819 Systematic Sampling Approach Reveals Fewer Falsified First Line Antimalarials than Previously Reported

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Malaria drug quality: Introduction

Malaria is a curable disease provided patients have timely access to efficacious drugs, namely artemisinin based-combination therapies (ACTs), recommended as first line treatment by the World Health Organization (WHO). The threat posed by falsified and substandard drugs is drawing increasing international attention.

Previous reports of the global problem of poor quality (substandard and falsified) drugs were based on small sample size collected using non representative sampling approaches in a given geographical region. Added to which most studies do not differentiate between substandard and falsified drugs confounded by lack of universal agreement on definitions.

Alarming reports

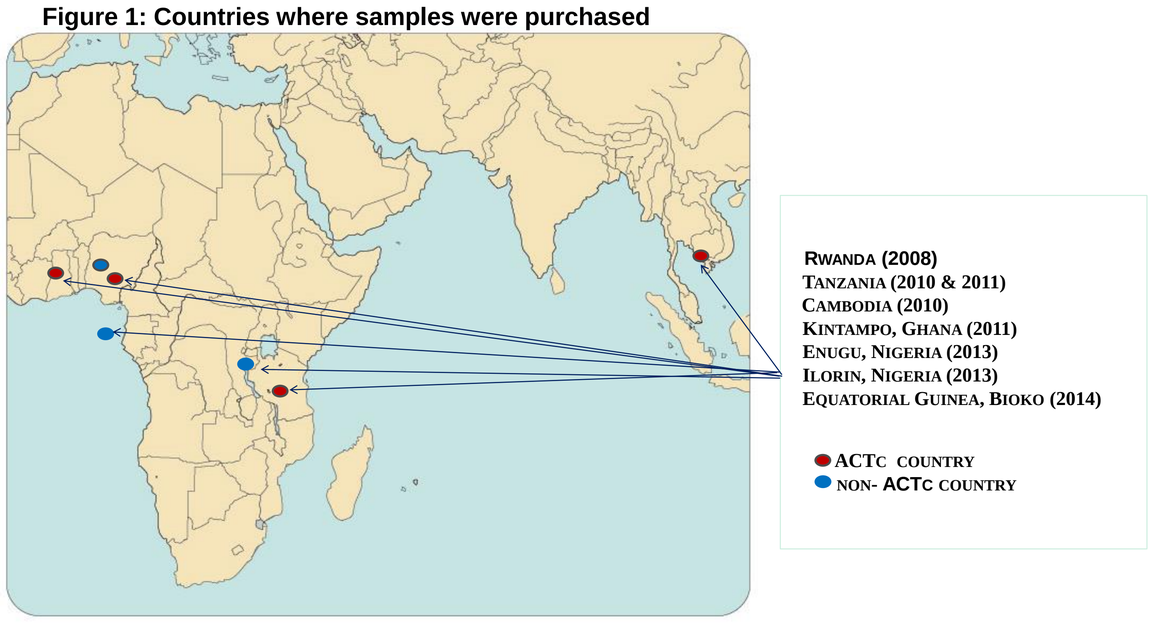
The WHO reported in 2011 that a third of anti-malarial drugs (ACTs and sulfadoxine/ pyrimethamine formulations) available in Cameroon, Ethiopia, Ghana, Kenya, Nigeria and Tanzania are substandard and possibly falsified. A meta-analysis review of published studies stated that 35% (796/2,296) of antimalarial drug samples from 21 Sub-Saharan African countries, purchased predominantly using convenience sampling, failed chemical content analysis.

Resource poor countries have limited technical, financial, and/or human resources required to inspect and police the drug supply. The lack of reliable estimates of poor quality drug prevalence and its causes make it difficult for national regulatory authorities to determine the need and scale of interventions to assure drug quality.

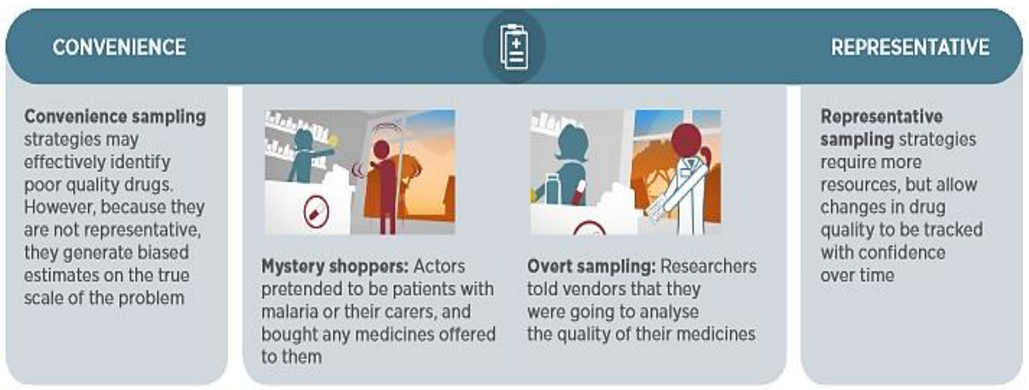
Our drug quality programme

To investigate the threat of poor quality drugs we purchased over 10,000 samples of ACTs in a number of malaria endemic countries (Figure 1)..

