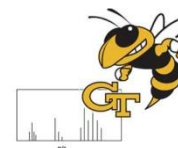# Findings from the ACT Consortium Drug Quality Studies in 6 Countries

Harparkash Kaur

London School of Hygiene & Tropical Medicine

Falsified Antimalarials Abound

Health professionals and patients assume that the medicines that they are prescribing/prescribed are of good quality.

nature
10 March 2005 Volume 434 Issue no 7030

Killers on the loose

news feature

In the line of fire

Dora Akunyili has spent the past four years facing down corruption and tackling Nigeria's rampant problems with fake drugs. This crusade has been phenomenally successful, but has placed Akunyili's life in danger. Peter Aldhous caught up with her on a recent trip to the United States.

Murder by medicine

Across the developing world, people are dying after being peddled fake pharmaceuticals. Peter Aldhous reports from southeast Asia, where scientists, doctors and regulators battle against organized crime.

BBC NEWS HEALTH

News | Sport | Weather | Capital | Culture | Autos

Home | UK | Africa | Asia | Europe | Latin America | Mid-East | US & Canada | Business | Health | Sci/Envi

22 May 2012 Last updated at 00:51 GMT

Third of malaria drugs 'are fake'

By Michelle Roberts
Health editor, BBC News online

A third of malaria drugs used around the world to stem the spread of the disease are counterfeit, data suggests.

Researchers who looked at 1,500 samples of seven malaria drugs from seven countries in South East Asia say poor-quality and fake tablets are causing drug resistance and treatment failure.

Data from 21 countries in sub-Saharan Africa

Some species in Thailand and Vietnam spread a drug-resistant malaria strain

OPEN ACCESS Freely available online

Policy Forum

Manslaughter by Fake Will Africa Be Next?

Paul N. Newton[*], Rose McGready, Facundo Fernandez, Michae **Souly Phanouvong, Pascal Millet, Christopher J. M. Whitty, Am** **Grace Malenga, Pratap Singhasivanon, Kalifa Bojang, Harpark** **François Nosten, Nicholas J. White**

Travel and fake artesunate: a risky business

Carlos J Chaccour, Harparkash Kaur, Prof David Mabey, Jose L Del Pozo

Lancet 2012; 380: 1120
Division of Internal Medicine (C J Chaccour MD), and Division of Infectious Diseases, Department of Medicine (C J Chaccour, J L Del Pozo MD), and Division of Clinical Microbiology and Parasitology (J L Del Pozo), Clinica

In October, 2011, a previously well 28-year-old woman from Spain was admitted to our hospital with a 5 day history of fever, rigors, headache, back pain, and myalgia. She was a regular traveller to Equatorial Guinea and usually took no chemoprophylaxis. She had acquired malaria on three previous occasions all of which resolved with a 3 day course of locally acquired artesunate mono-therapy combined with another antimalarial drug. On

asymptomatic and was reminded of the importance of chemoprophylaxis.

The suspected fake artesunate was sent to The London School of Hygiene & Tropical Medicine for analysis. Content analysis with rapid field test showed the tablets contained no artsunate, and high performance liquid chromatography and mass spectrometry confirmed that the tablets contained no active pharmaceutical

REPORTS

Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda — November 2009 (U.S. Pharmacopeia / USAID)

WHO January 2011
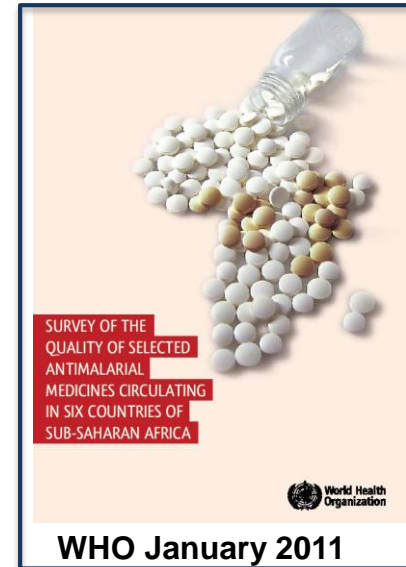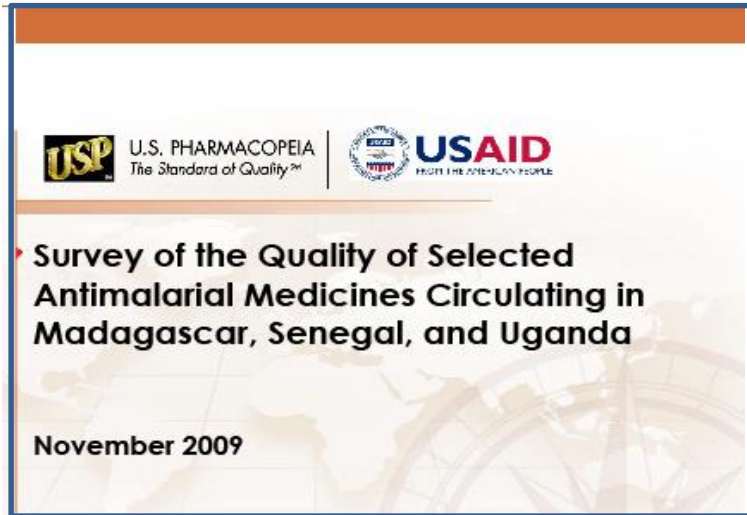
- Use 2 stage testing (MiniLab® and QC Lab) DO NOT differentiate drugs in terms of counterfeit, substandard or degraded

- WHO report of 6 countries in Africa highlights that 1/3 samples (ACTs and SP) are substandard possibly counterfeit. It also said that the MiniLab® underestimates the negative results by x3.

- Sampling method seems to be convenience, NOT random

  ACTc DQ-project set out to determine the quality of drugs following representative sampling in various geographical regions.

Criteria for Site Selection

Utility and relevance

- How useful are the findings likely to be to policy makers and other stakeholders both within and outside the country?

- Is there an important initiative in the country that may impact on drug quality, in particular AMFm?

- Absence of other ongoing DQ surveillance

Feasibility

- Is there an existing ACTc project in that country?

- Is there potential for piggy backing on to ongoing surveys?

- Local co-operation – willing, capable and resources available

- Conducive political and regulatory environment

Countries where samples collected
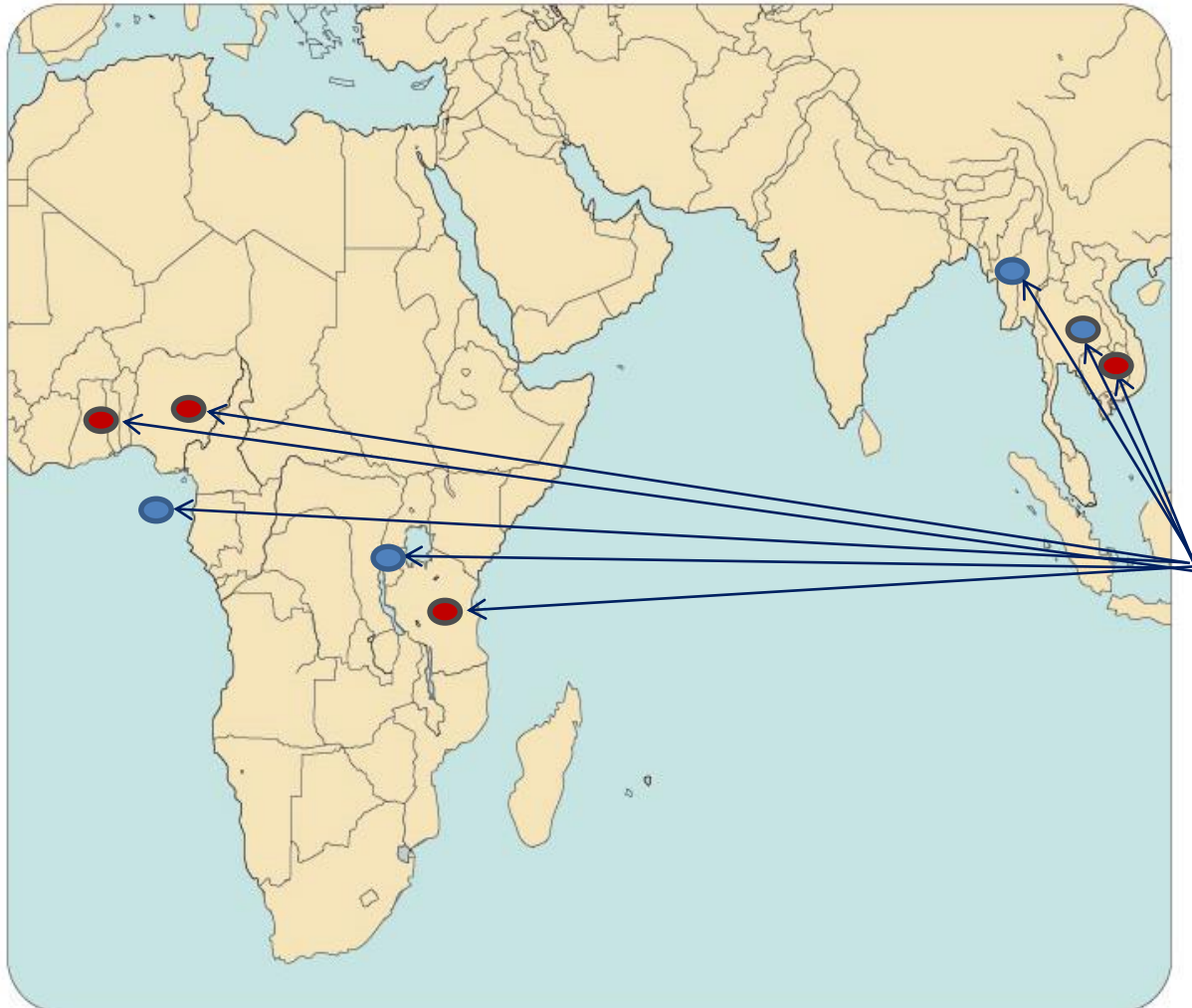
Rwanda (2008)
Tanzania (2010 & 2011)*
Cambodia (2010)*
Kintampo, Ghana (2011)*
Enugu, Nigeria (2013)
Equatorial Guinea, Bioko Island (2014)
Ilorin , Nigeria (2013) [†]
Thailand (2014)[†]
Burma (2014)[†]

