

Screening of Antimalarial Medicines Quality across Selected Sites in India

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Abstract: Despite introduction of newly introduced interventions for malaria control in India, to achieve the target of malaria elimination, strategic planning and concerned efforts for realization of timelines is urgently needed. Tools for effective vector control, efficacious and accessible antimalarial treatments, and awareness about preventive measures constitute a complete package for elimination of the disease in the country. Treatment of malaria with genuine and efficacious drugs provides complete cure and decreases economic burden. Treatment regimens are transported and supplied through various agencies to different level of health systems across country.

Methodology: Studies were undertaken during last three years to assess the quality of antimalarial medicines collected from selected licensed medicine outlets across five malaria endemic regions. A defined amount of branded/ generic antimalarials which included chloroquine (CQ), quinine (Q), primaquine (PQ), Artemisinin based combination therapy [ACT; artesunate + sulphadoxine-pyrimethamine (AS+SP) and artemether + lumefantrine (Am + LU)] wherein AS+SP was analyzed separately as artesunate (AS) and sulphadoxine-pyrimethamine (SP), were screened for quality using standard procedures that included visual inspection, disintegration test, color reaction and thin layer chromatography (TLC) for presence of Active Pharmaceutical ingredient (API), using GPHF Mini lab kit.

Results: The results of the study confirms genuine quality of active pharmaceutical ingredient (APIs) within 100% and 80% of the standards in majority of the samples collected from Rajasthan, Delhi, Jharkhand, Odisha and Tripura. Preliminary screening through GPHF minilab kit showed that eight (4.8%) out of one hundred sixty seven samples failed quality screening test; three (1.8%) failed visual inspection, three (1.8) colorimetric test, one (0.6%) disintegration test and one (0.6%) failed TLC test.

Conclusion: These findings highlight the possibility of quality deterioration due to storage, transportation or even use of substandard material for binding of antimalarial medicines. Further investigations in larger samples using sophisticated techniques is needed to quantify the problem. To provide quality antimalarial medicines, regular monitoring through systematic sampling across public and private sector should be given top priority.

Keywords: Antimalarial medicines, quality, malaria, Mini lab kit

1. Introduction

Malaria, a parasitic infection is endemic in nine of the 11 countries of South East Asia region (SEA), accounting for nearly 70% of the burden outside the WHO African Region (1). Under SEA, India accounted for 80% of reported cases and 60% of malaria deaths during 2016. During past decades, new antimalarial medicines and approaches were introduced for malaria treatment. Most of the antimalarials which include choloquinine(CQ), amodiaquine (AQ) and sulphadoxine pyrimethamine (SP), were effective against malaria and were affordable due to inexpensive nature, however, developed resistance in malarial parasites and led to change of drug policy to Artemisinin Combination Therapy (ACT) as per recommendation of World Health Organization in the country in 2005. The policy change had been implemented and successful in India (2) and similar policy change has been recommended in other countries like Ghana, Nigeria (3). The treatment of malaria requires quality antimalarial drugs in recommended doses with full compliance. Access to quality and effective treatment is a cornerstone of any health program and it requires an effective regulatory system for medicines. However, the problem of poor quality medicines is wide spread and potentially more devastating in low income countries where lack of resources to develop appropriate regulatory frame works and quality control (QC) systems and medicines may lead to treatment failure, development of drug resistance and can jeopardize patient safety, which represents a waste of financial resources (4). Quality assessment classifies drugs into four major groups, which include genuine, degraded, substandard and counterfeit or fake (5). According to WHO definition, genuine medicine contains the correct Active Pharmaceutical Ingredient (API) in the correct amount and packaging, with the

correct dissolution profile. A degraded medicine is produced by the claimed legitimate manufacturers and known to have once contained the correct amount of API, but no longer present does so due to suboptimal storage conditions. A substandard medicine contains the correct packaging and details of manufacturer, however, possesses unacceptable levels of impurities, exhibits incorrect dissolution properties, or the dosage of the API outside of the accepted range. A counterfeit medicine is manufactured with an intent to deceive the customer as the packaging may be a copy, the expected API may not be present, or present in a trace amount, or an unexpected active ingredient not listed on the packaging may be detected in the drug (6). Falsified and substandard are the two main categories of poor quality drugs whereas counterfeit is an only broad term and should be used for trademark. Although counterfeit drugs are categorized under substandard drugs that are deliberately and fraudulently mislabeled for profit making purposes, not many systematically planned studies have reported the findings. An analysis by World Wide Antimalarial Resistance Network (WWARN) on the epidemiology of poor-quality anti-malarial in the malarious world observed that there was no publicly available reports for 60.6% of the 104 malaria-endemic countries on quality of medicines (7). During last one decade, studies have highlighted the problem of substandard antimalarials across globe, more in Southeast Asia and other malaria endemic areas in Africa. Recent analysis (8) revealed substantial amount of failed chemical/packaging quality tests in antimalarial medicines with highest proportion of poor quality samples followed by falsified and substandard.