Figure 1: Countries where samples were purchased



Samples were purchased public and private healthcare providers using three sampling approaches (convenience, mystery client and overt).



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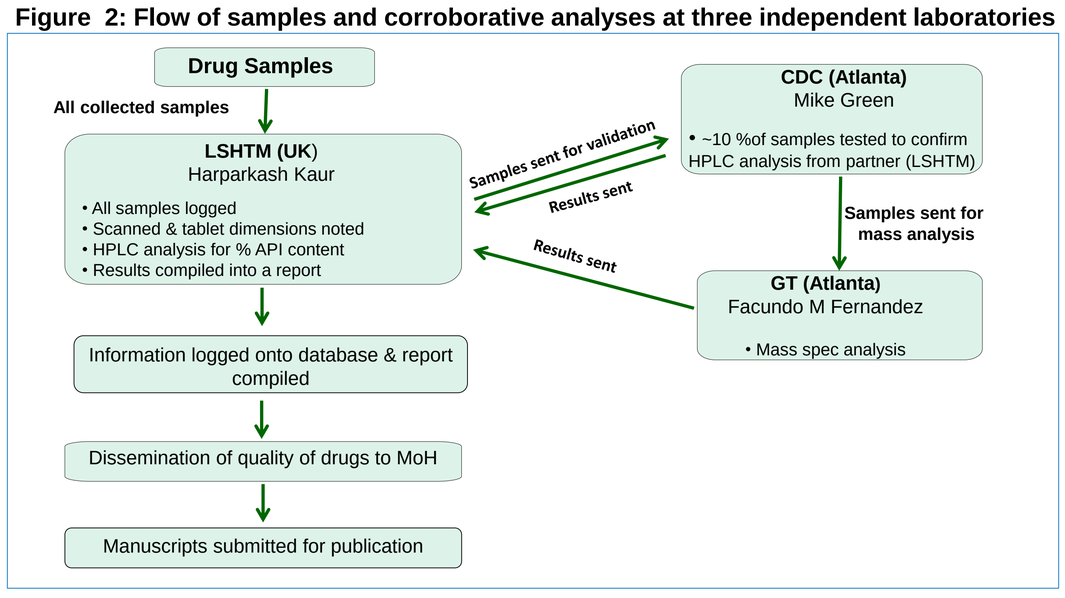
Processing the samples

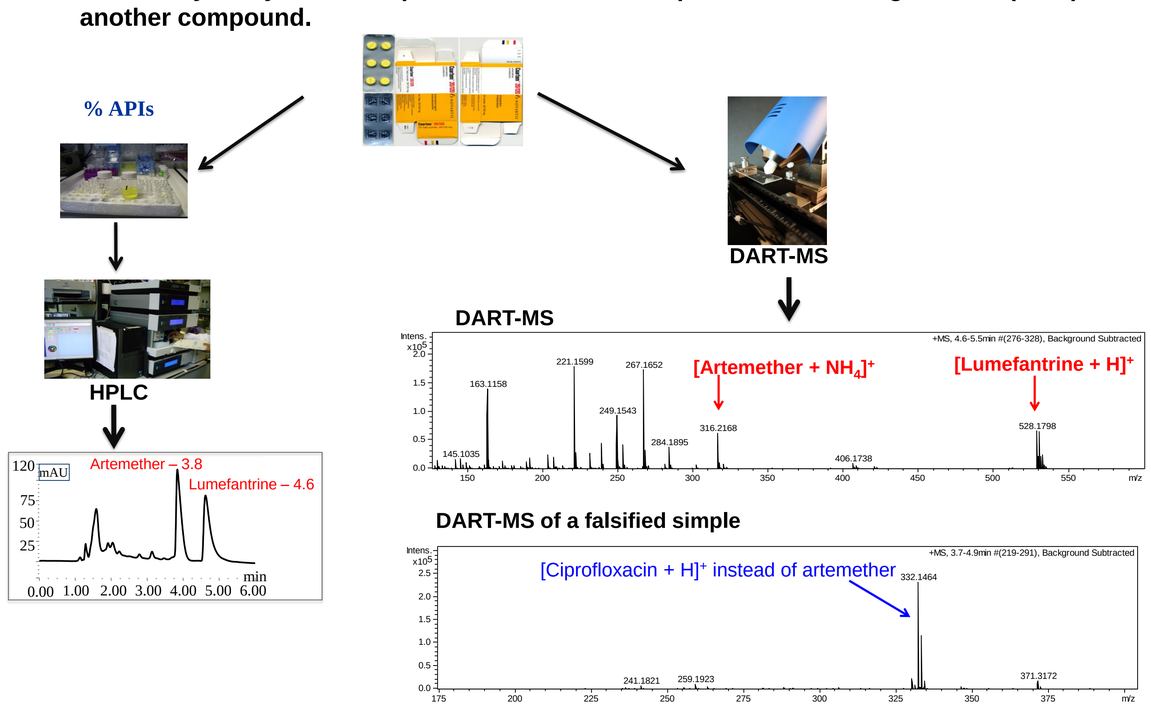
Each purchased sample was logged, scanned, photographed and issued with individual barcodes and analysed in 3 independent laboratories (Figure 2), for quantitative (high performance liquid chromatography - HPLC) and qualitative (mass spectrometry - MS) analysis. MS analysis confirmed the presence of the measured APIs or the presence of other compounds.

