J Antimicrob Chemother 2019; **74**: 2417–2425
doi:10.1093/jac/dkz164 Advance Access publication 2 May 2019

Journal of Antimicrobial Chemotherapy

A random survey of the prevalence of falsified and substandard antibiotics in the Lao PDR

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Received 19 December 2018; returned 14 January 2019; revised 18 March 2019; accepted 24 March 2019

Objectives: In 2012, a stratified random survey, using mystery shoppers, was conducted to investigate the availability and quality of antibiotics sold to patients in the private sector in five southern provinces of the Lao People's Democratic Republic (Laos).

Methods: A total of 147 outlets were sampled in 10 districts. The active pharmaceutical ingredient (API) content measurements for 909 samples, including nine APIs (amoxicillin, ampicillin, ceftriaxone, ciprofloxacin, doxycycline, ofloxacin, sulfamethoxazole, tetracycline and trimethoprim), were determined using HPLC.

Results: All the analysed samples contained the stated API and we found no evidence for falsification. All except one sample had all the units tested with %API values between 75% and 125% of the content stated on the label. However, we identified the presence of substandard antibiotics: 19.6% (201/1025) of samples had their units outside the 90%–110% content of the label claim and 60.2% (617/1025) of the samples had units outside of the International Pharmacopoeia uniformity of content limit range. Amoxicillin had a high number of samples [67.1% (151)] with units above the limit range, followed by ciprofloxacin [58.8% (10)] and ofloxacin [57.4% (39)]. Ceftriaxone, trimethoprim and sulfamethoxazole had the highest number of samples with low API content: 57.1% (4), 51.6% (64) and 34.7% (43), respectively. Significant differences in %API were found between stated countries of manufacture and stated manufacturers.

Conclusions: With the global threat of antimicrobial resistance to patient outcomes, greater understanding of the role of poor-quality antibiotics is needed. Substandard antibiotics will have reduced therapeutic efficacy, impacting public health and control of bacterial infections.

Introduction

Access to good-quality medicines is a critical factor for the effective management and control of diseases globally and universal health coverage.[1] The increased accessibility and inappropriate use of antimicrobials have led to enhanced selective pressure and development of resistant pathogens. Antimicrobial resistance threatens the effective prevention and treatment of infections in both the developed and developing world, and is growing at an alarming pace.[2–5]

Factors contributing to the development of antibiotic resistance include inappropriate use of antibiotics due to poor prescribing and patient adherence. Furthermore, poor storage conditions may result in physicochemical changes causing degradation or altered dissolution of active ingredients. In addition, subtherapeutic amounts of active pharmaceutical ingredients (APIs) and poor API

dissolution of antimicrobials engender resistance for some pathogens.[6] Resistance is most likely to develop when pathogens are exposed to low API concentrations, high enough to kill susceptible organisms, but not resistant ones.[6–9]

Although there is a logical relationship, quantification of the contribution made by poor-quality medicines to antimicrobial resistance remains unknown due to the lack of information and understanding. Few objective data on the prevalence of poor-quality antibiotics exist. Some research groups and international NGOs have tried, over the last two decades, to estimate their prevalence and highlight the problem in developing countries.[10–20] Examples include a study conducted in the late 1990s in Nigeria and Thailand, showing that 36% of the samples collected in Nigeria and 40% of samples collected in Thailand contained quantities of APIs outside pharmacopoeial limits.[21] The death of a patient from bacterial meningitis was associated with substandard ceftriaxone in Uganda in 2013.[13] The strong demand for antibiotics runs the risk of creating a market for falsification,[12] and they are widely falsified.[10] There is increasing awareness that poor-quality medicines are important impediments to public health.[14,22–25] Poor-quality medicines include those falsified and those which are substandard (from errors in manufacture) or degraded (in the supply chain). The latter two categories are included together in the 2017 WHO definitions.[26]

The problem is aggravated by the lack of testing facilities in low- and middle-income countries (LMICs) and poor data sharing.[27] Misdiagnosis and antimicrobial resistance are usually considered the main reasons for treatment failure, without consideration of the risk of poor-quality medicines (and, consequently, investigations on the latter are not prompted).

