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Assessing the quality of antimalarial drugs in Equatorial Guinea: a follow-up study

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ABSTRACT

Introduction Poor-quality antimalarial medications, including falsified and substandard formulations, pose significant public health risks, contributing to ineffective treatment and potential drug resistance. Our research conducted in 2013 on Bioko Island, Equatorial Guinea (EG), found 9.6% (n=61) of the artemisinin-containing antimalarials (ACAs) purchased were of poor quality. This study aimed to update the quality of all sold antimalarials and extend to include regions on the mainland.

Methods A total of 637 samples, 564 ACAs and 73 non-ACAs, were purchased from 424 outlets on Bioko Island and mainland EG using a mystery client sampling approach. Samples were analysed for content using high-performance liquid chromatography with diode-array detection and classified as acceptable, substandard or falsified based on pharmacopoeia tolerance limits. Additionally, bioavailability was assessed through dissolution testing for a select number of samples.

Results Overall, 40.5% of the samples were of acceptable quality, 31.2% were substandard and 28.3% were falsified. Regional differences showed a higher prevalence of falsified samples in Bata, Mangomo, Evinayong and Ebebiyín cities on the mainland (30.9%) compared with Bioko Island (25.6%). Artemether/lumefantrine, the first-line treatment for malaria in EG, showed 25.7% were of acceptable quality, 48.2% substandard and 26.1% falsified. Artemisinin monotherapy tablets had the highest rate of falsification (56.8%). For non-ACAs, 13.3% of sulfadoxine/pyrimethamine tablets were of acceptable quality, 48.9% substandard and 37.8% falsified. All quinine syrups were falsified, and most quinine tablets (87.5%) and injections (75.0%) were substandard.

Conclusion The prevalence of substandard and falsified antimalarials in EG has alarmingly increased from 9% in 2013 to 59.5% in 2018, highlighting the urgent need for enhanced regulatory measures. Immediate actions should include strengthening drug quality surveillance, particularly in private sector pharmacies, and implementing low-cost medicine screening methods for early detection of poor-quality medications. Ensuring the quality of antimalarials is critical to maintaining the efficacy of malaria control programmes and preventing the development of drug resistance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Substandard and falsified (SF) antimalarial medicines pose serious health risks, leading to treatment failures, increased mortality and the development of drug-resistant malaria strains. Previous studies have documented the prevalence of SF artemisinin-containing antimalarials in various malaria-endemic regions, including Bioko Island, in Equatorial Guinea (EG).

WHAT THIS STUDY ADDS

⇒ This study provides updated data on the quality of antimalarial medicines across Bioko Island and extends the analyses to mainland in EG. It reveals a substantial increase in the prevalence of SF antimalarials and significant regional differences in their quality. The findings highlight the persistent and escalating challenge of poor-quality antimalarials in the country.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study underscores the urgent need for enhanced regulatory oversight and stricter enforcement of pharmaceutical quality standards in EG. Measures crucial for effective malaria control and prevention of drug resistance calls for the implementation of routine surveillance programmes, improved regulatory frameworks by establishing a fully operational Medicines Regulatory Authority, implementing systematic quality testing at points of entry, and introducing the use of low-cost medicine screening technologies at distribution points. Additionally, continuing the comprehensive malaria control measures implemented by the Bioko Island Malaria Elimination Project since 2004 remains essential. Regular therapeutic efficacy studies, as currently conducted triennially, should be maintained to monitor potential drug resistance development and ensure treatment guidelines remain effective.

INTRODUCTION

Early diagnosis and prompt treatment of malaria with effective antimalarial drugs remain critical for reducing malaria-related

deaths in endemic countries.[1] In 2001, WHO recommended artemisinin combination therapies (ACTs) as the mainstay of treatment for uncomplicated *Plasmodium falciparum*, which causes the deadliest form of malaria.[2] ACTs have significantly contributed to reducing malaria morbidity and mortality.[3] However, WHO estimates that 1 in 10 medicines in developing countries are of poor quality (substandard or falsified), with antimalarials being among the most commonly reported.[4] Antimalarials, including patent and generic brands, are readily available without a prescription in many endemic countries. The latter may have been manufactured without adherence to WHO-recommended manufacturing practices and may indeed be substandard and falsified (SF) products.[5]