● ACTc country
● non-actc country

*Affordable Medicines Facility For Malaria (AMFm)

[†] Tracking Resistance to Artemisinin Collaboration (TRAC)

Drug Quality and Authenticity Surveillance System and Counterfeit Drug Forensic Network

Agreement between:
London School of Hygiene & Tropical Medicine
Rwanda Ministry of Health Malaria Unit / TRAC *Plus*

Introduction

The London School of Hygiene & Tropical Medicine (LSHTM) is a principal investigator in the Artemisinin Combination Therapy (ACT) Consortium. Bill and Melinda Gates foundation have awarded funds to support this coordinated research programme to identify how best to optimize the delivery and cost-effectiveness of ACTs for malaria in Africa and Asia across a range of epidemiological and healthcare settings.

The project entitled "A surveillance system and drug forensic network to monitor the quality and authenticity of artemisinin combination treatments in Africa" forms part of the group studying the deployment of ACTs to achieve maximum therapeutic and economic effectiveness and the desired public health goals by setting up a systematic surveillance system in areas that are most likely to trade in drugs of questionable quality. The proposal is designed to initially survey for the occurrence of substandard and counterfeit drugs in sentinel countries and subsequently undertake comprehensive surveys within selected settings found to be with maximum risk. Suspect samples are to be characterised by sophisticated reference chemical and botanical tests within the Counterfeit Drug Forensic Network (CODFIN) to determine the exact composition of the tablets, helping to determine the origin of counterfeit ACTs. One of the countries proposed for this study is Rwanda and we now invite you enter into this agreement so that we may assess the quality of ACTs in selected sites in Rwanda.

The Agreement:

The Rwanda Ministry of Health Malaria Unit / TRAC *Plus* has agreed to collaborate with the LSHTM in the collection and shipment of ACT samples for analysis in London, England.

Rwanda's Malaria Unit will provide the LSHTM:

(1) information on all artemisinin-derivatives available in country, containing detailed information on the appearance, packaging, batch numbers, date of manufacture/expiry, brand names and the quality of the drugs as well as the date and name of institute from which the sample has been obtained.

LSHTM will provide Rwanda's Malaria Unit:

(1) sample collection protocol and in-country orientation on collection methods;
(2) funds to cover the cost of ACTs and overseas shipment;
(3) results of the drug quality and authenticity analysis;

A Rwandan medical doctor working at Malaria Unit/TRAC *Plus* has been identified to coordinate the study in Rwanda. All Rwandans involved in this study will be cited appropriately in any publications resulting from the study of quality of drugs from Rwanda, either as authors (whenever they meet standard criteria for authorship as laid down by the International Commitee of Medical Journal Editors (ICMJE) 2008), or in acknowledgements.

Duration:

This Agreement will commence on 01/01/2009 and will remain in effect until 12/31/2013 (5 years).

Date: 26th January 2009

Date: 26th January 2009

Ms Penny Ireland
Research Contracts Officer
London School of Hygiene & Tropical Medicine
Keppel Street, London

Director of the Malaria Unit
CIDC/TRAC *Plus*
Rwanda Ministry of Health
Rwanda

Ethics clearance LSHTM & Local plus Permission

LSHTM ethics clearance

Local clearance and permission to sample

Sample Collection

Questionnaire for the collection of drugs declared as containing artemisinin derivatives

Country _____   City _____

Date of collection _____

Name of drug outlet   hospital ☐ dispensary ☐ pharmacy ☐ market ☐ health center ☐ Other (name it) _____

Type of drug outlet   public ☐   private ☐

Brand name of the collected medicine _____

Name of declared active artemisinin ingredient   artesunate ☐ artemether ☐ DHA ☐ Other (name it) _____

Dose of active ingredient/s _____ mg   combined with _____ _____ mg _____ _____ mg

Artemisinin ingredient formulated with ☐   separate from ☐   the other active ingredients

Type of preparation (formulation)   tablet ☐ suppository ☐ peadiatric suspension ☐ Other (name it) _____

Batch/lot number _____   Date of manufacture _____   Expiry date _____

Description of primary container _____   Description of secondary container _____

Pack size ___ x ___ x ___ cm   Quantity collected _____

Price per pack   local currency ___ £   Price per single dose   local currency ___ £

Special comments _____

Name and signature of collector _____

Packaged Carefully Before Shipping to LSHTM

Processing

Logging onto Epi info

Flow of Sample & Corroborative Analyses

Drug Samples

All collected samples

CDC (Atlanta)
Mike Green

• ~10 %of samples tested to confirm HPLC analysis from partner (LSHTM)

Samples sent for validation

Results sent

LSHTM (UK)
Harparkash Kaur

• All samples logged
• Scanned & tablet dimensions noted
• HPLC analysis for % API content
• Results compiled into a report

Samples sent for mass analysis

Results sent

GT (Atlanta)
Facundo Fernandez

• Mass spec analysis

All information is logged on to a database

Report complied and sent

INFORMATION ON QUALITY OF DRUGS DISSEMINATED TO MoH

Manuscripts

Chemical Content Analysis of ACTs at LSHTM

% Active ingredients

Degradation studies

Forced ageing at 60°C
0 - 21 days

HPLC

LC/MS
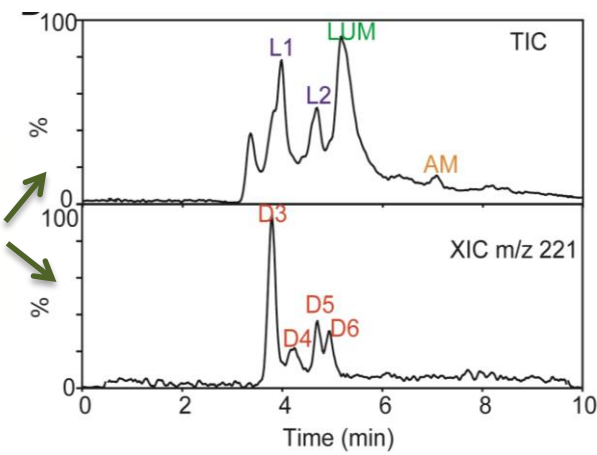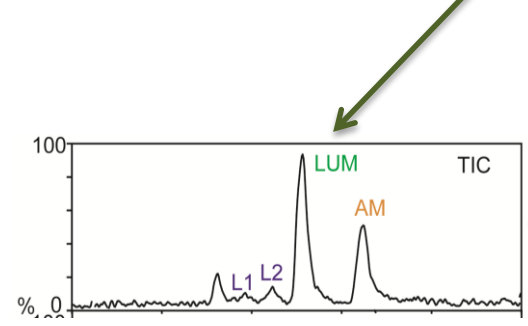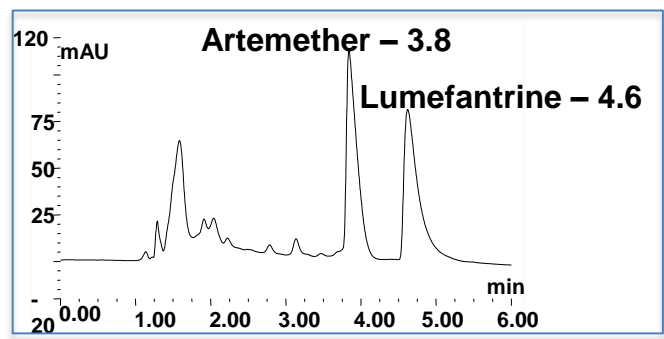
Stability Studies of AS/AQ and AM/LUM