Reports in the Greater Mekong subregion have demonstrated high frequencies of falsified and substandard antimalarials,[24,28–33] but there are few data on antibiotic quality in the public domain. Surveys conducted in the late 1990s investigated the availability of poor-quality antibiotics including ampicillin and tetracycline in the Lao PDR (Laos).[31,34] Operation Storm I and II, conducted in 2008–09, showed that 31% of seized antibiotics analysed were of poor quality.[35]

However, very few data were acquired using random sampling that would allow objective estimates of the proportion of a nation's or a province/region's antibiotic supply that is substandard or falsified, and there are none from Laos.[36–38] Data on antibiotic resistance in Laos are scarce, but ESBL Enterobacteriaceae are becoming more frequent.[39–41]

In 2012, we conducted a survey to investigate the availability and quality of selected antimalarials and antibiotics sold to patients in the private sector in five southern Lao provinces. The study methodology and results for antimalarials have been described,[37] and here we report the results on the quality of the antibiotics collected.

Methods

Setting

Laos has a population of ~6.8 million people, with the majority (60.3%) living in rural areas.[42–45] One urban and one rural district (i.e. stratified by urbanization) were selected using simple random selection, by random number tables, from each of the five southern provinces, and all known outlets in these districts were sampled.[37] The districts selected were Adsaphangthong and Sepon in Savannakhet Province, Salavan and Toumlane in Salavan Province, Sekong and Thateng in Sekong Province, Sammakkyxay and Sanamxay in Attapeu Province, and Pakse and Sanasoumboun in Champasak Province (Figure S1, available as Supplementary data at *JAC* Online).

Study design

A cross-sectional random sampling of private sector medicine outlets was conducted in the five southern Lao provinces starting in September 2012, lasting 4 weeks. One male and one female research assistant from Vientiane purchased, as mystery shoppers, the anti-infective medicines from all private retail outlets identified in the selected districts. Prior to the survey, a 1 week training was conducted in Vientiane. This included pre-testing of the data collection tools and the debriefing process.

Outlets were visited twice, first by a mystery shopper who stated that they were a friend of a sick malaria patient working in construction in southern Lao (for the antimalarial medicine quality survey[37]) and, secondly, by another mystery shopper with a handwritten list of essential antibiotics and anti-TB medicines (Text S1). Visits were conducted one day apart. Twenty tablets/capsules of each preparation of amoxicillin, ampicillin, ciprofloxacin, co-trimoxazole, ofloxacin, tetracycline and doxycycline were requested. Rifampicin, isoniazid, ethambutol and pyrazinamide were also requested.

If no staff were present at the first visit, two further attempts were made to visit outlets. Hand-held GPS (Global Positioning System) units were used to map outlet locations (within ±10 m). Debriefing of the mystery shopper was conducted after each outlet interaction on the same day using a semi-structured questionnaire (Form S1).

Inclusion criteria

All private pharmacies, private clinics or medicine sellers in the study districts, whether registered or unregistered, were eligible for inclusion in the survey. Private pharmacies are classified depending on the qualifications of the licensee:[31,46] class I pharmacies are run by a qualified pharmacist with a university degree; class II pharmacies are run by an assistant pharmacist; and class III pharmacies are run by any medical professional, usually an auxiliary nurse or a low-level pharmacist. Registered Private Clinics are run after Government working hours by medical doctors. These are licensed to sell antibiotics.

Poor-quality medicines were defined as falsified or substandard based on WHO definitions without consideration of intellectual property issues.[26] A sample was defined as a group of apparently physically identical dosage units (e.g. tablets or vials), from one brand and one batch obtained at the same time from the same outlet. Samples were kept in a foam box and sent to Vientiane within 3–4 days of collection, for storage in a refrigerator at +4°C before shipment for analysis.

All data were double-entered in a pre-established Epi-Data database. Data were analysed using STATA (v11.2, Stata Corp, College Station, TX, USA), RStudio Version 1.0.136 (RStudio Team, 2016) and Microsoft Excel.

Laboratory analysis of the samples

Anti-infective samples were sent for chemical analysis to the CDC in Atlanta, USA. Analysis was completed 24 months after sample collection. The API content measurements for each sample were determined using HPLC.[47] Between one and three dosage units were tested for each sample (when available) and the mean of the percentage API, with reference to the stated dose on the packaging, was calculated.

Samples were primarily classified as meeting the quality requirements if the amount of API in each of the units, as determined from their content uniformity,[48–52] lay within the range of the International Pharmacopoeia and/or British Pharmacopoeia percentage of the label claim; see Table S1. Typically, pharmacopoeial content and uniformity methods require at least

20 units for content analysis and at least 10 units for stage one dose uniformity analysis.[53] Using a lower number of units may thus under- or overestimate the conclusion. Since the numbers of units collected were limited and given the heterogeneity of within-specification threshold ranges between the different pharmacopeias (Table S1), we also categorized each unit using the 85.0%–115.0% and the 75.0%–125.0% API threshold ranges.