Antimalarials steadily reduced the mortality and morbidity rates associated with malaria globally, over the period between 2000 to 2019, from 897 000 to 568 000.[6] Malaria remains the most prevalent disease in Equatorial Guinea (EG).[7 8] Since 2004, the National Malaria Control Program (NMCP) has employed a wide range of methods in their continued efforts to combat the disease on Bioko Island chiefly through vector control interventions and enhanced case management.[9] Malaria diagnosis is primarily conducted using rapid diagnostic tests at the primary care level, with microscopy available at district hospitals and reference laboratories. Medicines are provided for free in public health facilities both for malaria case treatment and intermittent preventive therapies in pregnant women.[10 11] Malaria case management follows the national treatment guidelines, with artemether–lumefantrine recommended as first-line treatment for uncomplicated malaria across all age groups. Artesunate (AS)–amodiaquine serves as an alternative first-line treatment, while injections of AS or quinine are recommended for severe malaria cases, though stock-outs occasionally occur. Therapeutic efficacy studies have not confirmed any cases of artemisinin resistance.[12] However, little effort has been invested in controlling malaria in the mainland region of Rio Muni, which is reflected in significantly higher transmission rates.[12 13] This, together with the high connectedness between mainland and Bioko, has determined that importation is one of the main challenges faced for malaria elimination on the island.[8–10 12 13]

In 2013, the quality of first-line artemisinin-containing antimalarials (ACAs), both as mono or combination therapies, was assessed by purchasing (n=677 samples) on Bioko Island from 278 outlets using three representative sampling approaches (convenience, mystery client and overt).[14] Laboratory-based chromatographic analyses and classification of samples according to the pharmacopoeia guidelines found that overall 91.0% (n=616) of ACAs were of acceptable quality, 1.6% (n=11) were substandard and 7.4% (n=50) were falsified (ie, they contained none of the stated active pharmaceutical ingredient (API)). Samples purchased (n=31) using the convenience survey yielded 80.7% to be acceptable quality, 3.2% substandard and 16.1% were falsified (did not contain the stated APIs but contained unstated compounds that were not listed on the packets). Quality of samples (n=368) purchased using full island-wide survey using mystery client showed that 91.9% were of acceptable quality, 5% substandard and 7.6% were falsified. The purchases using a randomised survey using an overt sampling approach (n=278) found 91.0% were of acceptable quality, 2.9% substandard and 6.1% were falsified. Moreover, AS monotherapies (n=62) were found available, of which 37.1% (n=23) were falsified, containing the antibiotic ciprofloxacin instead of the stated API.[14]

This study aimed to update the status of the quality of antimalarial medicines on Bioko Island. Given the relevance for local malaria epidemiology of the interconnection between Bioko and mainland, the analyses included Rio Muni. It also expanded the assessment to non-ACAs, including sulfadoxine/pyrimethamine (SP) as a key medicine for intermittent preventive treatment in pregnancy on Bioko Island. This research is critical to provide insights for policy decisions surrounding malaria control efforts in EG.

METHODS

Patient and public involvement

This study did not involve any patients as it set out to assess the quality of antimalarials available for purchase at various outlets on Bioko Island and three regions of Rio Muni, EG.

Identification of medicine outlets

A census of medicine outlets was conducted as part of the assessment of ACAs quality in June 2013.[14] This census was supplemented in 2018 by more recent outlet data gathered during routine programmatic operations. A total of 714 outlets were identified, including brick-and-mortar pharmacies, health centres, consulting rooms, hospitals, markets, mobile vendors and medicine kiosks across Bioko Island and four locations in the mainland. All outlets on the list open for business were visited (n=424; 59%) and samples purchased using the mystery shopping approach (figure 1A, B and online supplemental table 1).

Acquisition of antimalarial samples

The study design and analyses methods reported in this article were informed by guidelines, including the conduct of surveys of the quality of medicines published by WHO[15] and the checklists of criteria for designing and reporting of medicine quality studies.[16 17] Samples of antimalarials were purchased from the 424 outlets using a 'mystery client' approach over 25 days (between 25 September and 14 November 2018).

