Antimalarial drugs quality monitoring in some provinces of VietNam

Nguyen Thi Minh Thu[1], Tran Thanh Duong[2]

[1] Vietnam University of Traditional Medicines, [2] National Institute of Malariology, Parasitology and Entomology (NIMPE)

ABSTRACT

This study was conducted between January and August, 2016 in some malarial prevalence areas of Vietnam including Dak Nong and Gia Lai provinces. Total of 114 anti-malarial medicine samples (of which 55 available antimalarials and 59 selected antibiotics for malaria treatment) were collected from public and private health facilities.

All of the collected samples were screen analized by GPHF-minilab kits at National Institute of Malariology, Parasitology and Entomology (NIMPE) according to GPHF monographs for specifications of visual and physical inspections, disintergration tests and thin layer chromatography assays. None of them was suspicious as substandard quality drugs.

Fifteen randomly chosen samples (13.16% of total samples) were sent to National Institute of Drug Quality Control (NIDQC) for comfirmatory tests according to United States Pharmacopoeia or Vietnamese Pharmacopoeia criteria. The results showed that: three of them (03/114, 2.63%) were found as substandard drugs. All three artesunate 50 mg tablet samples (had the same lot 012013, expiry date in March, 2016, registration number VD-13186-10, collected from private pharmacies in Dak Nong and Gia Lai) did not pass purity tests.

All three substandard drug samples were antimalarials with proportion of 2.63% of total samples and 5.45% of altimalarials.

Keywords: *Antimalarial medicines, drug monitoring, screen analizing, confirmatory tests, substandard drugs.*

1. BACKGROUND AND RATIONALE

In recent years, rate of substandard and fake drugs including antimalarials increased rapidly from year to year. Although many efforts of authority agencies were carried out to prevent poor quality medicines from their circulations, counterfeit and substandard drugs are still increasing. In Southeast Asia, an estimated of 10-35% of medicines are improperly made and illegally produced and sold. [9]

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According to the Promoting the quality of Medicines program (PQM), in 2004, proportion of fake artesuate with no active ingredient was found as 44% in countries of Mekong sub-region. In 2008, this rate of poor quality artesunate reduced and reached 11.2% [9]. Some studies on anti-infectious medicines quality in Vietnam in last few years found that rate of substandard and counterfeit antimalarials was between 1.3% to 2.4% and this rate increased annually. [6], [7], [8]

The goal of this study was to monitor and obtain evidence-based data on antimalarial drug quality in some malaria prevalence provinces in Vietnam including Dak Nong and Gia Lai.

2. METHODS

2.1. Sampling locations:

Two provincial sites of Vietnam were involved in this study including Dak Nong and Gia Lai. These sites have high malaria burden and border with *Plasmodium falciparum*'s artemisinin derivatives resistance area.

Samples were collected from various drug stores and pharmacies in urban, suburban, rural and remote areas of 2 sentinel sites belonging public and private sectors of supply and distribution systems.

2.2. Samples size:

In this survey, three criteria were taken into account in the determination of the sample size: The level of precision or sampling error of ± 4 percent, the confidence level of 95% of sample values and the degree of variability in the quality of antimalarial products distributed across the study sites in each country.

Adapted Yamane simplified formula was used:

Minimum sample size = $[Z^2 \times (p) \times (1-p)] / d^2$

Where: Z = critical value (e.g., 1.96 for 95% confidence level);

p = prevalence, expressed as decimal (failure rate) = between 4-5% per year;

d = confidence interval, expressed as decimal (e.g., 0.04).

A minimum of between 92 and 114 samples of antimalarials and selected antibiotics was suitable and enough for testing.

2.3. Radomization sampling:

Sample collection was conducted between January and February, 2016 by NIMPE staff. A simple randomization technique ensured against bias in selection of outlets for sample collection. From each sentinel site, two districts were chosen in which 2-3 communes or district hospitals and private drug stores provided randomly selected samples. All available antimalarials and selected antibiotics for malaria treatment (including clindamycin and doxycycline preparations) were picked randomly, labeled, kept (with sample collection forms), transported and stored as recommended by manufacturer to prevent deterioration, contamination and adulteration.