Indian government began enforcing pharmaceutical standards more systematically after the Drugs and Cosmetic Act of 1940 (9). Only in 2009, however, did the Indian Pharmaceutical Commission become an independent agency under the Ministry of Health, separate from the drug regulatory authority, Indian Pharmacopoeia Commission 2011 (10). Quality assessment of medicines involve standard procedures. This includes, visual and physical inspection, of the batch number, expiration date, insert provided, tablet size, markings, color, and chipped edges etc. (11). The other test include disintegration test for a preliminary assessment of drug solubility, simple color reactions to identify drugs, and semi-quantitative thin layer chromatography (TLC) to check for quantities of API present (12). A field laboratory kit compiled specifically for the analysis of antimalarials, the GPHF MiniLab kit uses a four-stage process to examine the quality of drugs with nominal training prior to utilizing the kit (13). An attempt was made to screen the purposely collected samples of antimalarial drugs for their quality from selected sites in India. The drug samples were collected from a selected five sites across different geographical zones of India so as to cover at least 4 malaria endemic regions. These sites were Delhi, Jharkhand, Odisha, Tripura and Rajasthan. The antimalarial samples included chloroquine (CQ), quinine (Q), primaquine

and artemisinin based combination therapy (ACT) samples which include artesunate plus sulphadoxine-pyremethamine (AS+SP), and artemether-lumefantrine (AL).

2. Methodology

A. Sampling sites

The surveys for sample collection were conducted in different geographical regions of Delhi, Jharkhand, Odisha, Tripura and Rajasthan. Collection of samples was done throughout the last three years from different geographical regions of India i. e., urban-suburban areas and from private and public sectors. Under this scheme, the sampling sites were selected based on endemicity of malaria, representing *P. falciparum* and *P. vivax* malaria predominant sites and Delhi site with reported cases of imported malaria. Medicine samples were collected and dispatched to the central laboratory for qualitative and semi-quantitative testing. The basic qualitative tests performed included visual inspection, disintegration, color reaction tests and thin layer chromatography (TLC) using GPHF-minilab kit.

B. Sample collection

A defined amount of branded/ generic antimalarials samples i.e. chloroquine (CQ, N=38), primaquine (PQ, N= 4) quinine (Q, N=4), artemether-lumefantrine (AL, N=23), sulfadoxine pyrimethamine (SP, N=7), were collected from selected study sites. The blister packs of artesunate + sulphadoxine-pyrimethamine (AS +SP) as artemisinin based combination therapy (ACT) were also collected and analyzed as individual active pharmaceutical ingredients namely artesunate (AS, N=45) and sulphadoxine-pyrimethamine (SP, N=45). Adequate care and measures were taken to transport the samples from collection site to the central testing laboratory under ambient conditions. Samples were collected from all the selected sites during post monsoon season. At least 3 samples of each brand were purchased or collected, where tablets in triplicate were used for visual inspection, disintegration test, color test and TLC test. The left over samples were retained for retesting, if required. The details of samples collected from Government (Govt.) health facility and Private (Pvt.) shop is shown in table 1.

C. Analytical tools

Each sample was identified by a unique code name, wherein the name of the site, type of the product and their generic name and brand, manufacturer detail, dosage form and strength, package size, packaging material, sampling date and sequential code number of sample was included.

1) Visual inspection

As a quick check for quality of samples, visual inspection of packaging and dosage form was undertaken. Using magnification glass, the packaging was checked for correct and legible labelling of active ingredients and strength, expiration date, batch number, manufacturer details, product designs, or

holograms. The appearance of the samples was also examined for shape, size, discoloration, chippings, moisture or excessive powder.

2) *Disintegration*

Each collected sample was examined for disintegration test where disintegration of the solid dosage form in distilled water at $37\text{oC} \pm 2^\circ\text{C}$ is measured.