Samples in a Chamber at LSHTM

Samples in dark
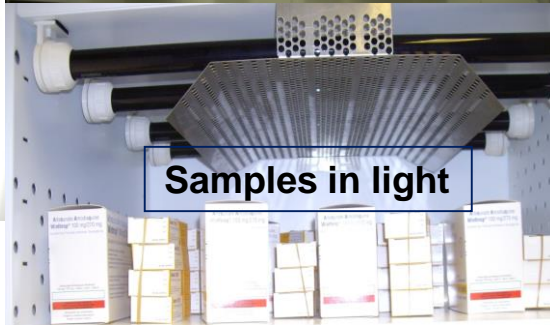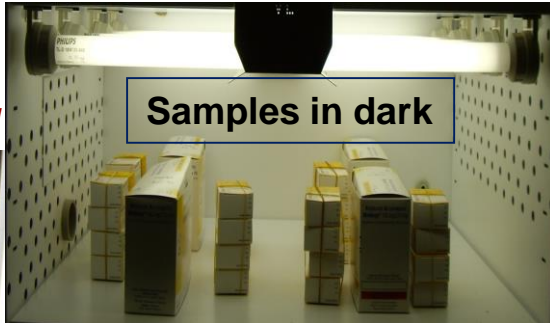
Samples in light

Storage of Samples in the Clinic Kintampo, Ghana
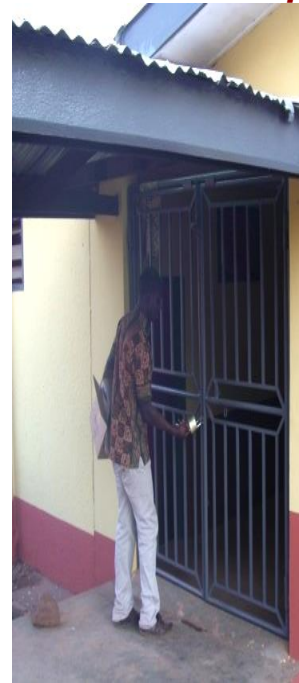
Samples in light

Conditions of the chamber set to mimic temperture and humidity in Ghana

Samples in the dark

Results of stability Studies of AS/AQ and AM/LUM

Laboratory analysis of ACTs aged in the stability chamber and clinic in Ghana over 4 years

- 3,000 tablets of AS/AQ

- 3,000 tablets of AM/LUM

Results
- After 18 months of ageing v low levels of degradation products detected.

- 0.7 % degradation of the artemisinin component of ACTs was found.

- Statically insignificant degradation in ACTs within expiry date.

- No difference in the samples aged in clinic and the chamber.

- None of the degradation products found exhibited antimalarial activity.

Degraded samples – Appearances are deceiving

Blister torn & buckled
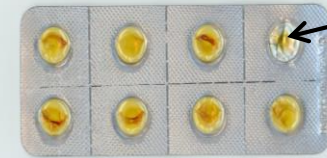
Residue

Residue

Mottled brown
Soft and sticky

Classification of ACTs

Drug quality	% Stated API detected	Method used
Acceptable quality	85-115	HPLC & MS & LC/MS
Falsified	0	HPLC & MS & LC/MS
Substandard	< 85 - > 115	HPLC & MS & LC/MS
Degraded	< 85 plus products of degraded API	MS & LC/MS

Hot off the Press – PLOS ONE
Drug quality survey in Enugu Metropolis, Nigeria
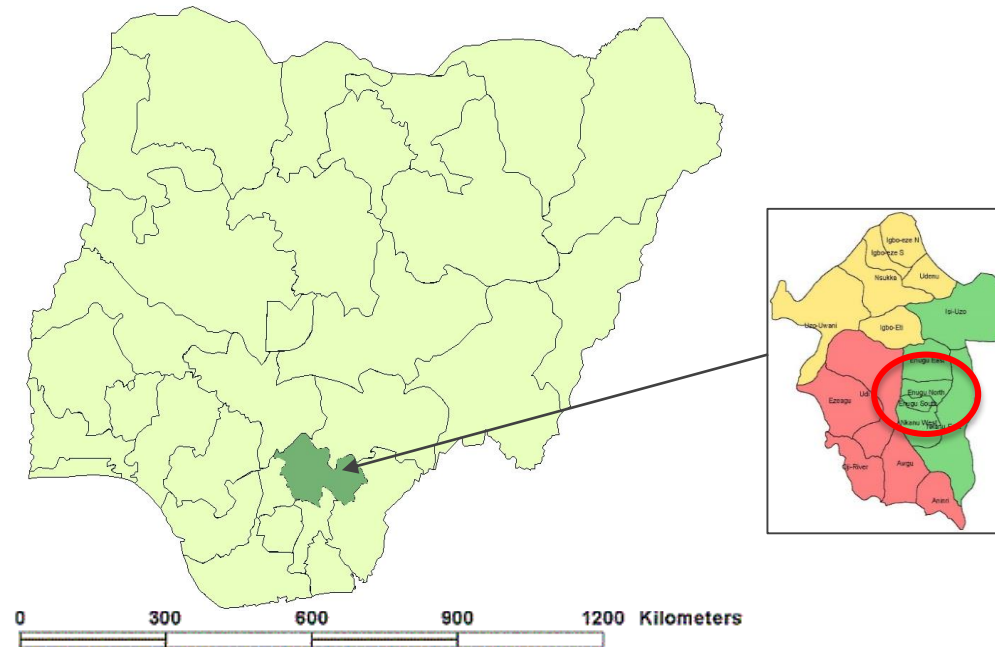
Malaria Burden – Highest in SS Africa; 48 Million clinical episodes; 180,000 deaths per year
ACTs adopted in 2005

Types of providers – pharmacy, patent medicine vendors and public health facilities

Sampling methods – convenience, mystery client and overt sampling approaches

Total no of samples analysed – 3024 artemisinin containing antimalarials

Results of Chemical Analyses ACAs purchased in Enugu, Nigeria; n = 3024

Outlets	Acceptable Quality	Substandard	Degraded	Falsified	Total
Convenience (n = 200; total brands = 49; brands per outlet = 2.1)					
Pharmacies (4)	62 (88.6%)	4 (5.7%)	2 (2.9%)	2 (2.9%)	70
PMVs (16)	97 (81.5%)	16 (13.4%)	2 (1.7%)	4 (3.4%)	119
Public health facilities (2)	4 (80.0%)	1 (20.0%)	0	0	5
Market stalls (1)	6 (100.0%)	0	0	0	6
All outlets (23)	**169 (84.5%)**	**21 (10.5%)**	**4 (2.0 %)**	**6 (3.0 %)**	**200**
Mystery clients (n = 1919; total brands = 102; brands per outlet = 0.4)					
Pharmacies (92)	803 (90.0%)	68 (7.6%)	16 (1.8%)	5 (0.6%)	892
PMVs (174)	94 (91.9%)	51 (5.2%)	9 (0.9%)	19 (2.0%)	973
Public health facilities (13)	51 (94.4%)	3 (5.6%)	0	0	54
All outlets (279)	**1748 (91.1%)**	**122 (6.4%)**	**25 (1.3%)**	**24 (1.2%)**	**1919**
Overt (n = 905; total brands = 79; brands per outlet = 0.7)					
Pharmacies (54)	488 (89.4%)	50 (9.2%)	8 (1.5%)	0	546
PMVs (65)	340 (94.7%)	13 (3.6%)	1 (0.3%)	5 (1.4%)	359
Public health facilities (0)	-	-	-	-	-
All outlets (119)	**828 (91.5%)**	**63 (6.9%)**	**9 (1.0%)**	**5 (0.6%)**	**905**

Quality of ACAs at 98 Outlets visited during both Mystery Clients and Overt *Sampling* in Enugu, Nigeria

Variable	Sampling method		p-value
	Mystery clients	**Overt**	
Outlets	98 of 277 (35.4%)	98 of 119 (82.4%)	
Samples	720	721	
Brands	78 (72.9%)	72 (67.3%)	0.37
Authentic	669 (92.9%)	665 (92.2%)	0.62
Substandard	35 (4.9%)	46 (6.4%)	0.21
Degraded	7 (1.0%)	5 (0.7%)	0.56
Falsified	9 (1.3%)	5 (0.7%)	0.28

Note: No of brands purchased = 107

Risk Factors Associated with Poor Quality ACAs
(substandard, degraded and falsified); n=2824.