A minimum of 40 units per sample was collected for solid dosage forms (tablets, capsules) and 30 vials for injectables. If this minimum number of units is unavailable, no sample was collected from the selected site, and the next closest site was chosen to collect samples. Information was recorded in the sample collection form that the sample was collected from the next closest/available site as opposed to the initial site selected. No expired products was collected either, nor those with less than two (2) months shelf-life remaining until expiration date. These quantities of medicines ensured being enough for at least two assays according to GPHF monographs and one re-confirmatory test.

At the same sampling site, if there is more than one brand or manufacturer and lot or batch number of an anti-infective preparation, samples from different brands and batches were also taken.

2.4. Handling, packaging, labeling and transporting of samples

All operations related to sampling were performed with care. Samples were collected in the original container or box, if possible. The container used to store a sample should protect physical damage to the samples that may affect the physical/ visual inspection. Following quality assurance measures to ensure that samples were transported in plastic container/box provided and protected in a paper box or wrap to ensure their integrity.

2.5. Sample storage

Samples collected were packed, transported, and stored in such a way to prevent any deterioration, contamination, or adulteration and physical damages. The samples collected were stored in accordance with storage instructions of manufacturers. If not specified, then they were stored in sample cabinet with a temperature not exceeding 25°C. Where air-conditioning environment was not applicable, to achieve this temperature condition, wrapped the samples in aluminum foil (especially, artesunate/DHA products), placed them in plastic container, and put them in 2-3 paper boxes. Dated and initialed the plastic bag and plastic container when opening a sample container for analysis.

2.6. Quality drug testing:

Each sample was subject to testing at two levels. Testing level 1 was done by basic tests using Minilab techniques and procedures at the laboratory of NIMPE. All products included in this study have their Minilab testing methods. Testing Level 2 known as confirmatory analysis was conducted at National Institute of Drug Quality Control (NIDQC). Each sample was analysed using its respective pharmacopeial method and procedures. These include United States Pharmacopoeia, Vietnamese Pharmacopoeia, unless otherwise specified.

2.6.1. Corrected labeling and packaging according to the following requirements. At minimum the following information should be available on the label:

- Product name (brand or trade name, and INN or generic name)
- Dosage form and strength
- Number of tablet or capsules (quantity) per dispensing unit
- Manufacture date and expiry date
- Lot or batch number
- Name and address of manufacturer and/or distributor
- Registration number
- Storage condition instructions
- Administration instruction and package insert, if applicable.

2.6.2. Organoleptic (physical/visual) examination for contaminant, uniformity of shape, and other physical characteristics (color, mark, score line, etc.).

2.6.3. Identification of active pharmaceutical ingredients (APIs) [2], [3], [4], [5]; if passed, continue with Assay test.

2.6.4. Assay for content of APIs; if passed, continue with dissolution test.

2.6.5. Dissolution test for tablet and capsule forms.

For injectables, the following tests should be performed and same cut-off measures applied: proper packaging and labeling, organoleptic (physical/visual inspection) test, identification test and assay for content of APIs.

2.7. Data analysis, reporting and feeding back:

Collected data were handled by NIMPE staff and reports were fed back to 2 provincial sites and also were submitted to the Drug Administration of Vietnam.

3. RESULTS AND DISCUSSION

Total of 114 samples including available antimalarials and selected antibiotics for malaria treatment were collected from both public and private sectors in Dak Nong and Gia Lai provinces of Vietnam between January and February, 2016 (see tables 3.1 and 3.2).

Table 3.1: Number of collected samples from 2 sites in Vietnam in 2016

Serial No.	Provincial sites	Number of collected samples		Sub-total
		Antimalarials (at Public -Private sectors)	*Antibiotics (at Public - Private sectors)*	
1	Dak Nong	27 (18-09)	31 (10-21)	58
2	Gia Lai	28 (21-07)	28 (08-20)	56
	Total	**55 (39-16)**	**59 (18-41)**	**114**

Between 2 provincial sites, Dak Nong had the higher number of collected samples (58 samples, 50.88%) with no significance. The number of collected available antimalarial drugs (55 samples, 48.25%) was lower than that of selected antibiotics (59 samples, 51.75%), $P > 0.05$. These samples were collected from provincial malaria control centres, district medical centers, drug stores and private pharmacies as well. In which, 39 antimalarial samples were collected from public facilities (39/55, rated 70.91% of antimalarials - 34.21% of all samples), higher significantly than that collected from private pharmacies (16/51, rated 29.09% of antimalarials - 14.04% of all samples), $P < 0.05$. In contrast, antibiotics for malaria treatment were mainly purchased from private facilities (41 samples, 69.49% of antibiotic samples - 35.96% of all samples) higher significantly than that collected from public sectors (18/59 samples, 30.51% of of antibiotic samples - 15.79% of all samples), $P < 0.05$.