3) *Colorimetric tests*

Basic colorimetric tests, for confirmation of the identity of active pharmaceutical ingredients (APIs) was employed for all the samples. To ensure that all the samples contained the requisite API, each of them was evaluated using methods described in the Mini lab kit. The presence of artesunate as active ingredient in antimalarials was confirmed with the Yellow color product in the Fast Red TR dye test. Similarly, reddish brown color with FTR indicate presence of artemether + lumefantrine and chloroquine. Reaction involving methanolic solution of 4(Di-methylamino)-benzaldehyde provide yellow orange colour or orange crystals and thus may indicate presence of SP. White blue fluorescence on reaction of quinine sulphate with conc. Supturic acid under 366nm UV light in dark indicate genuine presence of quinine.

4) *Semi-quantitative TLC Assay*

The TLC procedure was employed as a rapid, simple, and affordable quality monitoring tool to estimate the API content of the samples. TLC was performed on a precoated sheet of aluminium foil with silica gel. Standard solution of 100% and 80% were applied on the plate along with drug samples. The spotting of samples as well as standards on TLC plate was performed by using micro-capillaries. Detection of spots was observed under UV light or reaction with different chemicals as per standard procedure mentioned in Mini lab kit.

3. Results

One hundred and sixty seven samples were analyzed by rapid screening tests using GPHF Mini lab kit. These include physical and visual inspection, disintegration test, colorimetry and thin-layer chromatography following the standard procedure mentioned in the kit. All except three samples passed preliminary physical and visual inspection tests, which included hologram inspection, printed details on blister package and physical parameters of shape, size and color for the individual tablets. These three samples which failed visual examination were AS+SP-ACT blister packs. In one sample, purchased from private retail shop in Alwar district, Rajasthan, there was incorrect labelling in blister pack, while in two samples, collected from public health system in Deogarh district, Jharkhand and Rourkela district in Odisha, the tablets were fragile and had powder consistency when taken out of the blister. This could be due to exposure to high moisture while subjecting the blisters to storage conditions or transportation of samples. Since the samples are for lower age category, care needs to taken while storing such samples. The details of samples and the collection sites is given in table 2.

Disintegration test, wherein, the samples were observed for its complete dissolution, was within the acceptable limits for all samples of antimalarials except one sample of primaquine tablet purchased from Rourkela district in Odisha.

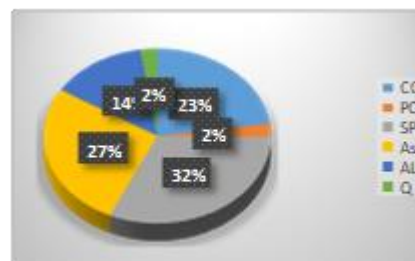


Fig. 1. Pie diagram showing percentage of anti-malarial drugs collected

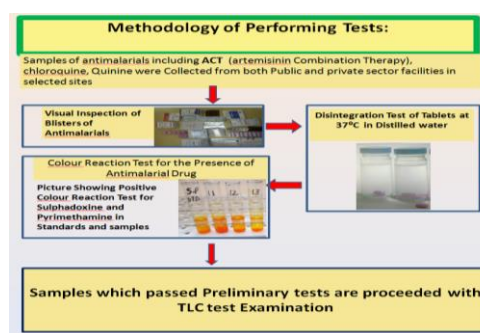


Fig. 2. Methodology followed during the study



Fig. 3. Details of study procedures and GPHF Mini lab kit used during the study

Colorimetric tests reactions for all antimalarials were performed as per standard method for identification of formulations corresponding to very low quality of antimalarial drugs. All samples collected from different sites successfully passed this test with majority of samples confirmed the genuine presence of active pharmaceutical ingredients of antimalarials in the packages. Three samples, two samples of AL-ACT, one from Bhadrak district, Odisha and other from Ranchi district, Jharkhand and the third AS+SP-ACT blister pack from Simdega district, Jharkhand did not show standard colorimetric test and need to be reconfirmed with the API content using more sophisticated technique like HPLC. However, these samples passed the visual inspection, disintegration and TLC tests. Except these three samples, all antimalarial samples in the

