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Poor quality malaria drugs:
how many and where?

Woman obtains medicines in Ghana

The Artemisinin-based Combination Therapy (ACT) Consortium Drug Quality programme collected and analysed the quality of over 10,000 artemisinin-based drugs from six malaria endemic countries: Cambodia, Equatorial Guinea, Ghana, Nigeria, Rwanda and Tanzania.

Previous reports had suggested that up to one third of antimalarials were "fake". The Drug Quality programme showed that falsified antimalarials are not as common as previously reported. However, substandard drugs are present in all countries studied and monotherapy tablets are still available in some places.

Why are poor quality malaria drugs dangerous?

Falsified drugs have received much attention globally. However, **substandard** drugs are of great concern too, especially those that contain too little active pharmaceutical ingredient (API). Not only do they leave patients undertreated, which could be fatal, but they may also contribute to the development of **resistance** to ACTs, the most effective drugs for malaria.

Monotherapy tablets are also considered to be a major contributing factor to the development of resistance to artemisinin derivatives. The World Health Organization (WHO) has urged malaria-endemic countries to ban these oral monotherapies and promote access to good quality ACTs.

Main findings

Of all **10,079** samples analysed, we found:

Country (collection date)	Samples	Brands	Acceptable quality	Substandard	Falsified	Artemisinin monotherapy tablets
Bioko Island - Equatorial Guinea (2014)	677	142	91.0%	1.6%	7.40%	Found
Cambodia (2010)	291	21	68.7%	31.3%	0 found	Found
Ghana – Kintampo (2011)	257	31	63.0%	37.0%	0 found	Not found
Nigeria - Enugu Metropolis (2013)	3024	131	92.2%	6.6%	1.20%	Found
Nigeria - Ilorin City (2013)	1450	77	91.5%	7.7%	0.80%	Found
Rwanda (2008)	97	1	93.8%	6.2%	0 found	Not found
Tanzania (2010)	1737	37	88.0%	12.0%	0 found	Not found
Tanzania (2011)	2546	46	97.8%	2.20%	0 found	Not found

Classification of medicines used by the ACT Consortium Drug Quality programme

- **Acceptable quality** medicines contain between 85% and 115% of the stated API for both the partner drug and artemisinin derivative compounds.
- **Substandard** medicines can result from inadequate quality control in the manufacturing process, meaning that they contain less than 85% or more than 115% of the stated API. When containing less than 85%, they may contain degraded compounds which can result from inappropriate storage conditions, for example in high temperature or humidity.
- **Falsified** (or fake) medicines do not contain any stated API and may carry false representation of their source of identity. (A falsified drug could signal a potentially counterfeit product, which does not comply with intellectual property rights or may infringe trademark law).

Packets of artemisinin-containing antimalarials analysed by the ACT Consortium

How did we collect the medicines?

Methods to sample medicines differed between the countries where we worked. In general, the medicines were mainly collected from private sector retail outlets, including pharmacies and drug shops. In some countries we undertook a nationally representative survey and in some countries we undertook more localised surveys.

Selecting outlets

In several countries we started by using a **"convenience sampling"** approach as a pilot collection method to gain perspective on the types of outlets and the brands of drugs available. In most countries we also carried out a complete or **random** survey using lists of private outlets obtained from the Ministry of Health (updating them as necessary), in order to attain a representative sample.

Purchasing medicines

Once the outlets were selected, medicine samples were collected using one of two approaches. Through a **"mystery client"** approach the person purchasing the medicines posed as a malaria patient or their relative; through an **"overt sample collection"** we told vendors that we were going to analyse the quality of the medicines they sold. In this overt approach we also interviewed vendors to obtain data on the availability and supply of antimalarials, their storage conditions, and the training of providers. In some countries, we used both approaches to assess whether the sampling method used might affect the results obtained.

Answering key questions on malaria drug delivery

Country	Primary method for sampling outlets	Method for sampling medicines
Bioko Island – Equatorial Guinea	Random / National	Mystery client & Overt
Cambodia	Random / National*	Mystery client & Overt
Ghana	Random / 1 Site	Mystery client
Nigeria	Random / 2 Sites	Mystery client & Overt
Rwanda	Unknown / National	Mystery client
Tanzania	Random / National	Overt

from malaria endemic areas

Which methods did we use to analyse the quality of the medicines?

The collected samples were analysed in **three different laboratories** in the UK and the USA. First, they were sent to the London School of Hygiene & Tropical Medicine (LSHTM), where they were logged and their packaging and blisters scanned. Each tablet was weighed and its dimensions recorded on the database.

Each sample was analysed using the analytical technique of **high performance liquid chromatography (HPLC)** to measure the amount of API, which was then expressed as the percentage of the stated API and used to classify the quality of the sample.

