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QUALITY OF ORAL DRUG FORMULATIONS OF ARTEMISININ-BASED COMBINATION THERAPY SOLD IN KATSINA STATE, NIGERIA

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ABSTRACT

There are increasing reports of substandard antimalarial drugs, and these have been a severe under-recognised public health problem especially in developing countries. For this reason, 21 samples of different brands of artemisinin-based combination therapies (ACTs) comprising of artemether/lumefantrine and artesunate/amodiaquine oral drug formulations that are available on sale in different hospital pharmacies and patent medicine stores in Katsina State, Nigeria were evaluated for microbial and chemical qualities. Microbial limit test (MLT) and assay for the content of the active pharmaceutical ingredients (APIs) using standard high performance liquid chromatography (HPLC) procedures were carried out as described in the official monograph of the United States Pharmacopoeia (USP) and the International Pharmacopoeia (IP). The results obtained had indicated that all the ACTs oral drug preparations were free from microbial contamination except one sample of artesunate-amodiaquine showing viable total combined yeasts/moulds count (TYMC) of 1.0 x 10^1 colony forming units (CFU)/g. All the samples complied with the USP and IP criteria for the microbiological quality of non-sterile oral dosage forms. On the other hand, 10 (47.6%) out of the 21 samples met the specific chemical quality standards. Moreover, 8 (57.1%) and 3 (42.9%) of the artemether/lumefantrine and artesunate/amodiaquine had active ingredient outside the set pharmacopoeial limit and, therefore, were none compliant to the IP specifications for percentage content. The presence of substandard ACTs may lead to possible therapeutic failure from the use of such kind of formulations, facilitate the development and spread of drug-resistance. There is the need for effective government regulation and adequate enforcement on the production, distribution and sales of good quality medicines.

Keywords: Artemisinin-based combination therapy, Microbial contamination, Active pharmaceutical ingredients, United States Pharmacopoeia, International Pharmacopoeia

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INTRODUCTION

The latest world malaria report stated an estimated 229 million cases of malaria worldwide with an estimated number of malaria deaths standing at 409,000, and of these figures, six countries accounted for approximately half of all malaria deaths worldwide and Nigeria has the highest, with 23% of cases globally, followed by the Democratic Republic of the Congo (11%), United Republic of Tanzania (5%), and 4% in Burkina Faso, Mozambique and Niger, respectively (World Health Organization [WHO] 2020).

The WHO has recommended the use of artemisinin-based combination therapy (ACT) as the first and second-line treatment regimens for uncomplicated falciparum malaria (Ndwigah *et al.* 2018). The availability of good quality ACTs at the right amount (the content of the active pharmaceutical ingredient [API]) is a requisite factor in the control of malaria (Newton *et al.* 2011). However, the loss of therapeutic efficacy of ACT would be disastrous and severely impede global malaria control and elimination progress in malaria-endemic countries (ACTwatch Group *et al*. 2017).

Poor quality antimalarials have resulted in several undesirable consequences ranging from treatment failure with increased morbidity and mortality, drug resistance, financial consequences for patients, health-care systems and the pharmaceutical companies producing the genuine product. In addition, patients may lose confidence in pharmaceutical drugs and the health-care system in general (Kaur *et al*. 2010; Nayyar *et al.* 2012).

There are increasing reports of substandard antimalarial drugs circulating in the markets of developing countries (Amin and Kokwaro 2009). A study of the quality of antimalarials collected from public and private healthcare providers in southeast Nigeria by Onwujekwe *et al.* (2009) found that 60 (37%) of the anti-malarial formulations tested did not meet the United States Pharmacopoeia (USP) specifications for the amount of active ingredients, with the suspect drugs either lacking the active ingredients or containing suboptimal quantities of the active ingredients. Quinine (46%) and sulphadoxine-pyrimethamine (SP) (39%) formulations were among drugs that did not satisfy the tolerance limits published in USP monograms.

In another study, Hetzel *et al.* (2014) reported the presence of poor-quality antimalarial medicines and antibiotics in 48.3% of providers at all levels of the health facility supply chain in Papua New Guinea. Moreover, a 2011 report of the WHO survey on the quality of selected antimalarials in six countries of sub-Saharan Africa reported 28.5% of products failed to meet set standards and that Nigeria was the country with the highest incidence of failing samples according to the survey results with 63.9%, and this implies that the possibility to be treated with an antimalarial medicine complying with international quality standards is less than that of receiving substandard medicine. In Ghana and Cameroon, the failure rates were 39.5% and 36.6%, respectively. This implies that patients from these areas have an approximately 60% chance of obtaining good quality medicine (WHO 2011).