Variable		Total samples	Poor quality samples	Adjusted odds ratios (95% CI)	LR test p-value
Risk factors for poor quality (substandard, degraded and falsified) ACAs					
Generic type	AM	1701	4.7%	1	<0.001
	DHA	501	14.4%	2.4 (1.6,3.4)	
	AS	622	6.9%	1.4 (0.9,2.2)	
WHO prequalified/ QAACT	Not prequalified	2047	9.3%	1	<0.001
	prequalified	777	0.6%	0.08 (0.02,0.3)	
AMFm	non AMFm drugs	2072	9.3%	1	0.012
	AMFm drugs	752	0.5%	0.24 (0.1,0.8)	
Region of <u>stated</u> country of manufacture	Asia	1940	8.2%	1	<0.001
	Africa	546	5.5%	2.1 (1.3,3.2)	
	Europe	141	0.7%	0.04 (0.06,0.4)	
	North America	197	2.6%	12.5 (2.7,56.9)	
Expired at time of analysis	not expired	2537	5.2%	1	<0.001
	expired*	275	21.5%	6.4 (4.4,9.3)	

Risk Factors Associated with Falsified ACAs

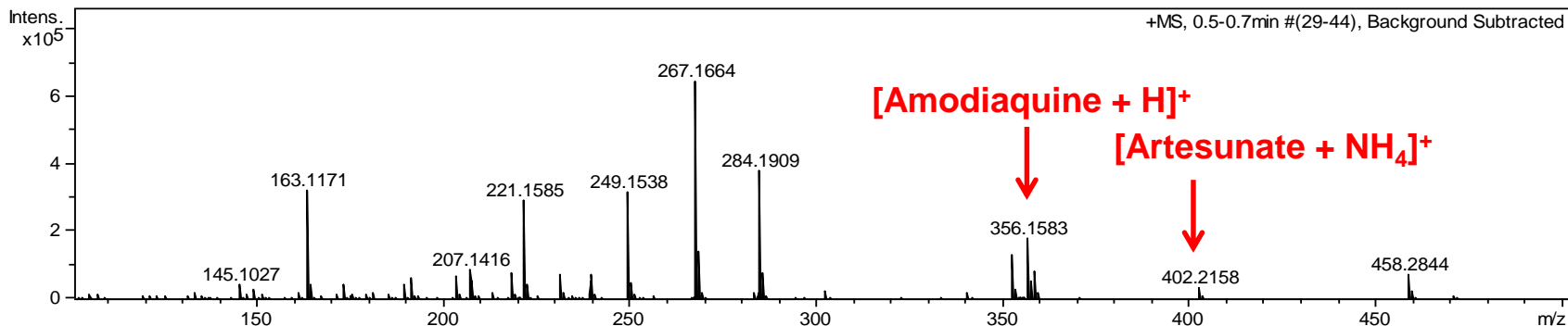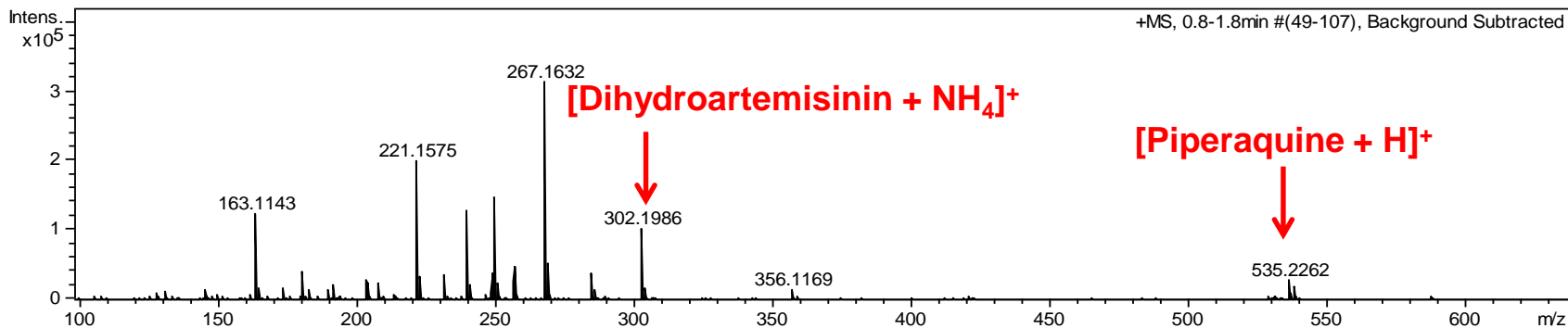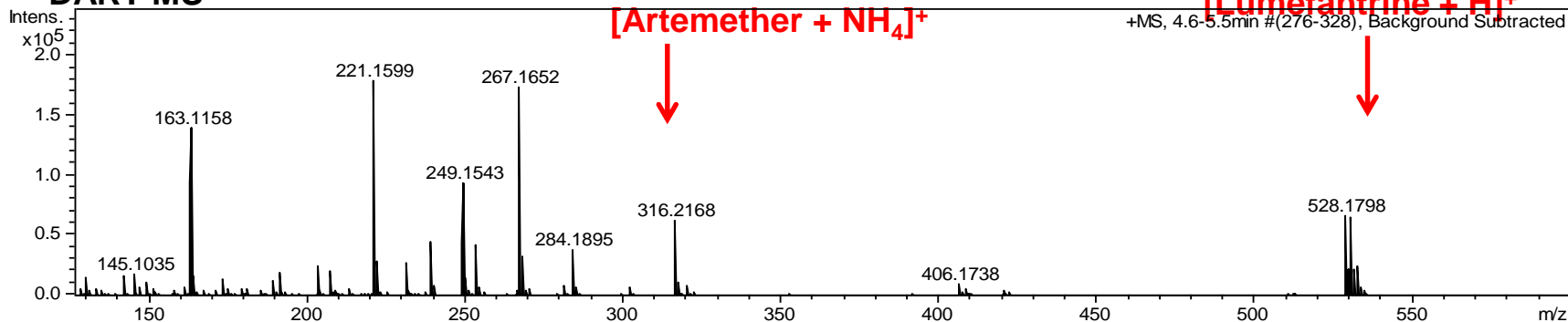| Variable		Total samples	Poor quality samples	Adjusted odds ratios (95% CI)	LR test p-value
Risk factors specifically for falsified ACAs					
Outlet type	pharmacies	1438	5 (0.4%)	1	0.002
	PMVs	1332	**24 (1.8%)**	**3.9 (1.5,10.1**)	
	public health facilities	54	0	1	
Generic type	AM	1701	8 (0.5%)	1	0.001
	DHA	501	**18 (3.6%)**	**5.9 (1.9,18.1**)	
	AS	622	3 (0.5%)	0.9 (0.2,3.5)	
Region of <u>stated</u> country of manufacture	Asia	1940	7 (0.4%)	1	0.002
	Africa	546	**17 (3.1%)**	**5.0 (1.9,13.2**)	
	Europe	141	0	1	
	North America	197	5 (2.5%)	27.9 (5.2,149.4)	

