has decreased significantly, from 53.0% in 2007 to 14.3% at present for phenobarbital and from 31.8% to 8.9% for carbamazepine, although many initiatives have been taken in the meantime to improve epilepsy management. The better availability in 2007 may be due to study area (4 central districts of Vientiane, the capital city of Lao PDR) where the main circulation center for pharmaceutical products is normally located. In addition, health centers and level III pharmacies were not included, while we covered

TABLE 2 Information on AED samples

	Number of samples		Brand name	Dosage form	Number of tablets collected	Manufacture country	Registration	Packaging
	Total	Public Private						
Urban area								
Phenobarbital								
60 mg	2	2	Phenobarbitone	tablet	200	Thailand	registered	non-available
100 mg	15	1	Phenobarbital	tablet	150	Lao PDR	registered	available
		1	Phenobarbital	tablet	60	Vietnam	non-registered	available
		1	Phenobarbital	tablet	1100	Cambodia	non-registered	available
Carbamazepine								
200 mg	11	2	PANTOL	tablet	891	Thailand	non-registered	available for only 5 samples
Phenytoin								
50 mg	1	1	DILANTIN 50 mg	tablet	250	USA	registered	available
100 mg	8	5	DITOIN	capsule	500	Thailand	non-registered	non-available
		1	Phenydan	tablet	801	Germany	non-registered	available
		2	DILANTIN 100 mg	extended-release capsule	800	USA	non-registered	available
Sodium valproate								
200 mg	8	2	DEPAKINE	gastro-resistant tablet	550	France	non-registered	available
500 mg	10	3	DEPAKINE CHRONO	slow-release scored film-coated tablet	510	France	non-registered	available
Rural area								
Phenobarbital								
100 mg	2	1	Phenobarbital	tablet	200	Lao PDR	registered	available
Carbamazepine								
200 mg	1	1	PANTOL	tablet	100	Thailand	non-registered	non-available
Phenytoin								
100 mg	2	2	DITOIN	capsule	200	Thailand	non-registered	non-available
Total	60	11	49		6312			