Table 1
Details of antimalarial medicines collected for quality assessment

Name of the drug	Total Number of samples collected (Govt./Private)	Manufacturing companies/ brand	Number of tablets analysed
Artesunate	45 (27/18)	10	135
Quinine	04 (03/1)	02	12
Artemether+ lumefantrine	23 (9/14)	08	69
Chloroquine	38 (23/15)	03	114
Sulphadoxine-pyrimethamine	53 (40/13)	14	159
Primaquine	4 (02/02)	2	12
Total	167 (104/63)	39	501

*Artesunate and sulphadoxine-pyrimethamine were part of AS+SP-ACT, however analyzed separately for quality

Table 2
Comparative analysis of physical properties and qualitative analysis of antimalarial samples

Serial no.	Name of medicines	Physical Properties			Qualitative Properties		
		Number of samples tested *	Visual Inspection	Disintegration Time (in min.)	Colorimetric Analysis	TLC Passed/Failed	Rf value Mean (SD)
1	Quinine	4	Passed	4.0±0.707	Passed	Passed	0.84±0.04
2	Chloroquine	38	Passed	7.687±1.479	Passed	1 failed	0.46±0.02
3	Artesunate	45	1 sample failed	3.460±1.343	1 sample failed	Passed	0.66±0.02
4	Sulfadoxine pyrimethamine	53	2 sample failed	3.512±0.467	Passed	Passed	0.91±0.02
5	Artemether-Lumefantrine	23	Passed	4.1±1.702	2 sample failed	Passed	0.77±0.03 0.45±0.01
6	Primaquine	4	Passed	1 failed	Passed	Passed	0.17±0.015

* The tests were conducted in triplicate samples

Table 3
Details of antimalarial samples with results of tests applied using Mini Lab kit

S. No.	Type of medicine & Combination	Collection site	Test failed	Recommended for Age group	Source of antimalarial
1	AS+SP-ACT kit	Alwar district, Rajasthan	Visual inspection incorrect labelling	1-4 yrs	Private retail shop
2	AS+SP-ACT kit	Dcoghar district, Jharkhand	Visual inspection-Moisture in tablet	5-8 yrs	Public health facility
3	AS+SP-ACT kit	Rourkela district, Odisha	Visual inspection-Moisture in Tablet	1-4 yrs	Public health facility
4	Primaquine tablet	Rourkela district, Odisha	Disintegration test	Adult	Private retail shop
5	Chloroquine phosphate (500mg)	Rourkela district, Odisha	TLC test	Adult	Private retail shop
6	AL-ACT kit	Ranchi district, Jharkhand	Colorimetric test	Adult	Private retail shop
7	AL-ACT kit	Bhadrak Odisha	Colorimetric test	Adult	Private retail shop
8	AS+SP-ACT kit	Simdega district, Jharkhand	Colorimetric test	1-4 yrs	Public health facility

present study passed the colorimetric tests thereby confirmed the presence of the respective API, as per mentioned on the corresponding medicines package. TLC tests when compared with respective standards provided in the GPHF Minilab kit confirm the presence of genuine active pharmaceutical ingredient in the samples. Only one sample of chloroquine from Rourkela district, Odisha, did not conform to TLC test. The TLC assay of the sample therefore suggests that this sample is noncompliant with respect to API content. The visual inspection, disintegration and colorimetric test for this sample were satisfactory.

4. Discussion

The results of the study confirms genuine quality of active

pharmaceutical ingredient (APIs) within 100% and 80% of the standards in majority of the samples. Out of a total of 167 samples comprising of six antimalarials, either alone or in combination, only eight, samples failed preliminary quality assessment screening through GPHF Mini lab kit. Since malaria is a preventable and treatable disease, its successful treatment is exclusively dependent on the efficacious antimalarial medicines. As the poor quality antimalarial drugs provide inadequate treatment leading to drug resistance, thus the quality of antimalarials (or of any drug, in general) must be maintained stringently (14).

This study used a mobile laboratory in the form of GPHF-Minilab kit in a protective suitcases (Global Pharma Health Fund, 2016), which claims to be able to test 80 compounds including drugs for priority diseases. This kit facilitates visual

inspection, disintegration tests and thin layer chromatography with detailed guide. The techniques employed are user friendly with minimum requirement of basic analytical chemistry skills. Reports are available on its usefulness for government agencies as part of national anti-falsifying Pharmacovigilance programmes (15) and/or screening imports at entry ports (16).