Nigeria Falsified samples; LSHTM - HPLC
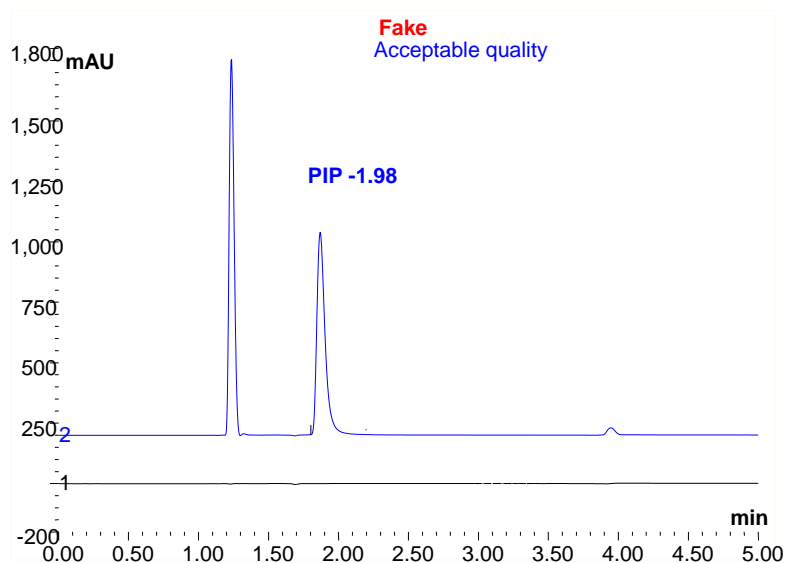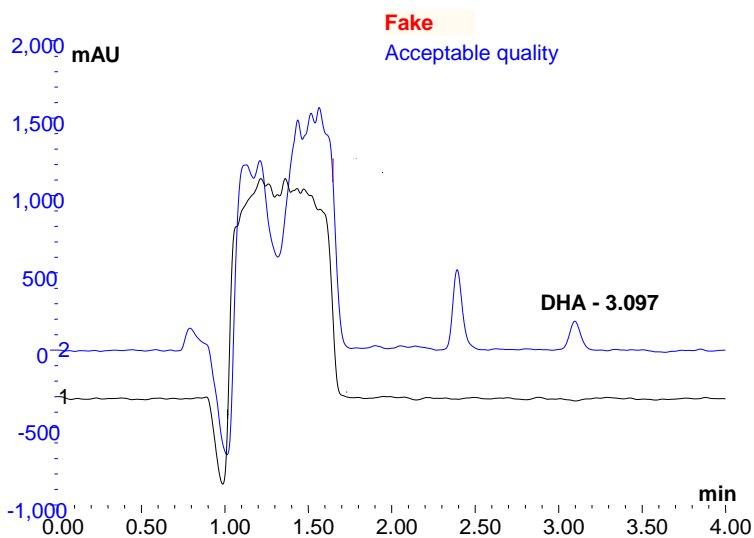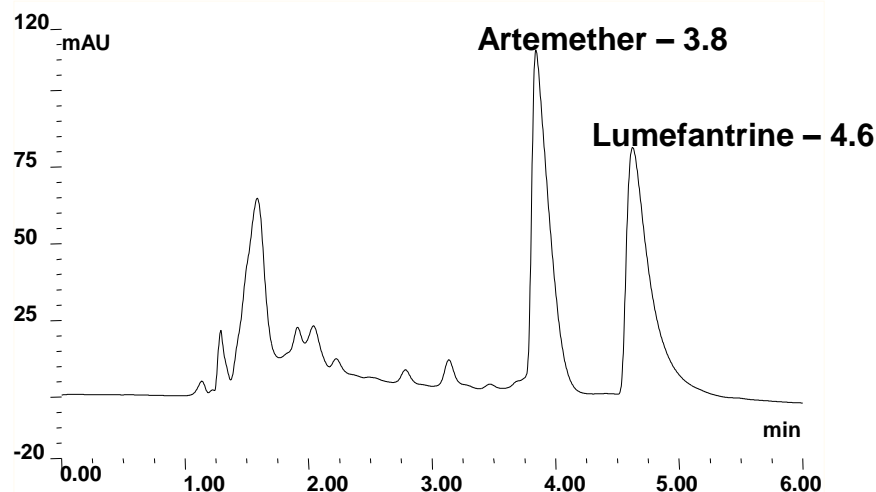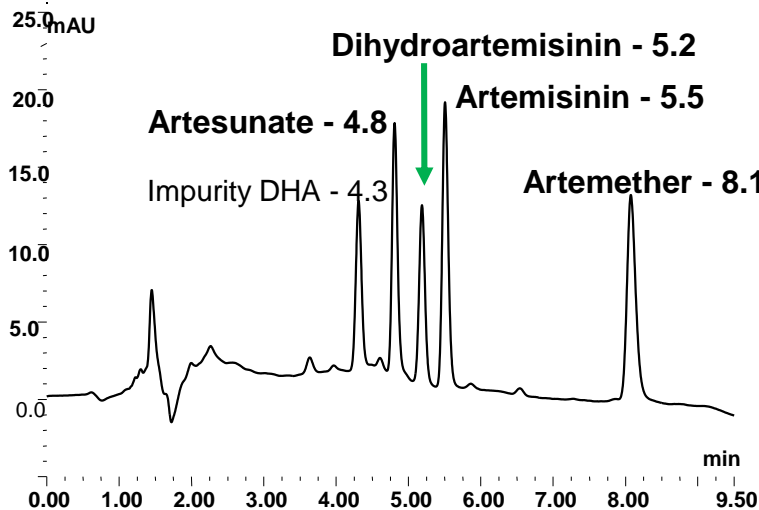
Nigeria ACT Results: Samples of Acceptable Quality

DART-MS

Top spectrum: +MS, 4.6-5.5min #(276-328), Background Subtracted

[Artemether + NH$_4$]$^+$ · [Lumefantrine + H]$^+$

Labeled peaks: 145.1035, 163.1158, 221.1599, 249.1543, 267.1652, 284.1895, 316.2168, 406.1738, 528.1798

Middle spectrum: +MS, 0.8-1.8min #(49-107), Background Subtracted

[Dihydroartemisinin + NH$_4$]$^+$ · [Piperaquine + H]$^+$

Labeled peaks: 163.1143, 221.1575, 267.1632, 302.1986, 356.1169, 535.2262

Bottom spectrum: +MS, 0.5-0.7min #(29-44), Background Subtracted

[Amodiaquine + H]$^+$ · [Artesunate + NH$_4$]$^+$

Labeled peaks: 145.1027, 163.1171, 207.1416, 221.1585, 249.1538, 267.1664, 284.1909, 356.1583, 402.2158, 458.2844