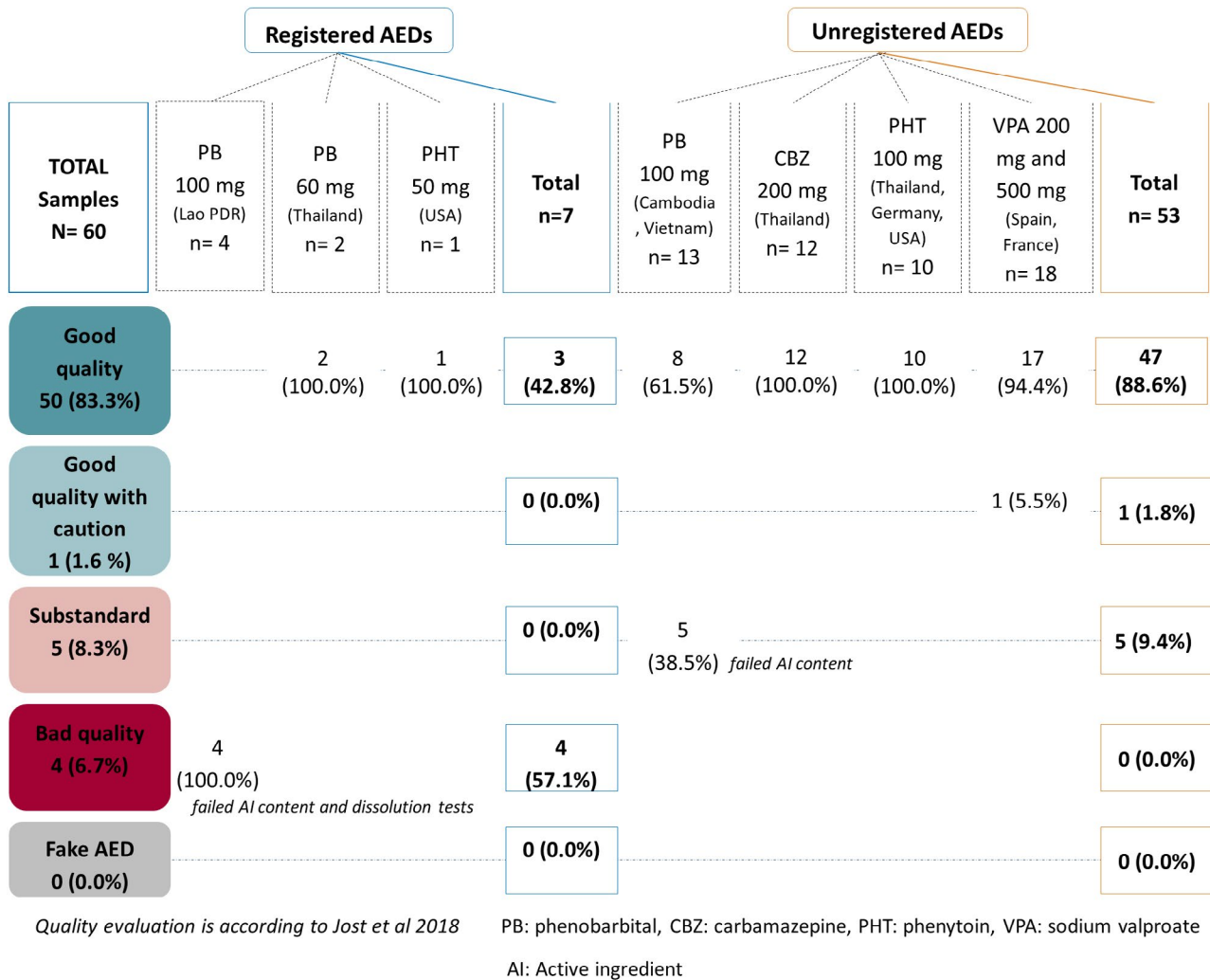


FIGURE 4 Quality of all AEDs samples

all types of healthcare facilities in both urban and rural districts in different provinces. In the present study, phenobarbital was the most available AEDs with good affordability in both urban and rural areas but half of the samples were of poor quality, while in 2007, no poor-quality drug was found among 34 samples of phenobarbital. This difference could be due to the criteria used to assess the quality of drugs. We used the US Pharmacopeia 2019 which indicated that the phenobarbital content was defined as correct if the amount was $\pm 10\%$ of the indicated dosage and the dissolution test was performed to define the AI release capacity of the dosage form. The previous study used a broader threshold of $\pm 15\%$ for active ingredient assay and the PB dissolution test was not performed.

Regarding the availability of at least one AED among the different types of health facilities in Lao PDR, we found that the availability of AEDs in provincial and district hospitals has improved progressively since the two previous studies: from 39.0% (2009) and 93.7% (2012) to 100.0% in our study for provincial hospitals, and from 12.5% (2009) and 18.2% (2012) to around 60.0% in our study for district

hospitals. Although availability was better in these facilities, PWE had limited access in terms of geographical distance. According to the WHO recommendations, the most cost-effective way to decrease the treatment gap of epilepsy would be to deliver the epilepsy services through primary healthcare.³⁹ Unfortunately, we observed a reduction of AEDs availability at a community level in Lao PDR: from 7.0% (2009) to not available at all in 2019. For level III pharmacies, the availability decreased from 10.0% (2009) to 5.7% in 2019.^{18,20} It may have been due to the absence of physician or neurologist and a lack of diagnostic equipment in these areas.