Figure 2: Flow of samples and corroborative analyses at three independent laboratories



Drug quality analysis

Figure 3: Laboratory analysis techniques to measure active pharmaceutical ingredients (APIs) or another compound.



Our findings

Table 1: Drug quality of antimalarial medicines purchased in Sub-Saharan Africa and Cambodia

Country (date collected)	Sampling Method	Number of Samples	Number of Brands	Acceptable Quality	Substandard	Degraded	Falsified
Cambodia (2010)	Mystery client Overt	291	21	68.7 %	**31.3 %**	Not det.	**None found**
Equatorial Guinea, Bioko (2014)	Convenience, Mystery Client, Overt Shopping	677	77	91.0 %	**1.6 %**	0 %	**7.4 %**
Ghana, Kintampo (2011)	Mystery client	270	31	85.2 %	**14.8 %**	Not det.	**None found**
Nigeria, Enugu Metropolis (2013)	Convenience, Mystery Client, Overt Shopping	3,024	131	90.7 %	**6.8 %**	1.3 %	**1.2%**
Nigeria, Ilorin City (2013)	Convenience, Mystery Client, Overt Shopping	1,450	142	91.5 %	**6.3 %**	1.4 %	**0.8%**
Rwanda (2008)	Mystery client	97	1	94.8 %	**5.2 %**	Not det.	**None found**
Tanzania (2010)	Overt	1,737	37	95.9 %	**4.1 %**	Not det.	**None found**
Tanzania (2011)	Overt	2,546	46	97.8 %	**2.2 %**	Not det.	**None found**

Note: Not det. = not determined as the methods had not been developed to detect degraded products
Acceptable quality = 85-115% APIs; substandard = <85 or >115% APIs; degraded = < 85% APIs plus products of degradation; falsified = 0% APIs

Analysis of over 10,000 ACT samples (142 brands) from 6 countries found that substandard drugs are present in all of the countries studied and falsified drugs were only found in just two (Table 1). Substandard drugs are produced with inadequate attention to good manufacturing practices and do not have the correct amount of API. Falsified drugs did not contain the stated APIs but were found to contain other compounds identified by MS-DART analysis (Table 2). Monotherapy tablets (not recommended by WHO) of artesunate and dihydroartemisinin are still on sale in some countries. The concern is that a number of them were analysed to be falsified.

Table 2: Falsified samples purchased in Nigeria and Equatorial Guinea

Stated brand	Stated country of manufacture	Stated manufacturer	Stated API	Compounds found
Artesunat®	Vietnam	Mekophar	AS	Acetaminophen; Ciprofloxacin; DEHA or DOA; Stearic acid
Cusnat®	China	Greenfield	AS	2-Mercaptobenzothiazole
Vatunate®	India	Sr Medical	AS	Disaccharide; Stearic acid
Coartem®	USA	Novartis	AM-LUM	Chlorzoxazone; Ciprofloxacin; DEHA or DOA ; polymer of sugar alcohol; Sildenafil; Stearic acid
Lonart®-DS	India	Bliss GVS	AM-LUM	Ciprofloxacin
Duo-Cotecxin®	China	Zheijang Holley	DHA-PIP	DEHA or DOA
WAIPA	Nigeria	Kunimed	DHA-PIP	Acetaminophen

Note: AS = artesunate; AM-LUM = artemether-lumefantrine; DHA-PIP = dihydroartemisinin-piperaquine; DEHA or DOA = petroleum products [Bis(2-ethylhexyl) adipate or Dioctyl adipate]

Summary

Falsified ACTs were only found in Nigeria and Equatorial Guinea but substandard ACTs were present in all the 6 countries studied. **Substandard drugs** may contribute to the development of **resistance** as a result of **under dosing** when they contain **too little API**.

Representative sampling approaches are important to obtain a true perspective of the quality of drugs in a given geographical region. However, this type of research is cost intensive, both for the purchase and analysis of drugs.

Analytical techniques mentioned here are not widely available leading to the **lack of data on quality of antimalarial drugs for most malaria endemic countries**. Funding is limited for such work and this situation needs to be urgently remedied.

Our data points to the need for ongoing surveillance of drug quality with establishment of affordable systems to sample drugs in a representative way and analyse them regularly with specialist laboratory techniques. This enables the quantification and tracking of the quality of any medication, not just antimalarials.