Packaging analysis was conducted in comparison with the genuine medicine when these were available, blinded to chemistry, by visual inspection and using the U.S. FDA CD-3.[54] The CD-3 is a handheld device that uses different wavelengths of light to compare an authentic medical product and packaging with a potentially falsified medicine and its packaging.

As 31% of samples were analysed after their expiry date, to better understand differences in %API in relation to the medicine's expiry date, a regression analysis of %API versus days until expiry (defined as expiry date−date of analysis) was conducted using a two-parameter decay equation [$y = a \times \exp(-bx)$, y=%API, x=days till expiry]. Sigmaplot 12.0 was used to calculate the non-parametric Spearman correlation value and the associated P value. The %API was normalized using the rate constant 'b' from the equation to compensate for any possible API degradation due to analysing samples past their expiry date.

This report has been written following the Medicine Quality Assessment Reporting Guidelines (MEDQUARG), and the results have been reported to the Lao FDD and WHO RapidAlert.[55–57]

Ethics

Ethical clearance was granted by the Lao PDR National Ethics Committee for Health Research (NECHR); approval reference number 054.

Results

Survey description

A total of 147 outlets were sampled in the 10 districts, 45 in the rural and 102 in the urban districts. Three outlets were closed and therefore 144 (98%) were included in the analysis (Figure S1 and Figure S2).

Registered outlets accounted for 97.2% (140) of those included. Pharmacy classes I and II accounted for 30.9% (43) and 30.9% (43) of outlets, respectively, and 33.8% (47) were pharmacy class III.[31,46] Only 4.1% (6) outlets were registered clinics, and one of the outlets sampled was a shop of a registered pharmaceutical manufacturer, Pharmaceutical Factory No. 2. Only four unregistered outlets (2.7%) were found, and they were general shops that were also selling medicines.

Antibiotics were bought from 96.5% (139) of the included outlets. Mystery shoppers were unable to buy antibiotics in five outlets. The provider was absent in one outlet and four did not have antibiotics in stock.

No provider requested to see a medical prescription.

Medicines offered to mystery shoppers

A total of 1173 medicine samples were collected and, of those, 158 were antimalarials and 1015 were medicines for the treatment of fever and TB and not for malaria.

Out of the 1015 medicine samples sold for the treatment of fever (as claimed by outlet staff), 95.5% (969) were labelled as antibiotics and 4.5% (46) were labelled as other types of medicines such as paracetamol, antihistamines and vitamins (Figure S3 and Table S2).

Of the antibiotics collected, 15.6% (151/969) of samples were sold as loose units of only one type of medicine in plastic bags with no label or patient information, stated manufacturer or expiry date, and, of those, 84.7% (128) had no trade name and 47.7% (72) had no dosage information. Of these 128 plastic bags, 88.3% (113) capsule samples were sold as containing tetracycline, 3.1% (4) capsule samples as containing doxycycline, 2.3% (2 tablets and 1 capsule) as containing ampicillin, 1.6% (2) samples as ciprofloxacin tablets, 1.6% (2) as chloramphenicol capsules, 1.6% (2) as isoniazid tablets, 0.7% (1) as amoxicillin capsules and 0.7% (1) as ofloxacin tablets. Only 9.6% (93/969) of the samples were sold with secondary packaging (i.e. boxes or containers) and 11.8% (115/969) of samples gave storage instructions on the package or in a leaflet.

Eight (0.8%) samples had expired at the time of sample collection and a further 308 (31.8%) by the time chemical analysis was conducted.

Ampicillin (26.5%, 257) and amoxicillin (23.4%, 227) were the medicines most frequently sold, accounting for half of the antibiotics collected. Other antibiotics collected include sulfamethoxazole/trimethoprim (12.9%, 125), tetracycline (12.1%, 117), doxycycline (9.0%, 87), ofloxacin (7.0%, 68), ciprofloxacin (1.9%, 18), cefalexin (1.2%, 12), norfloxacin (1.2%, 12), intravenous ceftriaxone (1.0%, 10) and four (0.4%) samples of chloramphenicol (Table S2).

Anti-TB monotherapy was collected in 13 (9.0%) outlets, consisting of 10 (1.0%) samples of rifampicin, 6 (0.6%) samples of isoniazid and 4 (0.4%) samples of ethambutol. These were not analysed chemically.