Poor quality antimalarials have been severely under-recognised public health problems (Kaur *et al.* 2010) and in the study area, in particular, there is a lack of knowledge about the actual quality of ACTs that are being used for the treatment of malaria. The objective of this study was to determine the quality of ACTs available on sale in different hospital pharmacies and patent medicine stores in Katsina State, Nigeria. For being one of the enlisted drugs by the WHO model list of essential medicines (WHO 2015), the ACTs remain the most effective treatment regimens for uncomplicated falciparum malaria, which make them one of the most widely used drugs. It is, therefore, very imperative to monitor the quality of ACTs being administered and used by the general population.

The study will provide relevant information on the availability and the extent of the problem of poor-quality antimarial medicines and their impact on public health especially in the malaria-endemic regions of Africa and other parts of the world. This information will help policymakers and regulatory bodies towards checking and regulating the availability and circulation of substandard drugs in Nigeria.

METHODS

Sampling

The selection of the ACTs (artemether/lumefantrine and artesunate/amodiaquine) oral drug formulations for the study was based on the high usage and their inclusion in the WHO model list of essential medicines (WHO 2015). A total of 21 samples were collected between the period of March and December 2018 from various drug outlets such as hospital pharmacies, pharmacy stores and patent medicine stores located within the state. Samples were purchased on sight and anonymously by adopting the method of Kolawole *et al.* (2002). The pharmaceutical details of the samples are presented in Table 1.

Assessment of Microbiological Quality of the Samples

A microbial limit test (MLT) was carried out on the sampled ACTs oral drug formulations as described by the USP Convention (2018). One in 10 dilutions was prepared by dissolving 10 g of the product to be examined in 90 mL of trypticase soy broth (TSB). One millilitre of the test samples were inoculated onto plates of casein soya bean digest agar and incubated at 37°C for 3–5 days and sabouraud-dextrose agar at 25°C for 5–7 days. Duplicate plates for each level of dilution were prepared and incubated. After the incubation period, colonies were counted, and the total aerobic microbial count (TAMC) and the total combined yeasts/moulds count (TYMC) was determined and expressed as the number of colony-forming units per gram or millilitre (CFU/g or mL) of the sample.

HPLC Assay for the Content of the Active Pharmaceutical Ingredient

The ACT samples were analysed for the presence and content of the API as described in the official individual monographs of the International Pharmacopoeia (IP) (IP 2016).

Assay for Presence and Amount of Artemether and Lumefantrine in the Sampled ACTs

Twenty microlitre (injection volume) of the standard chemical reference solution of artemether and lumefantrine and that of each of the samples were injected into the liquid chromatographic system with the mobile phase consisting of ion pair reagent, water, propanol and acetonitrile, using a column of 150 mm × 3.9 mm at a flow rate of 1.3 mL/min and at a detection wavelength of 210 nm for 28 min, and then at 380 nm.

Table 1: Pharmaceutical details of the sampled artemether-lumefantrine and artesunate-amodiaqiune used for the study.

S/N	Sample code	Batch/lot no.	NAFDAC no.	Mfd/Exp. date	Dosage form	Stated amount of API (mg)	Country of manufacture
1	ATL2	AL7004	A4-3489	01/2015–01/2018	Tablet	80/480	Malaysia
2	ATL3	CR17006	B4-5188	01/2017–01/2019	Tablet	20/120	India
3	ATL5	K0080	B4-0262	01/2017–01/2019	Tablet	20/120	India
4	ATL10	AL7004	A4-3489	01/2017–01/2019	Tablet	20/120	India
5	ATL11	GVAFM014	A4-6730	01/2017–01/2019	Tablet	20/120	India
6	ATL14	FM6001	A4-9653	02/2016–01/2019	Tablet	20/120	India
7	ATL18	LOK24	A4-0157	01/2017–01/2019	Tablet	80/480	India
8	ATL20	F2261	Nil	03/2017–03/2020	Tablet	20/120	India
9	ATL21	ALT18006	B4-1903	03/2018–02/2021	Tablet	20/120	India
10	ATL27	KL893	A4-1680	10/2017–09/2019	Tablet	20/120	India
11	ATL28	LU7026	A4-7395	2017–2019	Tablet	20/120	India
12	ATL30	NAA7250A	B4-2289	09/2017–08/2020	Tablet	20/120	India
13	ATL31	FIAFM048	04-9927	08/2016–08/2018	Tablet	20/120	India
14	ATL32	NE51004	B4-4018	06/2015–05/2018	Tablet	20/120	India
15	ATS1	11216	04-7848	2016–2019	Tablets	25/67.5	India
16	ATS2	440617	04-7848	2017–2020	Tablets	100/270	India
17	ATS4	161222	04-7737	12/2016–11/2019	Tablets	50/150	China
18	ATS5	1661161	04-3845	2016–2019	Tablets	25/67.5	India
19	ATS6	SH170101	A4-6250	2017–2019	Tablets	25/67.5	China
20	ATS8	71A106	A4-3406	2017–2020	Tablets	25/67.5	India
21	ATS9	11216	04-7848	12/2016–11/2019	Tablets	100/300	China