Four pairs of surveyors, overseen by two supervisors, were trained to visit the medicine outlets and purchase a sample of each antimalarial brand available. For every public facility, there were five private facilities visited as they are many more private than public. Surveyors

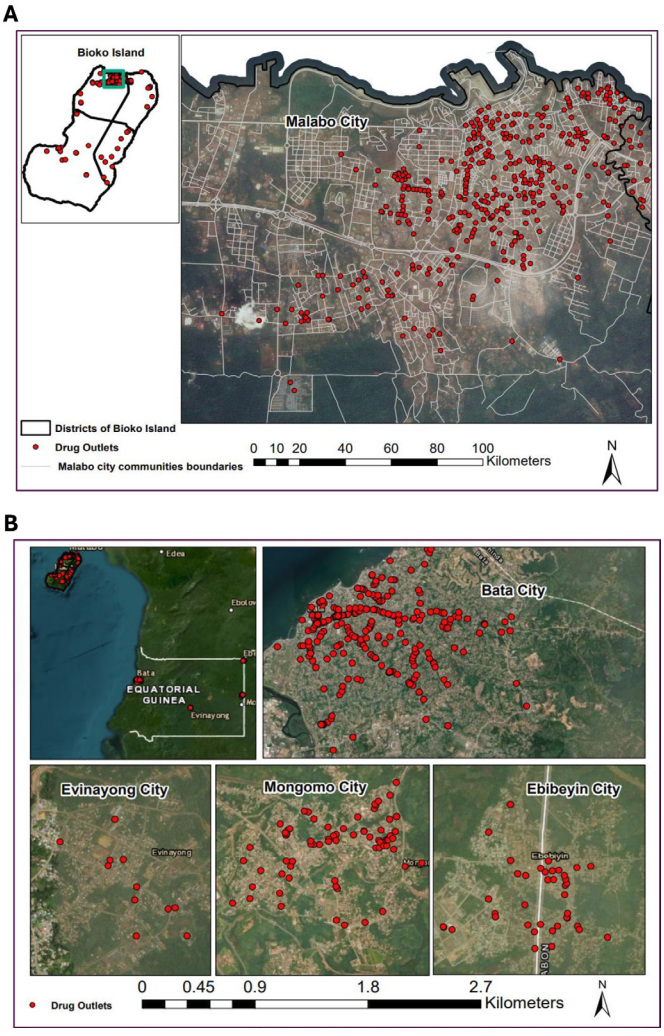

Figure 1 Distribution of outlets on (A) Bioko Island and (B) Rio Muni Mainland visited to purchase samples of antimalarial medicines.

approached the provider, feigning that they or a family member were sick with malaria symptoms and needed medications. They requested to see all medicines that the provider recommended before purchasing a course of treatment.

A total of 637 antimalarial medicines (564 ACAs and 73 non-ACAs; online supplemental table 2) were purchased, including various formulations (ie, injectables, capsules, tablets, syrups), brands and dosage packages. The ACAs purchased included artemisinin monotherapies (AS tablets and injectables, artemether (AM) tablets) and ACTs (AS+SP, artesunate/amodiaquine (AS/AQ), artesunate/mefloquine (AS+MF) and AM/LUM). The non-ACAs purchased were SP tablets, quinine tablets, quinine injections and quinine syrup.

Data entry

Drug data were recorded digitally using electronic tablets programmed to register brand name, stated API, dose form, outlet where purchased, including its location, date of purchase, name of the stated manufacturer, country of manufacture, presence of the Affordable Medicines Facility—malaria (AMFm) green leaf logo, batch number, date of manufacture, expiry date, number of tablets per packet and price paid. The AMFm is a drug subsidy programme aimed at improving access to high-quality affordable ACTs.[18]

Sample processing, laboratory analyses and classification of quality

Samples were placed in individual zip-lock bags, labelled with the unique outlet and product codes, and stored safely in an air-conditioned locked room at ~20°C before being dispatched to the London School of Hygiene and Tropical Medicine (LSHTM) bioanalytical facility for processing and laboratory analyses. Digital photographs of packaging and contents were taken, and sample information checked with the field data.