Nigeria Falsified samples; DART-MS at GT

DART-MS

+MS, 3.7-4.9min #(219-291), Background Subtracted

[Ciprofloxacin + H]⁺ instead of **artemether**

332.1464

241.1821   259.1923   371.3172

DART-MS/MS
Fragmentation pattern indicates ciprofloxacin

+MS2(332.1400), 4.4-4.6min #(262-272), Background Subtracted

288.1540

245.1113   332.1418

205.0784   231.0933   268.1451

Ciprofloxacin
NIST MS/MS

288.00

231.00   245.00   268.00   312.00   332.00

(nist_msms) Ciprofloxacin
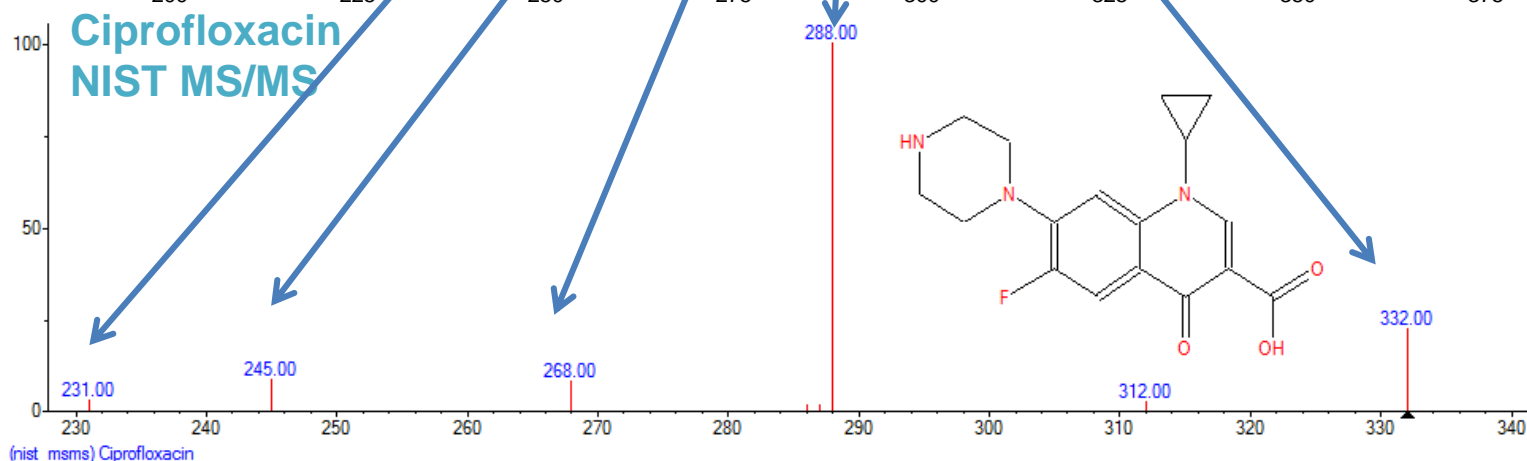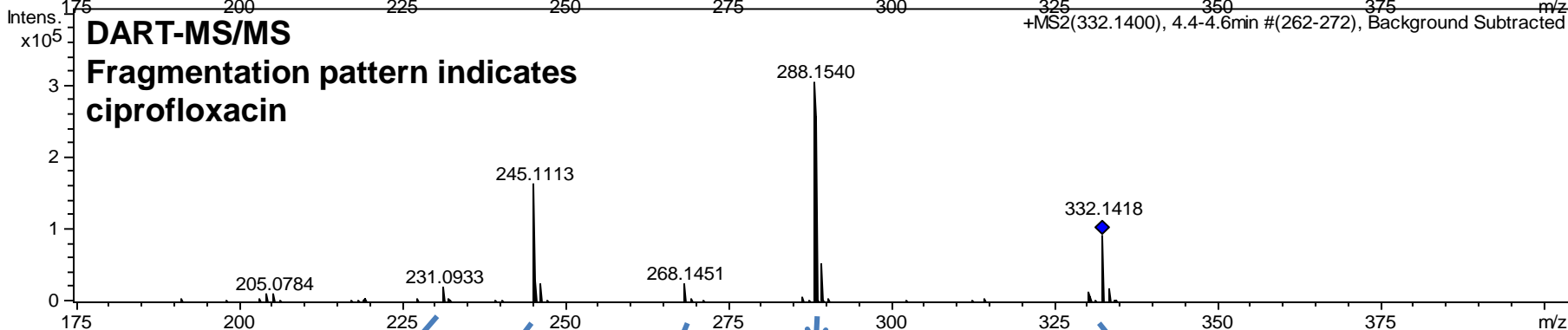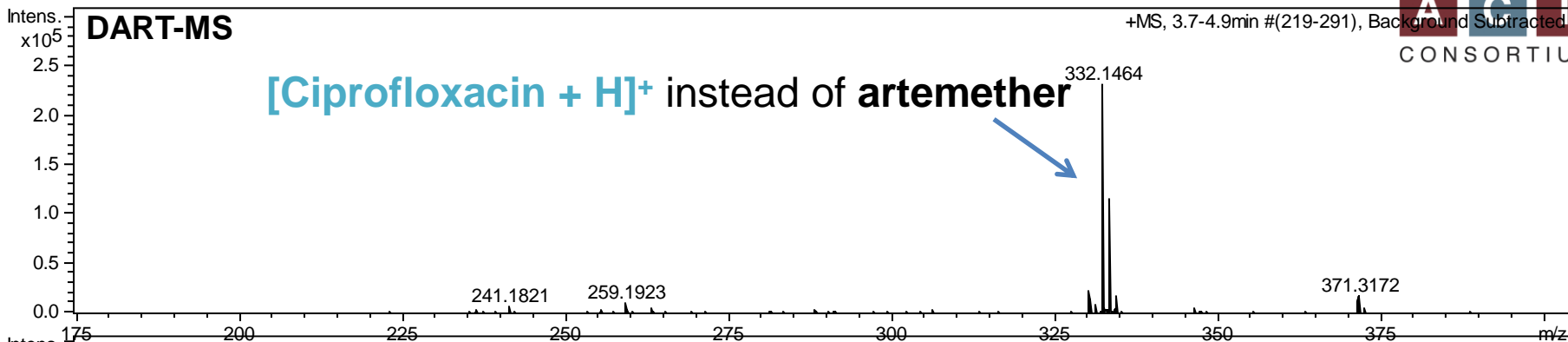
Falsified samples from Nigeria – Details

Stated brand	Stated country of manufacture	Stated manufacturer	Stated API	Compound found
Artesunat®	Vietnam	Mekophar	AS[†]	DEHA or DOA
Artesunat®	Vietnam	Mekophar	AS[†]	DEHA or DOA
Artesunat®	Vietnam	Mekophar	AS[†]	Acetaminophen
Artesmequine®	China	Greenfield	AS-MEF	Unidentified
Coartem® (USA)	USA	Novartis	AM-LUM	Chlorzoxazone (Muscle relaxant)
Coartem® (USA)	USA	Novartis	AM-LUM	Chlorzoxazone
Coartem® (USA)	USA	Novartis	AM-LUM	Chlorzoxazone
Lonart-DS®	India	Bliss GVS	AM-LUM	Ciprofloxacin (antibiotic)
Lonart-DS®	India	Bliss GVS	AM-LUM	Ciprofloxacin
Duo-Cotecxin®	China	Zheijang Holley	DHA-PIP	DEHA or DOA
Waipa Act	Nigeria	Kunimed	DHA-PIP	Acetaminophen

Note: **†** = mono therapy;
DEHA or DOA = petroleum products [Bis(2-ethylhexyl) adipate or Dioctyl adipate]
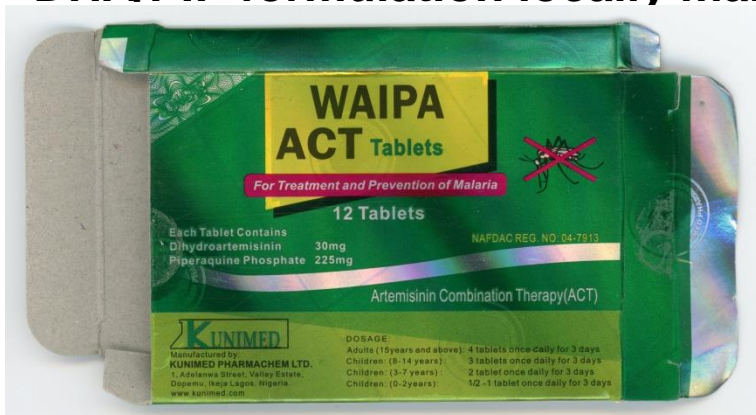
Examples of Falsified Samples from Enugu

AM/LUM

AS monotherapy

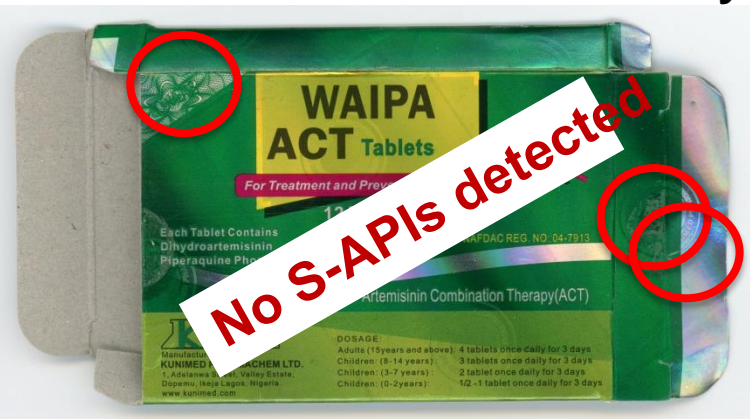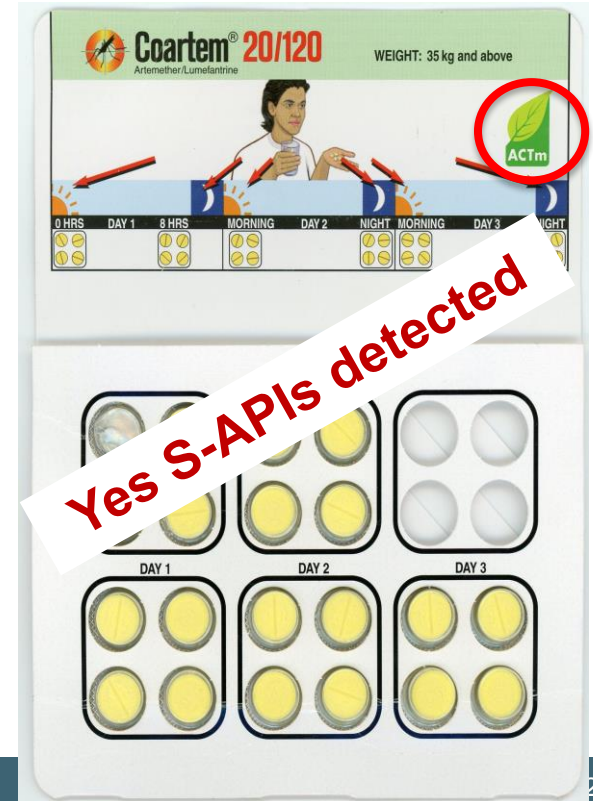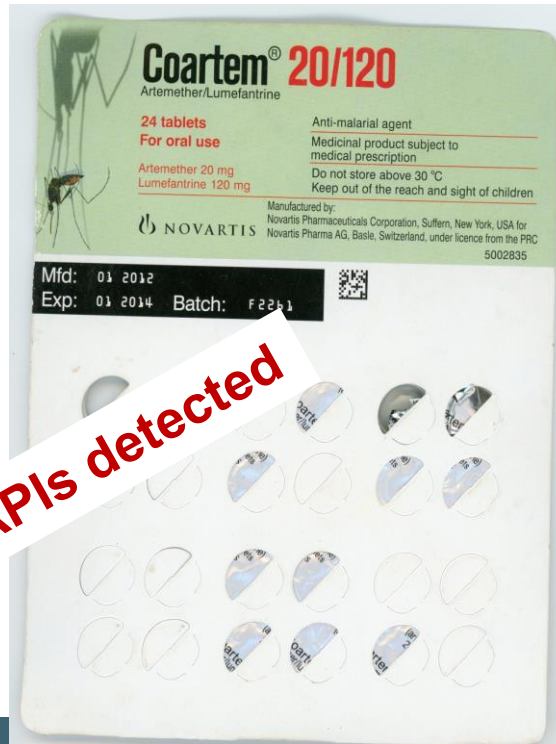**DHA/PIP formulation locally manufactured**