Assay for Presence and Amount of Artesunate in the Sampled ACTs

Twenty microlitre (injection volume) of the standard chemical reference solution of artesunate and that of each of the samples were injected into the liquid chromatographic system with the mobile phase consisting of acetonitrile and potassium dihydrogen phosphate (KH_2PO_4), using a column of 100 mm × 4.6 mm at a flow rate of 1.0 mL/min and a detection wavelength of 216 nm was employed for the assay.

The assay was carried out on an ELITE-Lachrom high performance liquid chromatography (HPLC) system consisting of ultra-violet visible detector L-2420, column oven L-2300, an autosampler/injector L-2200 and a pump L-2130. The procedure was repeated in triplicate for each of the standards and the samples, and the average peak response was determined.

Following analyses, the drug content was calculated as the percentage of the stated amount of API and compared with pharmacopoeial limits specified in the IP (2016). API in samples of artemether/lumefantrine and artesunate within the range of 90%–120% and 90%–110%, respectively, were considered as standard and compliant, while on the other hand, values out of this range were considered as substandard and non-compliant with the pharmacopoeial limit (IP 2016).

RESULTS

Results of the microbiological analysis of the sampled ACTs oral drug formulations have indicated that all the tested samples were free from microbial contamination except one sample of artesunate-amodiaquine showing viable TYMC of 1.0×10^1 CFU/g as shown in Table 2. The absence of detectable microbial growth among these samples and the presence of viable count of 1.0×10^1 CFU/g which is lower than the acceptance limit of TYMC- not more than (NMT) 10^2 CFU/g in only one of the sample implies that all the tested samples were compliant with the criteria for microbiological quality of non-sterile solid dosage forms as described by the official compendia of the IP (2016).

Assessment of the chemical quality of the ACTs samples in terms of the percentage content of the active drug, generally showed that of 21 samples tested, 10 (47.6%) had the API within the IP limit while 11 (52.4%) of them failed to comply with the IP specifications for percentage content.

Table 3 shows the results of the HPLC assay for the percentage content of artemether and lumefantrine as the API in the sampled ACTs (artemether-lumefantrine oral drug formulations). In this category, of the 14 samples analysed, 6 (42.9%) had the right amount of both the artemether and lumefantrine as the API in the tested samples and therefore were compliant with the IP specifications for percentage content.

Similarly, Table 4 presents the results of the HPLC assay for the percentage content of artesunate as the API in the sampled antimalarial drugs where 4 (57.1%) of the samples contained amounts of active ingredient within the appropriate limits while 3 (42.9%) had active ingredient outside the set pharmacopoeial limit and therefore were none compliant to the IP specifications for percentage content. Moreover, of the 3 samples that failed the drug content test, 2 had a low amount of the active ingredient while 1 sample contains a high amount of the API.

Table 2: Microbiological quality of the tested ACTs oral drug formulations.

Sample code	TAMC (CFU/mL)	TYMC (CFU/mL)	Remarks
ALT1	0	0	Compliant
ALT2	0	0	Compliant
ALT3	0	0	Compliant
ALT4	0	0	Compliant
ALT5	0	0	Compliant
ALT6	0	0	Compliant
ALT7	0	0	Compliant
ALT8	0	0	Compliant
ALT9	0	0	Compliant
ALT10	0	0	Compliant
ALT11	0	0	Compliant
ALT12	0	0	Compliant
ALT13	0	0	Compliant
ALT14	0	0	Compliant
ATS15	0	0	Compliant
ATS16	0	0	Compliant
ATS17	0	0	Compliant
ATS18	0	0	Compliant
ATS19	0	1×10^1 *Aspergillus fumigatus*	Compliant
ATS20	0	0	Compliant
ATS21	0	0	Compliant

Notes: Acceptance criteria: TAMC - NMT 10^3 CFU/g; TYMC - NMT 10^2 CFU/g; TAMC = total aerobic microbial counts; TYMC = total yeast and mould counts; ALT = artemether-lumefantrine; ATS = artsesunate-amodiaquine.