There were 145 branded products from 41 stated manufacturers of which 25.5% (37) were registered with the Lao Food and Drug Department, using the list of 2012. Of the 86.4% (886) antibiotic samples that specified a manufacturer, 25.3% (259) were labelled as made by 'Codupha-Lao Pharmaceutical Factory, Vientiane, Lao P.D.R.', 19.2% (197) were labelled as made by 'CBF Pharmaceutical Factory, Pakse-Champasack, Lao P.D.R.' and 12.8% (132) were labelled as made by 'KPN Pharma Co., Ltd, Vientiane, Lao P.D.R.'

Samples were labelled as manufactured in seven countries, with most of them (58.7%, 602) labelled as made in Laos. Other countries stated as the origin were India (11.5%, 118), China (7%, 72), Thailand (4%, 41), Vietnam (3.7%, 38), South Korea (0.2%, 2) and Bangladesh (0.1%, 1). For 14.7% (151) of the samples, the country of manufacture was not stated.

CD-3 analysis could be conducted on 345 samples as genuine comparators were not available for 62.0% (564) of the medicines sampled. Of those, 56.2% (194) of the samples failed packaging analysis; 61.2% (71) of the tetracycline samples collected had the same tablet design and were consistent with each other under the CD-3 light, but were not consistent when analysed against the only genuine comparator available. No correlation between failing visual inspection and failing chemical analysis was found (P=0.056).

A total of 25.11% (57) of the amoxicillin, 16.9% (7) of the sulfamethoxazole/trimethoprim, 15.5% (40) of the ampicillin, 13.7% (12) of the doxycycline, 11.1% (2) of the ciprofloxacin and 7.3% (5) of the ofloxacin samples failed packaging analysis.

Chemical quality of the antibiotics

Of the 969 antibiotics collected, 909 samples and nine APIs (amoxicillin, ampicillin, ceftriaxone, ciprofloxacin, doxycycline,

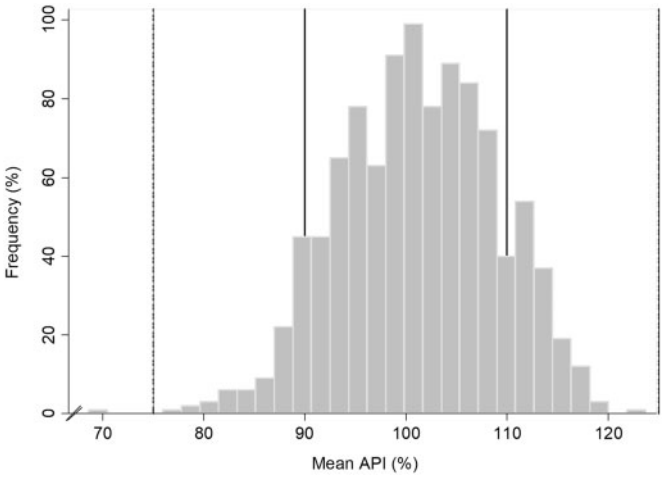

Figure 1. Frequency of antibiotic mean %API found in the samples (n=1025). The two outer lines represent 75% and 125% cut-offs and the two inner lines represent 90% and 110% pharmacopoeial %API limits.

ofloxacin, sulfamethoxazole, tetracycline and trimethoprim) were analysed; 60 samples stated as containing other APIs were not analysed (Figure S3 and Table S3).

Out of the 1034 APIs analysed (909 samples plus 125 trimethoprim from the co-formulated sulfamethoxazole/trimethoprim), 9 samples were lost during analysis. All the 1025 API samples analysed labelled as antibiotics contained the stated API.

All except one sample had all the units tested with %API between 75% and 125% of the content stated on the label. Most of the samples (96.1%, 985) had their units' mean %API between 85% and 115%, and 80.4% (824) had their units' mean between 90% and 110% (Figures 1 and 2).

The sample with %API outside the range 75%–125% was a sulfamethoxazole/trimethoprim co-formulated syrup (stated as manufactured by PDC, Pharmaceutical Factory No. 3, Laos) in which one of the two sulfamethoxazole units analysed had a %API below the 75% cut off (API values: 60% and 77% per sulfamethoxazole unit tested; 82% and 102% per trimethoprim unit tested).

In total, 39.8% (408) of the samples had all their units within the API-specific limit range of the International Pharmacopoeia uniformity of content assay (Table 1 and Table S1).