Tablets were weighed, and their dimensions recorded prior to screening testing of the ACAs and non-ACAs, followed by confirmatory laboratory analyses for content and dissolution testing (only when an authorised pharmacopoeia monograph was available).

Chemicals, materials and instruments

Reference standards of the APIs were obtained from Sigma-Aldrich, UK (amodiaquine dihydrochloride dihydrate, quinine, AS and pyrimethamine); Novartis, Switzerland (artemether); WHO, Switzerland (lumefantrine) and Roche Chemicals, Switzerland (sulphadoxine and mefloquine). Laboratory consumables (solvents, columns, vials) from Thermo Scientific, UK, and the high-performance liquid chromatography with diode array detection (HPLC-DAD) system, Thermo Scientific Dionex Ultimate 3000 from Thermo Fisher, Hemel Hempstead, UK. Dissolution analyses were performed using the Pharma Test PT 017 dissolution apparatus (Pharma Test Group, Pharma Test, Hamburg, Germany) and measuring the amount of dissolved stated API over time using HPLC-DAD.

Laboratory analyses

Screening test for the specific detection of the artemisinin derivative in ACAs

An easy-to-use, robust, inexpensive, specific and rapid colour reaction screening test previously described was used to detect the presence of artemisinin derivative component (ie, AS, AM or dihydroartemisinin) of ACAs.[19] The test results in the production of pink colour only when a sample contains an artemisinin derivative. Lack of colour was interpreted as samples not containing the stated API; hence, falsified and results are verified by confirmatory testing using HPLC-DAD.[19] DAD allows simultaneous acquisition of a spectrum across the ultraviolet-visible (UV-Vis) region for every data point in the chromatogram, providing information beyond a single wavelength leading to the accurate identification and quantification by comparing UV-Vis spectra with that from reference standards.

High-performance liquid chromatography-diode array detector conditions

Quantitative analyses were carried out using Thermo Scientific Dionex Ultimate 3000 HPLC-DAD system (Thermo Fisher, Hemel Hempstead, UK), and separation of each API was achieved using an Acclaim 120 C_{18}, 5 µm, 120 Å 150 × 4.6 mm column (Fisher Scientific UK Ltd, Leicestershire, GB), using eluent composition, flow rate and detection wavelength as outlined in our publications.[14 20] The authenticity of the detected peaks was determined by comparison of retention time, spectral extraction and spiking the sample with commercially available pure reference standard of each API in the formulation.[20]

Laboratory API content and dissolution analyses

Content of the formulations was measured by solubilising each in an appropriate solvent to produce a 1 mg/mL solution, centrifuged and the supernatant was further diluted before injecting onto the HPLC column. The content of each sample (tablet, injectable or syrup) was determined from the concentration of each stated API (presented as a per cent), comparing the detected amount in each sample to the indicated dose packaging and multiplying by 100. The per cent of each stated API was used to classify the quality of each sample, referencing the United States Pharmacopeia 24 (USP-24) tolerance limits (online supplemental table 3). The sample was classified as acceptable if the measured % API was within the specified tolerance limits and substandard if above or below the limits. If the stated API was not detected but potentially contained an unspecified compound/s, it was classified as falsified.

Dissolution analyses of formulations

Dissolution analysis can only be carried out following the in vitro dissolution testing protocols detailed in the authorised monographs outlined in pharmacopoeias for a given formulation. Absence of authorised monographs for ACAs; therefore, only tablets of SP and quinine were subjected to dissolution testing. The USP tolerance limits stipulate that not less than 60% of the API-SP should be detected at 30 min for the sample to be accepted as having passed the specified tolerance limits. Similarly, for tablets of quinine, not less than 75% of the API should be detected at 45 min. When less than the specified amount of stated API was detected, the sample was classified as not compliant.

RESULTS

Chemical quality of antimalarial formulations

During the period (January–December 2019) of laboratory (content and dissolution) analyses, the majority of the samples (67.1%, n=428; see online supplemental table 4) were within expiry date as stated on the packaging. Overall quality of these samples (figure 2), adhering to the pharmacopoeia tolerance limits, revealed that 40.5% (n=258) were of acceptable quality, 31.2% (n=199) were substandard and 28.3% (n=180) were falsified.