Table 3: Results of the HPLC assay for the percentage content of artemether and lumefantrine in the sampled ACTs.

Sample code	Stated amount of API (mg)	% Artemether from HPLC assay	Calculated drug content (mg/tablet)	Remark	% Lumefantrine from HPLC assay	Calculated drug content (mg/tablet)	Remark
ATL1	80/480	91.15	72.92	Compliant	104.49	501.55	Compliant
ATL2	20/120	106.26	21.25	Compliant	85.82	102.98	Non-compliant
ATL3	20/120	615.95	123.19	Non-compliant	108.02	129.62	Compliant
ATL4	20/120	104.54	20.91	Compliant	102.22	122.66	Compliant
ATL5	20/120	667.9	133.58	Non-compliant	158.16	189.79	Non-compliant
ATL6	20/120	102.94	20.59	Compliant	92.38	110.86	Compliant
ATL7	80/480	565.5	452.4	Non-compliant	104.6	502.08	Compliant
ATL8	20/120	0.45	0.09	Non-compliant	18.06	21.67	Non-compliant
ATL9	20/120	92.68	18.54	Compliant	109.01	130.81	Compliant
ATL10	20/120	101.66	20.33	Compliant	91.85	110.22	Compliant
ATL11	20/120	100.09	20.02	Compliant	68.5	82.20	Non-compliant
ATL12	20/120	99.11	19.82	Compliant	85.21	102.25	Non-compliant
ATL13	20/120	92.57	18.51	Compliant	97.72	117.26	Compliant
ATL14	20/120	104.49	20.90	Compliant	85.34	102.41	Non-compliant

Notes: Acceptable limit (% of API) for artemether and lumefantrine: 90%–120% (IP, 2016).

Table 4: Results of the HPLC assay for the percentage content of artesunate in the sampled ACTs.

Sample code	Stated amount of artesunate (mg)	% Artesunate from HPLC assay	Calculated drug content (mg/tablet)	Remark
ATS15	25	107.61	26.90	Compliant
ATS16	100	98.03	98.03	Compliant
ATS17	50	90.13	45.07	Compliant
ATS18	50	38.81	19.41	Non-compliant
ATS19	25	114.20	28.55	Non-compliant
ATS20	25	90.12	22.53	Compliant
ATS21	100	77.28	77.28	Non-compliant

Notes: Acceptable limit (% of API) for artesunate: 90%–110% (IP, 2016).

DISCUSSION

ACTs hold a greater hope for the control of malaria in Africa, however, it is very worrisome that poor-quality ACTs are already widespread (Newton *et al.* 2010). In malaria-endemic countries, up to 35%, poor-quality antimalarial drugs have been reported (Nayyar *et al.* 2012; Tabernero *et al.* 2014). In the present study, the proportion of antimalarial drugs that were substandard and non-compliant to the tolerance limits was 47.6%. This means that only 52.4 % were standard, which implies that patients have approximately only a 50% chance of obtaining good quality of antimalarial drugs.

The proportion of substandard ACTs observed in our study is comparable to the report of Tivura *et al.* (2016) where 35.4% of the ACTs sold in central Ghana were substandard and failed to comply with the required amount of APIs. A much higher proportion of substandard ACTs have been reported. Osei-Safo *et al*. (2014) report on the quality of 132 artemisinin-based antimalarial medicines distributed in Ghana and Togo showed that 83.7% of the ACTs and 57.9% of the artemisinin-based monotherapies failed to comply with IP requirements due to insufficient API content.

However, a study by Ndwigah *et al.* (2018) indicated the circulation of good quality anti-malarial medicines in Embu County, Kenya, where all the collected samples from public and private facilities passed the quality control tests. Similarly, in a field survey of the quality of antimalarial drugs in Gabonese pharmacies conducted using the Global Pharma Health Fund Minilab tests reported the prevalence of poor quality in only 2 (0.5%) of the 432 samples obtained from selected pharmacies in Gabon. Further analysis using HPLC with ultraviolet photodiode array detection confirmed the absence of APIs in the artemether-lumefantrine sample, and thus, classified as falsified while the sulfadoxine-pyrimethamine sample was substandard because it contains the stated APIs but the amount was half the stated dose (Visser *et al.* 2015). In another study from the South Western part of Nigeria, it was reported that all the 10 brands (100%) of the artemether-lumefantrine tablets met the assay requirement for artemether and 8 (80%) met the assay requirement for lumefantrine, however, only 15 (75%) of the 20 brands of artesunate-containing brands met the standard assay requirement for artesunate (Izevbekhai *et al.* 2017).