Ampicillin sodium in injection form was the API with the highest proportion of samples with all the units within the International Pharmacopeia specifications (80.8%, 84), followed by sulfamethoxazole with 61.3% (76) samples, doxycycline with 56.5% (48) samples and amoxicillin trihydrate with 50.0% (1) samples (Table 1).

Samples of ampicillin trihydrate (1) and doxycycline hyclate (2) had all their units outside the International Pharmacopeia specifications.

Of the 124 co-formulated sulfamethoxazole/trimethoprim samples analysed, 42.7% (53) had both APIs within the limit range.

Of the 60.2% (617) samples that were outside the %API specifications of the International Pharmacopeia limit range, 62.7% (387) samples had units with higher amounts of API, 33.2% (205) samples had lower amounts of API and a significant minority 4.0% (25) of samples contained units in samples both above and below the limits (Table 2).

Inter-tablet variability was also measured for up to three tablets per dosage unit from the same sample. Ciprofloxacin had the highest variability between its units, with mean relative standard deviation (RSD) of 5.2 (Figure 3, Table S4 and Table S5).

Of the samples with units outside the pharmacopoeia limit ranges, a significant difference was found between the stated country of manufacture and the %API of the sample (Kruskal–Wallis P=0.0001); 60.3% (372) of the failed samples were labelled as being made in Laos, 15.4% (95) with missing manufacturer, 11.8% (73) from India, 5.5% (34) from China, 4.1% (25) from Thailand, 2.6% (16) from Vietnam, 0.1% (2) from South Korea and 0.1% (1) from Bangladesh. The API failure frequency was significantly associated with the stated manufacturer (Kruskal–Wallis P=0.0001).

Half of the samples stated as manufactured in Vietnam, China and South Korea were within the limit range (57.9%, 52.8% and 50%, respectively) and only 39.2%, 38.2% and 38.1% of the samples labelled as manufactured in Thailand, Laos and India had all units of acceptable quality.

Stability

Stability plots revealed trends in API degradation with days until expiry. Characterization of the variation of the %API in relation to the medicine's remaining time to expiry was determined by regression analysis (Figure 4).

In this figure, dashed lines represent time trends associated with degradation in %API content. The %API of medicines with significant slopes ($P < 0.05$) was normalized by adjusting the slope to zero to compensate for these changes and is represented by the solid line.

Stability plots demonstrate changes in %API in time before and after the expiry date. Trimethoprim, ciprofloxacin and amoxicillin ampoules showed a weak to moderate correlation between %API reduction and expiry date ($P < 0.05$; Figure 4). For ciprofloxacin tablets and amoxicillin ampoules, %API significantly declined with increased sample age, but the reverse was found for trimethoprim.

Discussion

Despite their key importance for treating infections, little is known in the public domain about the quality of antimicrobials in the Greater Mekong subregion, notwithstanding the significant anecdotal evidence that poor-quality antibiotics are present in south east Asia and elsewhere.[10,11,23,28,29,34,58,59]

All samples contained the stated API and most of the samples contained the correct mean amount of API, although there was a significant variation in the quantity of active ingredient within the samples. Results obtained from these antibiotics are consistent with the findings of the quality of antimalarials collected in the same survey.[37]

There was only one sample (sulfamethoxazole/trimethoprim co-formulated syrup) for which the dosage units contained %API <75%, but there was no genuine comparator available to