AS/MF

Visual inspection of Falsified samples from Nigeria

DHA/PIP formulation locally manufactured

No S-APIs detected

Yes S-APIs detected
Pkt has 1 extra marking

AM/LUM formulations

No S-APIs detected

No S-APIs detected

Yes S-APIs detected

No falsified Co-formulation of ASAQ found

WHY?

Anti-Counterfeiting Measure? – Shape & Layers
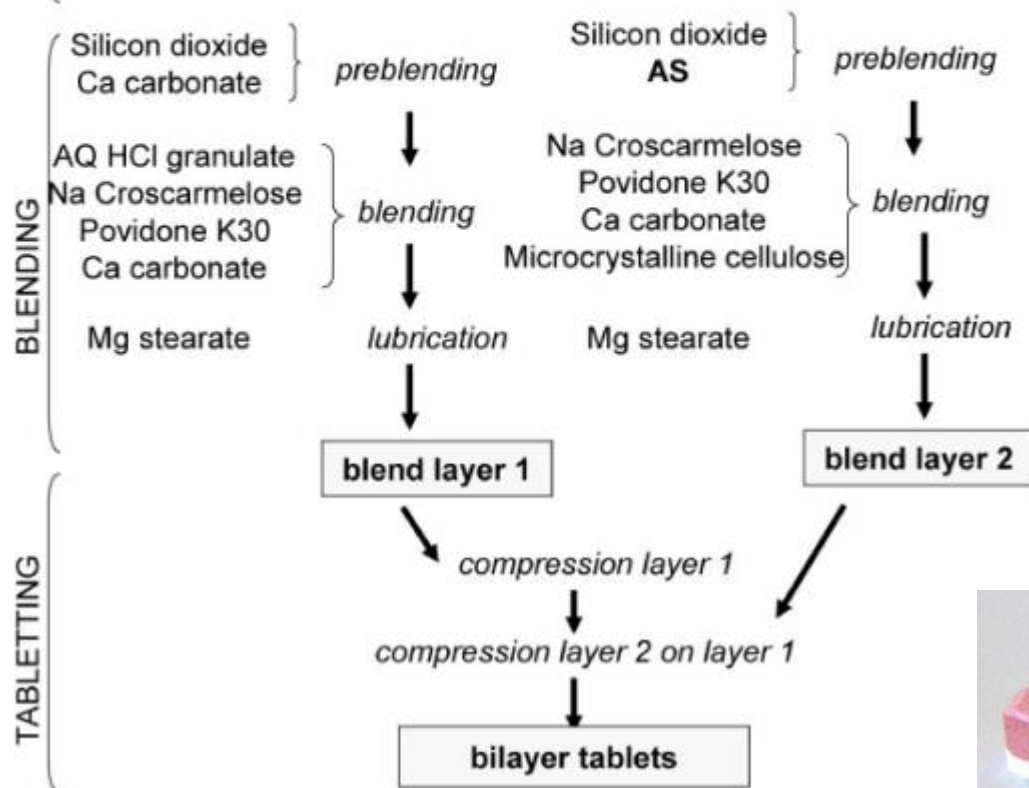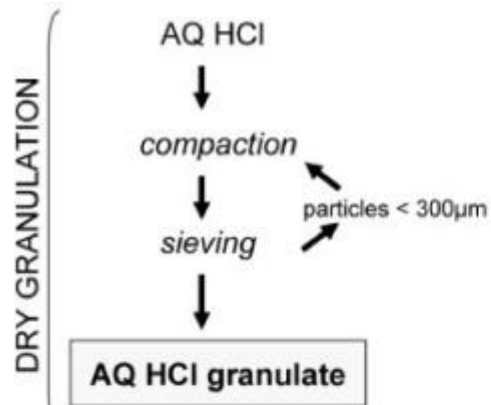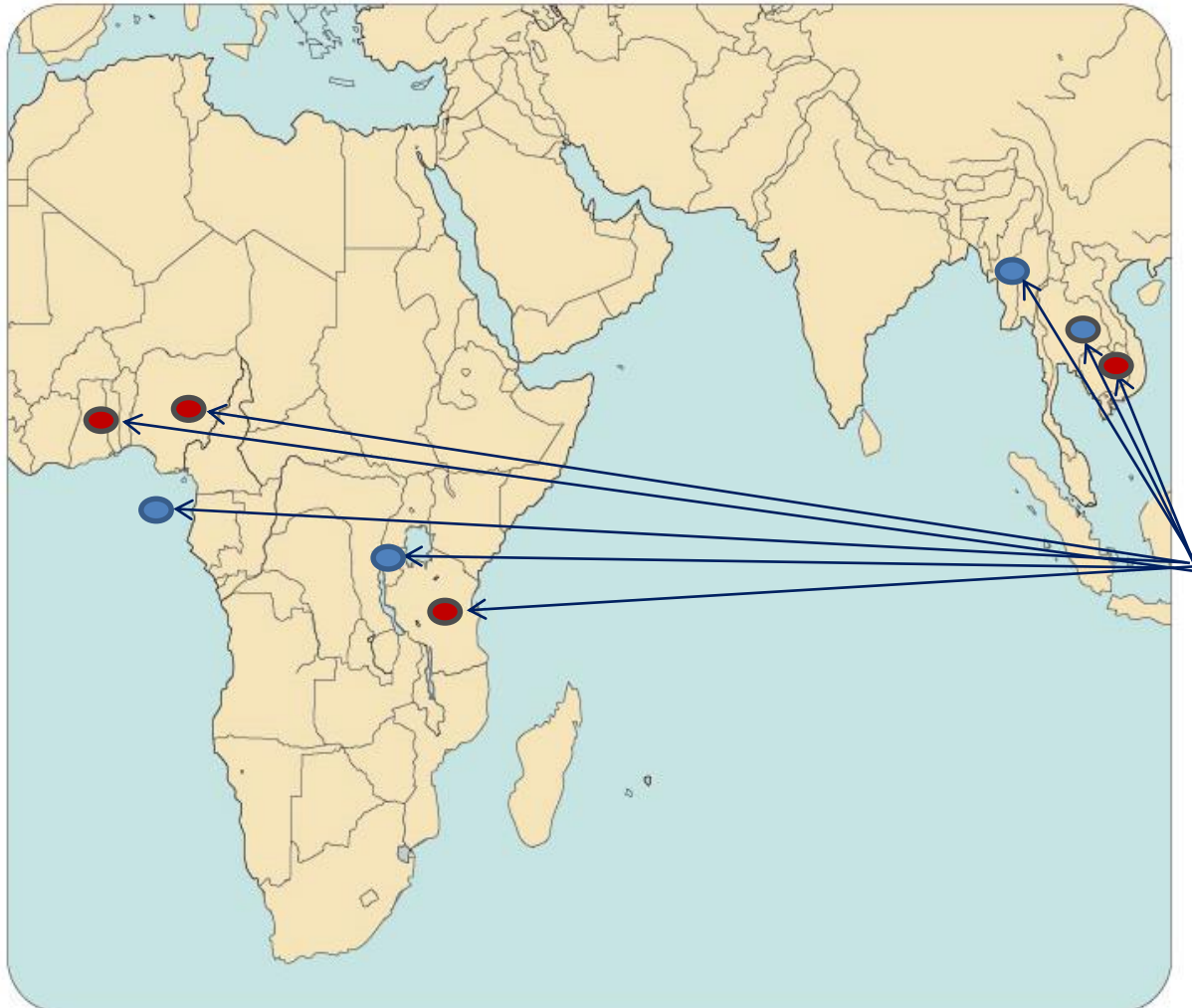
DRY GRANULATION