Our result regarding the availability of each AED (<15.0%) in health facilities was lower than previous studies in Vietnam (>30.0%)⁴⁰, Thailand (>80.0%),^{41,42} and Madagascar⁴³ (>80.0%). We observed better affordability of carbamazepine (2.3 day wages) and phenytoin (1.0 day wages) in Lao PDR compared to Malawi⁴⁴ which reported more than 5.0 day wages required for these two drugs. As well as for sodium valproate, in our study, we found 17.5 days wages in private clinics, whereas in Malawi, this drug required

40.0 days wages. Our result on affordability was similar to a previous multicenter study conducted in 46 countries which reported the day wage patient price of generic carbamazepine was less than 5.0 day in all healthcare facilities, although this study pulled data from developing and developed countries.⁷ The proportion of poor-quality AEDs found in our study (15.0%) was lower than that observed in a study performed in sub-Saharan Africa⁸ which reported 32.3% of poor quality. In that study, carbamazepine and sodium valproate were the poorest in terms of quality, probably due to high sensitivity to humidity and heat under tropical conditions, whereas our study found poor quality only for phenobarbital samples. This proportion was higher than in the previous study in Mauritania which found 13.7%.⁴⁵ Our results identified that different samples of phenobarbital (imported from Cambodia and Vietnam) from the same batch vary randomly in their quality. Samples manufactured locally showed the poorest quality. Poor-quality control and/or lack of conformity during the manufacturing process may be a cause. This problem was reported as common in local pharmaceutical industries in most LMICs.^{46,47} This poor-quality issue could lead to side effects, loss of efficacy, lack of confidence in medication, and a reduction in adherence to AEDs. Carbamazepine, sodium valproate, and phenytoin were of good quality in both urban and rural areas, although most were sold in bulk. Despite the good quality, these AEDs were imported from different countries and were not labeled in the Lao language. More than 88% of all AED samples collected in our survey have no marketing authorization in Lao and poor quality was observed in both registered and unregistered samples. Cross-border trade flows seem to interfere with official drug supply channels. Although irregular, they are part of reality and raise several questions in terms of control of batches marketed on the territory, traceability, pharmacovigilance, etc In addition, cross-sectional quality controls should be encouraged on these medicines in view of the observations made in countries where storage conditions are often unfavorable and poorly considered. Around 33.6% of the Lao population lived below the poverty line and they often earned less than the lowest-paid government worker, AEDs would be even less affordable than reported here.⁴⁸ Another concern was for children with epilepsy (CWE) because pediatric strength and formulation were available in less than 1% of all facilities (eg, phenobarbital 60 mg, phenytoin 50 mg, no liquid formulation). This issue was documented in several other areas.^{49,50} Parents of CWE or adolescents are constrained to manipulate adult dosage forms and split the tablet. Despite the theoretical homogeneous distribution of the active ingredient within the tablet, based on the assumption that all steps in the manufacture of dry forms of drugs are controlled, tablet splitting does not systematically result in equal shares and the reproducibility of this operation is not ensured. In addition, it may

modify the pharmacokinetics of the medication especially for extended-released formulation of carbamazepine and sodium valproate. To this, we can add the fact that for some drugs, coatings are added not for kinetic purposes but for environmental protection; a damaged coating is all the more exposed to possible degradation.

This study has been undertaken with both strengths and weaknesses. The major strengths include the fact that the survey data have been adjusted to ensure that the price data are compared to an international reference. Quality analyses were consistent with international, reproducible, and standardized methodologies. Of particular concern is the fact that we had not measured price components in the pharmaceutical supply chain and did not explore the factors affecting the availability and use of AEDs in healthcare facilities. This availability and affordability or price data only apply to the specific day of the survey and may not reflect average availability over time.

5 | CONCLUSION

Overall availability of AEDs in all different supply chains in Lao PDR was significantly (<15%) below the threshold recommended by the WHO³², which requires a minimum availability of 80% of affordable essential medicines for NCDs. The Ministry of Health in Lao PDR should urgently reassess AEDs current requirements, therefore develop and implement policy options to increase availability, develop pricing regulation, and improve affordability in both public and private sectors. For the poorest part of the population and in rural areas, health centers and level III pharmacies should be authorized to dispense essential AEDs by improving knowledge and qualification of healthcare workers. There is also a need to promote the registration of medicines, remove taxes on essential medicines, and ensure that the products on the market meet the quality standards for both imports and local production.

CONFLICT OF INTEREST

The authors declare no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURES

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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