Duplicate samples from each packet of tablets analysed at LSHTM were sent to the US Centers for Disease Control and Prevention (CDC) laboratories in Atlanta, USA where a random 10% were analysed for confirmatory HPLC results. A duplicate set were also sent to the Georgia Institute of Technology, Atlanta, USA for **ambient mass spectrometry** analyses to verify the pharmaceutical ingredients present and identify any unstated compounds.

We adopted the range between **85% and 115% of the stated API** (for both compounds of the combination therapy) to classify samples as acceptable quality. Medicines with less than 85% or over 115% of the stated API of any of the partner compounds were classified as substandard. In some surveys, substandard medicines were also examined to detect the presence of degradation, caused by poor storage conditions such as heat and humidity. Medicines were regarded as falsified when either one of the stated APIs was not present.

All results were compiled into a report and disseminated to the relevant Ministries of Health before being submitted as a manuscript to peer reviewed journals.
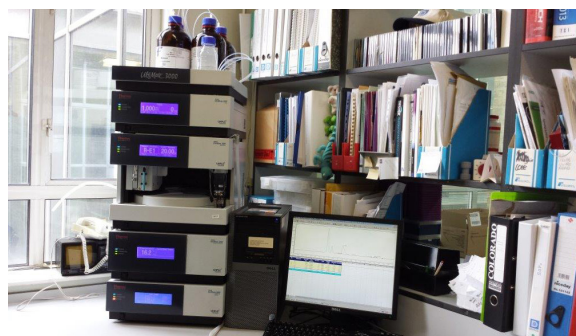
HPLC equipment at the London School of Hygiene & Tropical Medicine

What did we find?

We found no evidence of falsified medicines in 4,928 samples (over 50 brands) from Cambodia, Ghana, Rwanda and Tanzania. Of the 5,151 samples that we collected in Bioko Island - Equatorial Guinea and Nigeria (over 142 brands), **1.9% were falsified**, i.e. contained neither of the stated APIs. Instead, they contained compounds including clorzoxazone (a muscle relaxant), ciprofloxacin (an antibiotic) or acetaminophenon (a commonly used painkiller).

The falsified medicines found in this research are far fewer than the 35% fakes suggested in previous reports.

We found **substandard** drugs in all the countries that we studied.

Acceptable quality antimalarials

Falsified antimalarials

Why is our research different from previous reports?

Previous alarming reports were based on studies that predominantly used non-representative methods for selecting drugs for analysis, with study teams often selecting antimalarial sellers because they were easily accessible, or because they believed sellers were more likely to sell poor quality medicines based on their appearance or anecdotal reports. This "convenience approach" for sampling may not be representative of the places where patients buy their medicines.

Results based on low cost convenience sampling approaches are still useful in drawing attention to a potential problem. However, alarming messages could be counter-productive by undermining the confidence in drugs and health care providers and systems.

A key strength of our work was the use of representative sampling approaches in many of the countries surveyed, as well as the substantial number of drugs analysed and the validation of results in three independent laboratories.

Conclusion

Malaria is a leading cause of morbidity and mortality in tropical countries. ACTs are the first line treatment endorsed by the WHO for uncomplicated P. *falciparum* malaria, and have been adopted in endemic countries.

Both patients and health professionals assume that their medicines are of good quality, but reports have drawn attention to the presence of large amounts of "fake" drugs.

Overall, our Drug Quality programme provides reassuring findings, but there is no room for complacency.

- One fake malaria drug is one too many.
- Substandard medicines are present in every country that we studied.
- Monotherapy tablets of artesunate and dihydroartemisinin are still available.

Our research showed how representative methods to sample medicines are important for generating reliable estimates of the prevalence of poor quality drugs in a given country.

However, this type of study is cost intensive, both for the purchase and analysis of drugs.

It is important to establish affordable systems that sample medicines in a representative way and robust laboratory techniques to analyse them on a regular basis. This will allow us to accurately quantify and track the scale of poor quality medicines that threaten the treatment of this life threatening disease.

Children in Uganda

Collaborating Institutions

London School of Hygiene & Tropical Medicine, UK/ US Centers for Disease Control and Prevention, Atlanta, USA / Georgia Institute of Technology, Atlanta, USA / Ifakara Health Institute, Dar es Salaam, Tanzania / Cambodia National Malaria Centre, Cambodia / Ministry of Health and Social Welfare Malabo, Equatorial Guinea (through Medical Care Development International Bioko Island Malaria Control Project) / Rwanda Ministry of Health Malaria Unit, Rwanda / Enugu State Ministry of Health, Nigeria / Kintampo Health Research Centre, Ghana

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For a full list of investigators and collaborators in each country, as well as the latest news, resources and peer reviewed publications, visit **www.actconsortium.org/drugquality**

The ACT Consortium is funded by a grant from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine.

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