Poor quality of anti-malarials can result in therapeutic failure leading to emergence and spread of drug resistance strains of plasmodium, eventually causing serious side effects or even deaths of patients. In addition, there will be economic burden on the patients as well as health system leading to loss of confidence in the healthcare systems (17). Medicines quality is increasingly becoming topic of concern in many parts of the world due to the recent increase in the cases of counterfeit medicines. The threat of counterfeit appears to be invisible due to the nature as well as the neglect and has sugared over the years from the stakeholders involving in the pharmaceutical supply chain (18). Medicines are a particular target to counterfeit because they are of high value items in relation to their bulk and the demand for medicines is infinite (19). In addition, one of the most difficult tasks in screening of poor quality drugs is determining whether a drug fits into the classification defined as substandard or degraded. In both classes, a lower than expected quantity of API can be present. The ability to distinguish between these classes, however, is crucial, as the solutions to these problems are very different. If the poor quality medicines are substandard, the problem must be presented to the manufacturers, as the error is occurring during the production of the medicine. Degraded drugs, however, are caused by poor storage conditions, so it must be problem of the pharmacies and other distributors.

As not much information is available on the quality of antimalarial medicines in the country, which are recommended by National programme for treatment of malaria, studies were performed for preliminary screening through qualitative and semi quantitative analysis. The drugs were collected from different study sites and were analyzed using GPHF Minilab kit, which acts as the first line of defense against counterfeit and substandard medicines threatening the health of millions of people in developing countries. Preliminary screening through GPHF minilab kit showed that eight (4.8%) out of one hundred sixty seven samples failed quality screening test; three (1.8%) failed visual inspection, three (1.8) colorimetric test, one (0.6%) disintegration test and one (0.6%) failed TLC test. Amongst these samples, 3 (37.5%) were from Public health system, while 5 (62.5%) were purchased from medicine retail shop. In general, 5-8 samples of antimalarial packs with different batch numbers were purchased from private retail medicine shops or collected from public health facilities through surveys at selected study sites. The samples included medicine strips in triplicate, which helped in undertaking tests as per standard protocol.

A recent study on surveillance for falsified and substandard medicines in Africa and Asia has shown around 2.5 % samples

as substandard or falsified. Even 1.4% samples did not contain the stated active pharmaceutical ingredient (API), while 0.7% contained insufficient amounts of the API, and 0.3% showed insufficient dissolution of the API. The highest proportion of substandard and falsified medicines was found in Cameroon, followed by the Democratic Republic of Congo and Nigeria (8).

The results of preliminary screening studies with GPHF–minilab kit showed that the antimalarial samples that are recommended, prescribed and consumed in different states of India are of standard quality in general. This has become possible since when the Indian pharmaceuticals and manufacturers have started following the Drug regulatory rules and systems strictly. However, high moisture content and altered disintegration behavior requires more emphasis to be given on proper storage and transportation of medicines. All drugs were manufactured in Indian pharmaceuticals company and were well within their expiry dates.

India is an increasingly important exporter of drugs for both developed and developing countries with high burden of malaria. Several investigators have reported the analysis of various antimalarials and exhibited the effectiveness of these medicines as much as possible, through evaluation, safety and quality, and hence ensured their appropriate use (20, 21). In the present study, majority of antimalarials assured the presence of mentioned APIs qualities between 100% and 80% of the standards provided in the GPHF Minilab Kit. Moreover, qualitative tests of different tablets using Fast Red TR (FTR) dye technique for examining the active ingredient in the studied antimalarials have confirmed the presence of the respective APIs (as mentioned on the corresponding drugs package). All of these results indicated that these antimalarial medicines maintain international standards; which strengthened the position of Indian pharmaceuticals in the global drug market. The present study has further strengthened the national medicines regulatory authority and ensured better alignment and responsiveness to disease control strategies employed in the country.

Due to the absence of the declared anti-malarial ingredients and due to the presence of other pharmaceutical ingredients, the identified falsified medicine represents a serious health risk for the population. Thin-layer chromatography (TLC) using different solvent systems proved to be a powerful method for the identification of this type of counterfeiting, presenting a simple and affordable technology for use in resource-limited settings. However, further reassurance of quality of antimalarials can be assessed using other sophisticated techniques like High performance liquid chromatography (HPLC), liquid chromatography mass spectrometry.

5. Conclusion

These findings highlight the possibility of quality deterioration due to storage, transportation or even use of substandard material for binding of antimalarial medicines in few samples. None of the other samples collected from any

other site show any signs of deterioration in quality of medicines

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