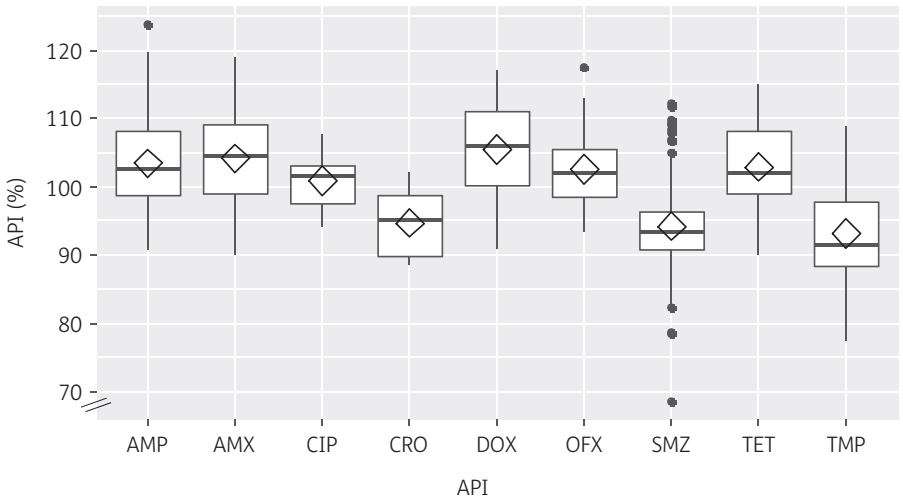

Figure 2. Box plot showing the mean API (%) by medicine. It includes both intravenous and oral forms. Diamonds represent mean values and horizontal lines represent median values. Box borders represent the lower and upper quartiles (25th and 75th percentiles, respectively). AMP, ampicillin (n=256); AMX, amoxicillin (n=225); CRO, ceftriaxone (n=7); CIP, ciprofloxacin (n=17); DOX, doxycycline (n=87); OFX, ofloxacin (n=68); SMZ, sulfamethoxazole (n=124); TET, tetracycline (n=117); TMP, trimethoprim (n=124).

Table 1. Quality of the samples surveyed classified by the International Pharmacopoeia uniformity of content limit range

Medicines surveyed, labelled API	Analysed samples, no.	Lost samples, no.	International Pharmacopoeia specifications of limit range, % content	Samples with all units within limit range		Samples with units outside limit range	
				no.	%	no.	%
Amoxicillin anhydrous	15		95–102	3	20.0	12	80.0
Amoxicillin	152	1	95–102	21	13.8	131	86.2
Amoxicillin sodium	56		95–102	5	8.9	51	91.1
Amoxicillin trihydrate	2	1	95–102	1	50.0	1	50.0
Ampicillin trihydrate	1		95–102	0	0.0	1	100.0
Ampicillin	151		95–102	53	35.1	98	64.9
Ampicillin sodium intravenous	104	1	90–110	84	80.8	20	19.2
Ceftriaxone	7	3	96–102	3	42.9	4	57.1
Ciprofloxacin	17	1	98–102	1	5.9	16	94.1
Doxycycline hyclate	2		95–102	0	0.0	2	100.0
Doxycycline	85		90–110	48	56.5	37	43.5
Ofloxacin	68		99–101	2	2.9	66	97.1
Sulfamethoxazole	124	1	90–110	76	61.3	48	38.7
Tetracycline	117		96–102	51	43.6	66	56.4
Trimethoprim	124	1	90–110	60	48.4	64	51.6
Total	1025	9		408	39.8	617	60.2

ascertain the authenticity of the sample; whether it was substandard or falsified cannot therefore be confidently ascertained.

The main problem identified was the presence of probably substandard, rather than falsified, antibiotics; 60.2% of the samples had units outside of the uniformity of the content limit range of the label claim. In the absence of chemical assays to distinguish degradation from poor factory production in field-collected samples, it is very difficult to distinguish failed samples as degraded or substandard, or both.[32,60] There is an urgent need for research to develop such techniques. MS fingerprinting of degradation products may allow this distinction.[61,62] An additional issue is that smaller companies may not have the human capacity, equipment and consumables to check the quality of the imported bulk API. For substandard medicines, the quality defect may have been in the API producer rather than the factory formulating the finished product. The storage conditions up to the time of purchase are unknown. Poor storage conditions may have contributed to degradation of APIs and excipients. Changes in crystalline morphology caused by high temperature can affect the dissolution or disintegration of the active ingredients, impairing bioavailability.[63–66] This is also true

Table 2. Units within, above and below the International Pharmacopoeia specifications of limit range of uniformity of content assay

	Good quality		Under limit range		Over limit range		Under and over limit range		
API	no.	%	no.	%	no.	%	no.	%	Total no.
Amoxicillin	30	13.3	36	16.0	151	67.1	8	3.6	225
Ampicillin	137	53.5	24	9.4	88	34.4	7	2.7	256
Ceftriaxone	3	42.9	4	57.1	0	0.0	0	0.0	7
Ciprofloxacin	1	5.9	5	29.4	10	58.8	1	5.9	17
Doxycycline	48	55.2	0	0.0	39	44.8	0	0.0	87
Ofloxacin	2	2.9	18	26.5	39	57.4	9	13.2	68
Sulfamethoxazole	76	61.3	43	34.7	5	4.0	0	0.0	124
Tetracycline	51	43.6	11	9.4	55	47.0	0	0.0	117
Trimethoprim	60	48.4	64	51.6	0	0.0	0	0.0	124
Total	408	39.8	205	20.0	387	37.8	25	2.4	1025