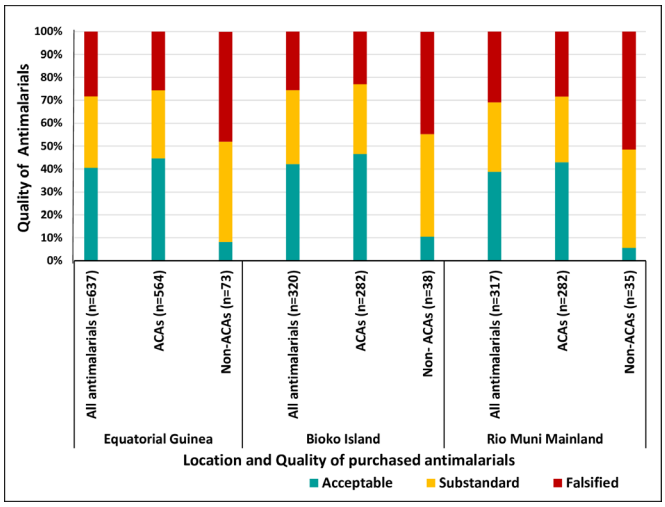

Figure 2 Quality of total antimalarials, artemisinin-containing antimalarials (ACAs) and non-ACAs from Equatorial Guinea as a whole, on Bioko Island, and on Rio Muni Mainland.

Regional differences in quality

Comparable number of samples were obtained on Bioko Island (n=320; comprising ACAs n=282; non-ACAs n=38) and the mainland (n=317; comprising ACAs n=282; non-ACAs n=35). A higher percentage of samples purchased from the mainland were falsified (overall 30.9%, n=98; comprising ACAs, 28.4%, n=80; and non-ACAs, 51.4%, n=18) compared with those from Bioko Island (overall 25.6%; n=82; comprising ACAs, 23.0%, n=65; and non-ACAs, 44.7%, n=17). Almost half of the non-ACAs purchased on the island were falsified. Similar percentages of substandard samples were from Bioko Island (32.2%, n=103; comprising 30.5%, n=86 ACAs and 44.7%, n=17 non-ACAs) and mainland (30.3%, n=96; comprising 28.7%, n=81 ACAs and 42.9%, n=15 non-ACAs). Higher percentages of samples from Bioko Island were of acceptable quality (42.2%, n=135; 46.5%, n=131 ACAs and 10.5%, n=4 non-ACAs) compared with the mainland (38.8%; n=123; 42.9%, n=121 ACAs and 5.7%, n=2 non-ACAs).

Quality of various formulations

The quality of individual artemisinin derivative and non-artemisinin derivative containing antimalarial formulations purchased in EG is shown in figure 3. Among the samples of AS monotherapy tablets (n=155), 27.7% (n=43) were of acceptable quality, 15.5% (n=24) were substandard and more than half (56.8%; n=88) were falsified. AS injections (n=65) were predominantly of acceptable quality (93.8%, n=61), with only 6.2% (n=4) substandard and none were falsified. AS plus MF (separate tablets; n=11); 90.9% (n=10) were of acceptable quality, only one was substandard and none were falsified. Among AS/AQ (n=55, combination in a tablet),

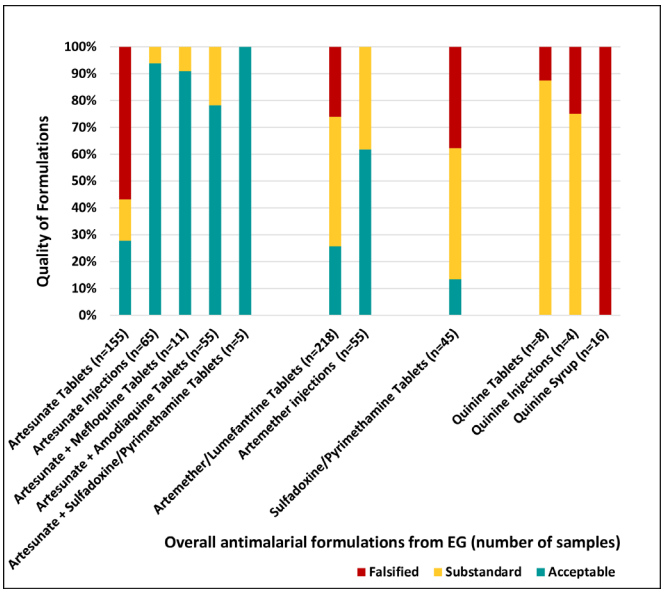

Figure 3 Quality of various formulations of antimalarials purchased in Equatorial Guinea (EG).