The potential health implications from the use of substandard antimalarial drugs are of great concern, especially in malaria-endemic countries. This can lead to increased morbidity and mortality, development of drug resistance and waste of resources (Nettey *et al.* 2014; Frimpong *et al.* 2018). In cases where the drugs contain an insufficient amount of the API, this could lead to serious under dosage leading to possible therapeutic failure, selection and proliferation of drug-resistant organisms (Taylor *et al.* 2011). And where the amount of the active drug is well above the stated amounts, the use of such preparations could result to adverse events as was found in Nigeria where 94 of 160 (59%) of antimalarials tested contained 110% or more of the stated active ingredients (Newton *et al.* 2006; Taylor *et al.* 2001). The presence of an excessive amount of API could lead to toxicity in patients and the implications are even more crucial especially in pediatric formulations (Osei-safo *et al.* 2014).

Factors such as lack of political will and cooperation from stakeholders, the rapid increased in the number of small pharmaceutical industries without adequate quality assurance, lack of sufficient detection facilities to check the quality of antimalarial drugs, lack of good knowledge among the consumers and health workers about the authenticity/ poor-quality medicines, and the dearth of appropriate regulatory, enforcement and punitive actions are the major reasons contributing to poor quality antimalarial drugs (Nayyar *et al.* 2012).

Sustained political will, support and strengthening of regulatory authorities, effective government regulation, and improving the quality of production, distribution, and sales of good quality medicines are key factors in improving drug quality (Newton *et al.* 2010).

CONCLUSION

The study has revealed that the ACTs oral drug formulations complied with the microbiological quality control tests, however, a relatively high proportion of the ACTs were non-compliant with the IP specification for the percentage drug content and thus signifies the existence of substandard artemisinin-based antimalarial medicines in the study area.

REFERENCES

ACTWATCH GROUP, CHINAZO, U., JENNIFER, A., PAUL, N. N. & GODWIN, N. (2017) When it just won't go away: Oral artemisinin monotherapy in Nigeria, threatening lives, threatening progress, *Malaria Journal*, 16: 489. https://doi.org/10.1186/s12936-017-2102-7

AMIN, A. A. & KOKWARO, G. O. (2009) Antimalarial drug quality in Africa, *Journal of Clinical Pharmacy and Therapeutics,* 32(5): 429–440. https://doi.org/10.1111/j.1365 -2710.2007.00847.x

FRIMPONG, G., KWABENA, O. K., NOBLE, K., KWAME, O., YAAASANTEWAA, O., MARIAM, E. B. G. *et al*. (2018) Quality assessment of some essential children's medicines sold in licensed outlets in Ashanti region, Ghana, *Hindawi Journal of Tropical Medicine,* 2018: 1–14. https://doi.org/10.1155/2018/1494957

HETZEL, M. W., PAGE-SHARP, M., BALA, N., PULFORD, J., BETUELA, I., TIMOTHY, M. E. D. *et al*. (2014) Quality of antimalarial drugs and antibiotics in Papua New Guinea: A survey of the health facility supply chain, *PLoS ONE,* 9(5): e96810. https://doi.org/10.1371/journal.pone.0096810

INTERNATIONAL PHARMACOPOEIA (IP) (2016). *Tests and general requirements for dosage forms. Quality specifications for pharmaceutical substances and tablets,* 6th edition (Geneva, Switzerland: WHO press).

IZEVBEKHAI, O., BABATUNDE, A., ADENIYI, O. & OLUSEYE, B. (2017) Quality of artemisinin-based antimalarial drugs marketed in Nigeria, *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 111: 90–96. https://doi.org/10.1093/trstmh/trx019

KAUR, H., MICHEAL, D. G, DANA, M. H., FACUNDO, M. F. & PAUL, M. N. (2010) Antimalarial drug quality: Methods to detect suspect drugs, *Therapy,* 7(1): 49–57. https://doi.org/10.2217/THY.09.84.

KOLAWOLE, J. A., OLURUNMI, P. O., OKENIYI, S. O. & SHAWRPSHAKA, Y. J. (2002) Quality and availability of ampicillin products in Jos, Nigeria, *Nigerian Journal of Pharmacy*, 33: 27–42.