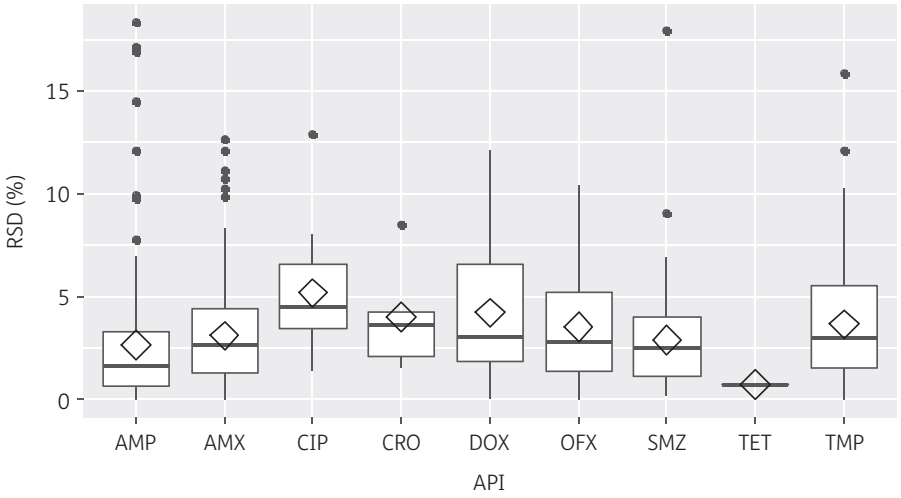

Figure 3. Interunit variability between units per sample measured as the RSD by medicine. It includes both intravenous and oral forms. Diamonds represent mean values and horizontal lines represent median values. AMP, ampicillin (*n*=256); AMX, amoxicillin (*n*=225); CRO, ceftriaxone (*n*=7); CIP, ciprofloxacin (*n*=17); DOX, doxycycline (*n*=87); OFX, ofloxacin (*n*=68); SMZ, sulfamethoxazole (*n*=124); TET, tetracycline (*n*=117); TMP, trimethoprim (*n*=124).

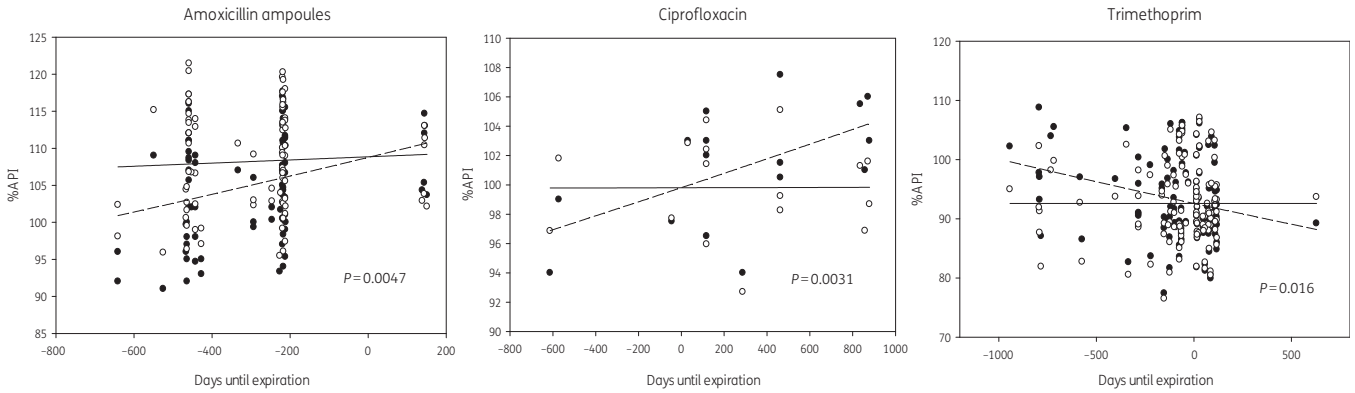

Figure 4. Stability plots showing changes in API content relative to expiration date. Dashed lines represent trends associated with these changes. The %API values of medicines with significant slopes ($P < 0.05$) were normalized and are represented by solid lines. Amoxicillin ampoules, *n*=246; ciprofloxacin, *n*=51; trimethoprim, *n*=372.

when analysing expired samples, as the medicine may or may not maintain its potency beyond the expiry date. Stability plots demonstrated potency before and after the expiry date and show the variability associated with the analysis as well as the tablets.