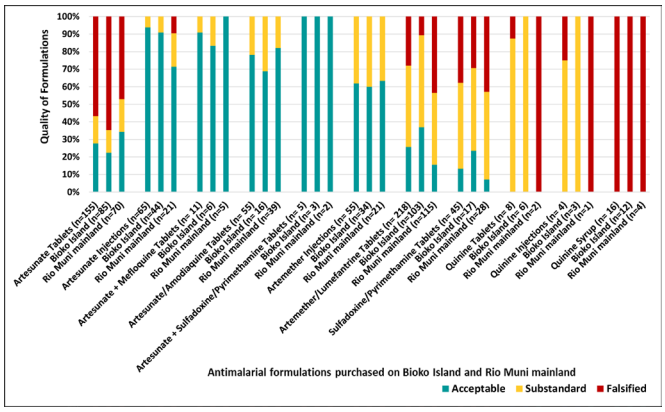

Figure 4 Quality of various antimalarial formulations purchased on Equatorial Guinea as a whole and then separated into Bioko Island and Rio Muni Mainland.

78.2% (n=43) were of acceptable quality and 21.8% (n=12) were substandard and none were falsified. AS plus SP (two separate tablets; n=5) were all analysed to be of acceptable quality.

Tablets of AM/LUM (n=218) comprised 34.2% of all samples purchased, with 25.7% (n=56) found to be of acceptable quality, 48.2% (n=105) substandard and 26.1% (n=57) to be falsified. Majority of artemether injections (n=55) were found to be of acceptable quality (61.8%, n=34), with 38.2% (n=21) being substandard and none were falsified

Non-ACAs comprised SP (n=45), where 13.3% (n=6) were of acceptable quality, 48.9% (n=22) were substandard and 37.8% (n=17) were falsified. Among quinine-based formulations (n=28 comprised tablets, injections or syrups), quinine tablets (n=8) consisted of substandard 87.5% (n=7) and 12.5% (n=1) falsified. Among quinine injection (n=4), one was falsified and three were substandard. Quinine syrups (n=16) were all falsified.

Chemical content analyses by region

Chemical content analyses of the antimalarial samples were further categorised by the region of purchase (Bioko Island or Rio Muni Mainland), and full results are shown in figure 4 and further broken down by districts in table 1. Important differences are highlighted here, particularly for drugs for which large sample sizes were obtained. Notably, a significantly higher proportion of AM/LUM was of acceptable quality on Bioko (36.9%) than on the mainland, where only 15.6% of samples were acceptable and 40.9% were falsified (vs 9.7% on Bioko). Conversely, for the second-line antimalarial, ASAQ, a higher proportion were of acceptable quality on the mainland (82.1%) than on Bioko Island (68.8%). Whereas a significantly lower proportion of SP samples were of acceptable quality on mainland and just 7.1% passed the check, while on Bioko 23.5% satisfied the analyses.

Artesunate tablets

AS monotherapy tablets (n=155) purchased in EG were from Bioko Island (n=85) and mainland (n=70). Over half (64.7%; n=55) were found not to contain the stated API, thus categorised as falsified. These were predominantly found in Malabo (63.9%; n=46), Baney (70.0%; n=7) and Luba (100.0%; n=2). Samples from the mainland (n=70) found 47.1% (n=33) were falsified and purchased from Bata, 42.1% (n=24) from Ebebiyín and 75.0% (n=3) from Evinayong (75.0%, n=3). Most of the falsified samples (n=48) were of the batch number 12006 and stated to be manufactured in Vietnam and analysed to contain the antibiotic ciprofloxacin instead of AS. Samples of the same batch number stated country of origin and containing the antibiotic had also been found in our previous study on Bioko Island[14] and in Enugu, Nigeria.[20] The substandard samples were from districts on the island (Malabo, 13.9%, n=10; and Baney, 10.0%, n=1) and the mainland (Bata, 19.3%, n=11; Mongomo, 12.5%, n=1; and Ebebiyín, 25.0%, n=1).