Especially, Artesunate 50 mg tablets were only purchased from private pharmacies and could not find at public health facilities because Artesunate 50mg tablet has not been used as monotherapy for malaria in Vietnam since at the end of 2009.

Table 3.2: Some information of collected samples

Serial No.	Trade names, generic names, concentrations, preparations	Number of collected samples at health facilities		Sub total
		Public sectors	*Private sectors*	
1	Chloroquine phosphate 250 mg, tablet	12	04	16
2	CV artecan (DHA-PIP 40-320 mg), film coated tablet	11	0	11
3	Primaquine diphosphate 13,2 mg, film coated tablet	08	0	08
4	Artesunate 60 mg, vial of powder for injection	02	0	02
5	Artesunate 50 mg, tablet	0	05	05
6	Quinine sulfate 250 mg, tablet	06	05	11
7	Agino Quinin (Quinine sulfate 50mg- paracetamol 200 mg), tablet	0	02	02
8	Doxycycline 100 mg, capsule	10	35	45
9	Clindamycin 150 mg or its trade names, capsule	0	04	04
10	Clindamycin 300 mg or its trade names, capsule	08	02	10
	Total	**57**	**57**	**114**

The antimalarial drug and antibiotic with the highest numbers of collected samples was chloroquine phosphate 250 mg tablets and doxycycline 500 mg capsules (16/114 samples, 14.04% and 45/114 samples, 39.47%, respectively).

All of collected antimalarial drugs were produced by internal pharmaceutical companies while antibiotic preparations (doxycycline or clindamycin) were manufactured by both internal and external pharmaceutical factories/companies with Vietnamese registration numbers.

Samples were collected from 12 public facilities (12/53, 22.64%) and 41 private sectors (41/53, 77.36%).

All of the collected samples were screen analyzed at the laboratory of NIMPE by GPHF minilab-kits. None of them were been suspicious as substandard quality drugs.

Fifteen randomly chosen samples passing screening tests (15/114, 13.16% of total samples) were sent to NIDQC for confirmatory tests according to the 34th United Sates Pharmacopoeia and the 4th Vietnamese Pharmacopoeia criteria.

The results showed that 03 (3/114, 2.63%) of them did not passed confirmatory tests and were considered as substandard samples. All three substandard samples were artesunate 50 mg tablets (had the same lot 012013, expiry date in March, 2016, registration number VD-13186-10, collected from private pharmacies in Dak Nong and Gia Lai) and did not pass purity tests. In contrast, all antibiotics for malaria passed GPHF-minilab and confirmatory tests.

In this study, the test result of Artesunate 50 mg tablet quality was similar to that of Artesunate tablet collected from a private pharmacy in Ha Tinh province in 2013. Rate of substandard samples in 2016 (3/114, 2.63%) was higher than that in 2011 (2/589, 0.34%), 2013 (10/421, 2.38%) and in period of 2003-2009 (47/3117, 1.51%) but lower than that in 2014 (4/107, 3.74). In which, rate of substandard antimalarial samples (3/55, 5.45%) was significantly higher than that in 2013 (6/273, 2.20%), 2011 (2/307, 0.65%) and in period of 2003 - 2009 (2/804, 0.25%), P values < 0.05 [6], [7], [8]. This is due to total numbers of samples collected in 2013, 2011 and period of 2003-2009 five to fifteen fold higher than that in 2016.

4. CONCLUSIONS

4.1. Total of 114 samples including 55 antimalarials (48.25%) and 59 antibiotics for malaria treatment (51.75%) were collected from Dak Nong and Gia Lai provinces and quality analysis in 2016.

4.2. Three antimalarial samples (3/114, 2.63%) were considered as substandard drugs and none antibiotics samples did not meet quality specifications.

4.3. Identified availability and sources of antimalarials in Dak Nong and Gia Lai in 2016.

Recommendations

1. Expending the study of monitoring antimalarial drugs quality in other provinces of Vietnam exept the old ones.

2. Strengthening comunication to community in order to reduce the circle of substandard and forbidden medicines in the markets.

3. More source investment for identifying counterfeit and substandard drugs in the fields.

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