The significance of these data is important for individual patients as they risk impaired therapeutic efficacy and/or adverse drug reactions. Almost two-thirds of medicines outside the specification range had a high %API concentration. This is of particularly great concern for medicines with narrow therapeutic indices, such as chloramphenicol, which can cause bone marrow toxicity and even death. Tetracycline is easily degraded under unfavourable storage conditions, resulting in potentially noxious degradation products.[31,34] Even if clinical consequences are relatively rare, they would be very difficult to detect and manage in rural Laos.[67]

A significant minority of the samples (15.6%) were sold loose with no labelling or manufacturing information. This finding is consistent with other surveys conducted in Laos.[31,35] Inadequate labelling not only results in poor information on drug use, for patients and health workers, but it also provides opportunities for the sale of unregistered and falsified medicines.[68] Eight samples had expired at the time of the survey when there should have been none.

Antimicrobials with low %API, poor bioavailability or degradation may engender drug resistance. Modelling studies suggest that high β-lactam antibiotic doses at low frequencies produced more highly resistant *Streptococcus pneumoniae* strains, but at far lower prevalence than repeated exposure to subtherapeutic doses, which resulted in the highest prevalence of resistant strains.[6,69]

In addition, unregulated provision of antibiotics, dispensing of insufficient doses and the reduced adherence to complete dose regimens may contribute to the spread of antibiotic resistance.[70] The high over-the-counter availability of antibiotics found in this survey suggests that overuse of antibiotics may be common. This problem becomes increasingly complex as many medicine sellers have not been trained in diagnosis and have limited knowledge on antibiotic posology and resistance.

Furthermore, anti-TB medicines, such as single agent isoniazid and rifampicin, were also sold by some outlets, even though fixed dose combination therapy for TB is available for free for patients through the Global Fund via the National TB Programme. The unregulated use of these monotherapies is likely to precipitate treatment failure and engender TB multidrug resistance.

Accurate prescribing decisions, appropriate treatment and rational use of drugs are major concerns among healthcare services in Laos.[71] Nevertheless, enhanced pharmacy regulation, health education programmes and improvements in medicine labelling in Lao language are needed to promote appropriate antibiotic use.

Limitations

Itinerant drug sellers were not included in the survey, but they may stock anti-infective medicines and may reach remote communities. As the sale of medicines from unlicensed outlets is illegal, we have underestimated these sources. We did not examine the quality of antibiotics in the public sector.

Dissolution and disintegration tests were not performed, and the numbers of dosage units collected per sample were low. Medicines sold in small unlabelled plastic bags may already have expired at the time of sample collection and the storage conditions of the samples before collection are not known. That 31% of samples were analysed after their expiry date is an important limitation and cautions against overinterpretation of these data. With the significant human investment needed to analyse samples, conducting analysis of many units before their expiry date is problematic; few papers describe the date of analysis in relation to sample expiry date.

The differences found in the packaging analysis suggest that samples may have been from a different manufacturer, brand or batch. Analysis of CD-3 data was impaired by difficulties in obtaining appropriate genuine samples for all the collected samples. Excipient variation between different manufacturers or the coating of the samples may have had an impact; or medicines may have been degraded due to poor storage conditions. Dose to dose variations within the samples were found, and it is unclear as to how many failed dosage units in a sample should be regarded as minimally acceptable.[72]

Acknowledgements

We greatly appreciate the support of the Lao Food and Drug Department, the Lao Bureau of Food and Drug Inspection, the Centre of Malariology, Parasitology and Entomology (CMPE), Lao PDR and their provincial and district health departments for their support and knowledge throughout the survey. We thank the Directors of Mahosot Hospital and the late Dr Rattanaphone Phetsouvanh and staff of the Microbiology Laboratory for their help. We also thank Anousone Duangnouvong, Danoy Chommanam and Outhevanh Kounnavongsa for their help with analysis and the scanning and logging of the medicines, Drs Serena Vickers and Céline Caillet for their help obtaining the pharmacopoeial limit ranges, and Dr Luis Merino-Martín for advice regarding statistical analysis.

Funding

The study was funded by the Project Priority Solidarity Funds (FSP) Mekong, with finance from the French Ministry of Foreign Affairs and International Development and the Wellcome Trust of Great Britain and the Artemisinin Combination Therapy Consortium (ACTc) via an award from the Bill and Melinda Gates Foundation to the London School of Hygiene and Tropical Medicine (LSHTM).

Transparency declarations

None to declare.

Supplementary data

Figures S1 to S3, Text S1, Form S1 and Tables S1 to S5 are available as Supplementary data at *JAC* Online.

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