NDWIGAH, S., ANDY, S., KENNEDY, A., HANNINGTON, M. & ISAAC, K. (2018) The quality of antimalarial medicines in Embu County, Kenya, *Malaria Journal*, 17: 330. https://doi.org/10.1186/s12936-018-2482-3

NAYYAR, G. M, BREMAN, J. G, NEWTON, P. N. & HERRINGTON, J. (2012) Poor quality antimalarial drugs in Southeast Asia and sub-Saharan Africa, *Lancet Infectious Disease,* 12: 488–496.

NETTEY, H., GRACE, L. A., PHILIP, D., OFOSUA, A. D., MANAL, S., ISAAC, K. *et al*. (2014) The quality and *in vitro* efficacy of amoxicillin/clavulanic acid formulations in the central region of Ghana, *Pharmacology & Pharmacy*, 5: 49–60. https://doi.org/10.4236/pp.2014.51009

NEWTON, P. N., MICHAEL, D. G., FERNANDEZ, F. M., DAY, N. P. J. & WHITE, N. J. (2006) Counterfeit anti-infective drugs, *Lancet Infectious Disease,* 6: 602–613.

NEWTON, P. N., MICHAEL, D. G. & FERNANDEZ, F. M. (2010) Impact of poor-quality medicines in the 'developing' world, *Trends Pharmacological Sci*ence, 31(3–3): 99–100.

NEWTON, P. N., MICHAEL, D. G., DALLAS, C. M., ALINE, P., HENRY, N., LEONARD, N. *et al*. (2011) Poor quality vital antimalarials in Africa—an urgent neglected public health priority, *Malaria Journal*, 10: 352. http://www.malariajournal.com/content/10/1/352

ONWUJEKWE, O., KAUR, H., DIKE, N., SHU, E., UZOCHUKWU, B., HANSON, K. *et al*. (2009) Quality of antimalarial drugs provided by public and private healthcare providers in south-east Nigeria, *Malaria Journal,* 8: 22.

OSEI-SAFO, D., AMEGNONA, A., DANIEL, Y. K., JERRY, J. E., KINGSLEY, H., MAMADOU, E. *et al*. (2014) Evaluation of the quality of artemisinin-based antimalarial medicines distributed in Ghana and Togo, *Malaria Research and Treatment*, 2014: 1–12. https://doi.org/10.1155/2014/806416

TABERNERO, P., FERNANDEZ, F. M., GREEN, M., GUERIN, P. J. & NEWTON, P. N. (2014) Mind the gaps—the epidemiology of poor-quality antimalarials in the malarious world—analysis of the World Wide Antimalarial Resistance Network database, *Malaria Journal,* 13: 139.

TAYLOR, R. B., SHAKOOR, O., BEHRENS, R. H., EVERARD, M., LOW, A. S., WANGBOONSKUL, J. *et al*. (2001) Pharmacopoeial quality of drugs supplied by Nigerian pharmacies, *The Lancet,* 357: 1933–1936.

TIVURA, M., ISAAC, A., ALBERT VAN, W., STEPHANEY, G., NAIELA, M., EMMANUEL, M. *et al*. (2016) Quality of artemisinin based combination therapy for malaria found in Ghanaian markets and public health implications of their use, *BMC Pharmacology and Toxicology*, 17: 48. https://doi.org/10.1186/s40360-016-0089-2

UNITED STATES PHARMACOPOEIA CONVENTION. (2018) The United States Pharmacopoeia 2018: USP 41; The National Formulary: NF 36, pp 605 (Rockville, MD: United States Pharmacopoeial Convention Inc.)

VISSER, B. J., JANNEKE, M. G., DANIËLLE, K., JUDITH, M., RIEKE, V., EMMANUEL, B. *et al*. (2015) Assessing the quality of antimalarial drugs from Gabonese pharmacies using the MiniLab: a field study, *Malaria Journal,* 14: 273. https://doi.org/10.1186/s12936-015-0795-z

WORLD HEALTH ORGANIZATION (WHO) (2011) Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa: WHO_QAMSA_ report, January, 2011 (Geneva, Switzerland: WHO Press).

WORLD HEALTH ORGANIZATION (WHO) (2015) WHO model lists of essential medicines. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

WORLD HEALTH ORGANIZATION (WHO) (2020) World Malaria Report. https://www.who.int/news-room/fact-sheets/detail/malaria