AQ HCl
↓
compaction
↓
sieving → particles < 300μm
↓
AQ HCl granulate

BLENDING

Silicon dioxide / Ca carbonate → *preblending*
↓
AQ HCl granulate / Na Croscarmelose / Povidone K30 / Ca carbonate → *blending*
↓
Mg stearate → *lubrication*
↓
blend layer 1

Silicon dioxide / **AS** → *preblending*
↓
Na Croscarmelose / Povidone K30 / Ca carbonate / Microcrystalline cellulose → *blending*
↓
Mg stearate → *lubrication*
↓
blend layer 2

TABLETTING

compression layer 1
↓
compression layer 2 on layer 1
↓
bilayer tablets

Countries where samples collected

RWANDA (2008)
TANZANIA (2010 & 2011)*
CAMBODIA (2010)*
KINTAMPO, GHANA (2011)*
ENUGU, NIGERIA (2013)
EQUATORIAL GUINEA, BIOKO ISLAND (2014)
ILORIN , NIGERIA (2013) †
THAILAND (2014)†
BURMA (2014)†

● ACTc COUNTRY
● NON-ACTc COUNTRY

*AFFORDABLE MEDICINES FACILITY FOR MALARIA (AMFM)

† TRACKING RESISTANCE TO ARTEMISININ COLLABORATION (TRAC)

ACTc DQ: Sampling methods used

| COUNTRY	Method of sampling OUTLETS	Method of sampling DRUGS
Bioko Island, Equatorial Guinea	Random / National survey	• Mystery client • Overt
Cambodia	Random / National survey*	• Mystery client • Overt
Ghana	Random / 1 locality	• Mystery client
Nigeria	Random / 1 region	• Mystery client • Overt
Rwanda	Random / National survey	• Mystery client
Tanzania	Random / National survey	• Overt

* from malaria endemic areas only

Quality of ACTs found per country

Of all 10,079 samples analysed we found:

Country (date of collection)	Samples	Brands	Quality assured	Substandard	Falsified	Artemisinin Monotherapy Tablets
Rwanda (2008)	97	1	93.8%	6.2%	0 found	Not 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
Tanzania (2010)	1737	37	88.0%	12.0%	0 found	**Found**
Tanzania (2011)	2546	46	97.8%	2.2%	0 found	**Found**
Nigeria - Enugu Metropolis (2013)	3024	131	92.2%	6.6%	**1.2%**	**Found**
Bioko Island- Equatorial Guinea (2014)	677	142	91.0%	1.6%	**7.4%**	**Found**
Nigeria - Ilorin city (2013)	1450	77	91.5%	7.7%	**0.8%**	**Found**

Quality of ACTs in the Countries where we sampled
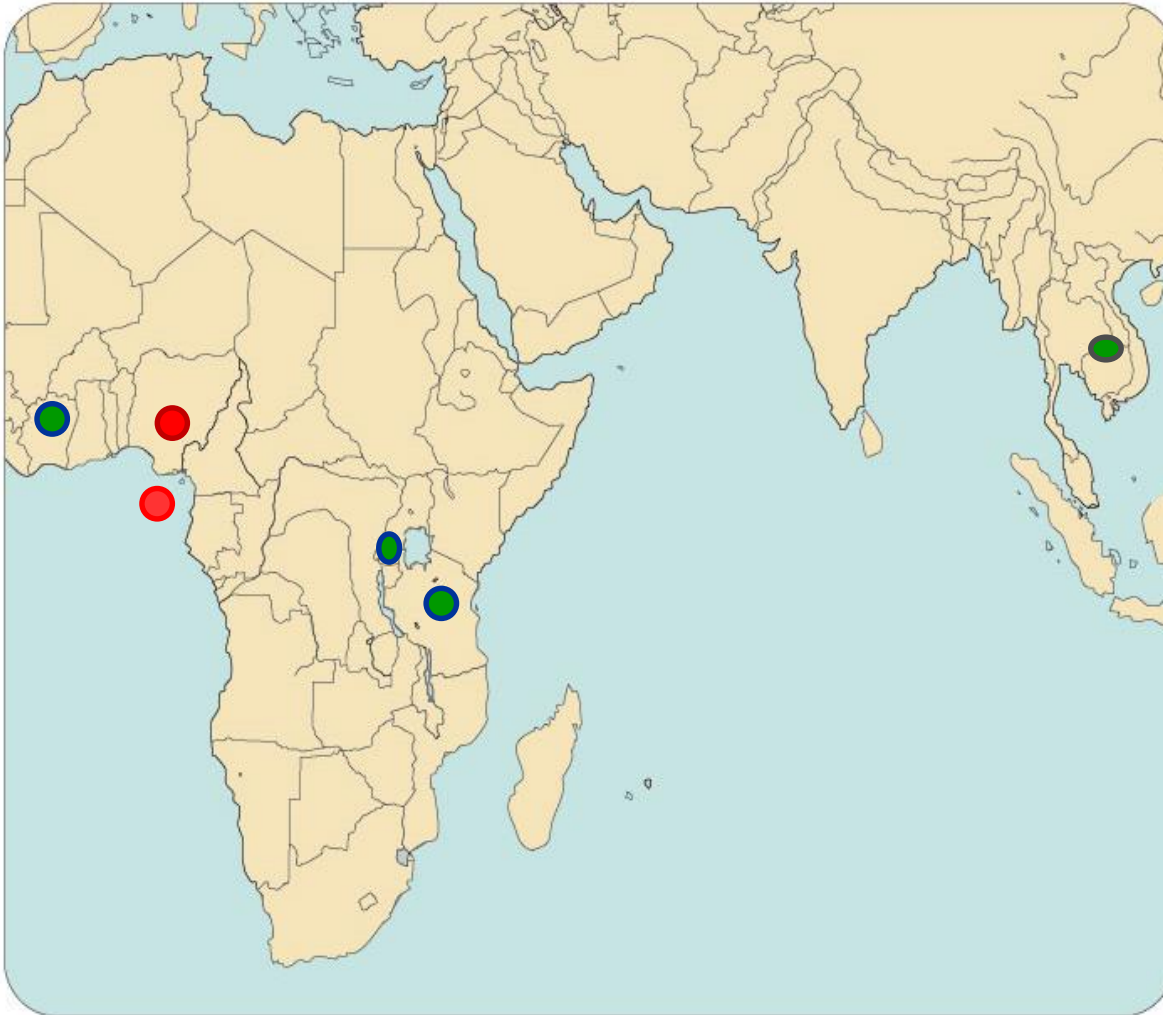
- **NO falsified ACTs found in 4 of 6 countries**

🟢 No falsified ACTs found
🔴 Falsified ACTs found

- **Substandard drugs were found in all countries**

Summary of Findings

Large sample sizes in a wide range of geographic settings.
- Corroborated between 3 laboratory findings and 2 different detection
    methods.
- Results inform understanding of the reliability of stated APIs, unexpected
    (toxic) compounds and risk factors

Overall reassuring results, but "no room for complacency"
- Results from Nigeria and Bioko Island show falsified
- Substandard drugs are prevalent in all countries (up to 1 in 3 samples)
- Monotherapy tablets still available

Data highlights the need for continuous drug quality monitoring by NRAs
- ACTcDQ provides insights into the performance of different sampling
    approaches and sample analysis methods.

**We are happy to share our experience and methods to ensure better
monitoring to stop this scourge of poor quality drugs.**

ACKNOWLEDGEMENTS

ACTc – DQ teams at LSHTM, CDC and GT

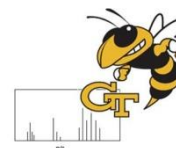**ACTc – IMPACT-2 teams at LSHTM, CDC and Tanzania, Ghana team**

GUARD team – Cambodia

LSHTM Co-investigators – D Schellenberg, S Clarke, C Goodman, M Chico, S Yeung, B Cundill, C Lynch, R Thompson, B Dsouza, P Verstraete, D Miranda

Masters students - M El Sherbiny, I Fadeyi & I Mamadu

Teams on the ground purchasing and packaging the samples

More information

www.actconsortium.org/drugquality

http://malaria.lshtm.ac.uk/facilities/analytical-service-measuring-antimalarials-drugs-and-insecticides