Regional quality of ACTs

Samples, including AS+MF and AS/AQ, were found to be either of acceptable quality or substandard. All samples of AS+MF (n=11) purchased on the mainland (in Bata, n=4, and Mongomo, n=1) were of acceptable quality. Samples (n=6) purchased in Malabo on the island were either of acceptable quality (83.3%, n=5) or substandard (16.7%, n=1). Similarly, a higher percentage of AS/AQ samples from the mainland (total 82.1%; n=32)—Bata (81.1%, n=27), Mongomo (80.0%, n=4) and Ebebiyín (100.0%, n=1)—were of acceptable quality compared with Bioko Island (total 68.8%; n=11): Malabo (66.7%, n=8), Baney (100.0%, n=2) and Luba (50.0%, n=1). Substandard samples (21.8%, n=12) were found both on the island (31.3%, n=5)—Malabo (33.3%, n=4) and Luba (50.0%, n=1)—and on the mainland (17.9%, n=7)—Bata (18.2%, n=6) and Mongomo (20.0%, n=1). Formulations

Table 1 Overall quality of antimalarials per formulation in EG and per districts of Bioko Island and Rui Muni Mainland of EG

Formulation	Classification	Overall in EG	Districts of Bioko Island (outlets visited)			Districts of Rui Muni mainland (outlets visited)			
			Malabo (n=133)	Baney (n=14)	Luba (n=4)	Bata (n=106)	Ebibeyín (n=13)	Evinayong (n=8)	Mongomo (n=12)
Artesunate tablets (n=155)	Acceptable	27.7% (n=43)	23.6%(n=17)	20.0% (n=2)	0	38.6% (n=22)	12.5% (n=1)	0	100.0% (n=1)
	Substandard	15.5% (n=24)	13.9% (n=10)	10.0% (n=1)	0	19.3% (n=11)	12.5% (n=1)	25.0% (n=1)	0
	Falsified	56.8% (n=88)	63.9% (n=46)	70.0% (n=7)	100.0% (n=2)	42.1% (n=24)	75.0% (n=6)	75.0% (n=3)	0
Artesunate injection* (n=65)	Acceptable	93.8% (n=61)	90.5% (n=38)	100.0% (n=2)	0	100.0% (n=14)	100% (n=4)	100% (n=2)	100% (n=1)
	Substandard	6.2% (n=4)	9.5% (n=4)	0	0	0	0	0	0
	Falsified	0	0	0	0	0	0	0	0
Artesunate+mefloquine tablets (n=11)	Acceptable	90.9% (n=10)	83.3% (n=5)	0	0	100% (n=4)	0	0	100% (n=1)
	Substandard	9.1% (n=1)	16.7% (n=1)	0	0	0	0	0	0
	Falsified	0	0	0	0	0	0	0	0
Artesunate/amodiaquine tablets† (n=55)	Acceptable	78.2% (n=43)	66.7%(n=8)	100.0% (n=2)	50.0% (n=1)	81.8% (n=27)	100.0% (n=1)	0	80.0% (n=4)
	Substandard	21.8% (n=12)	33.3% (n=4)	0	50.0% (n=1)	18.2% (n=6)	0	0	20.0% (n=1)
	Falsified	0	0	0	0	0	0	0	0
Artesunate+sulfadoxine/pyrimethamine tablets (n=5)	Acceptable	100% (n=5)	100% (n=2)	100% (n=1)	0	100% (n=2)	0	0	0
	Substandard	0	0	0	0	0	0	0	0
	Falsified	0	0	0	0	0	0	0	0
Artemether injections‡ (n=55)	Acceptable	61.8% (n=34)	60.9% (n=14)	50% (n=1)	0	58.8% (n=10)	100% (n=3)	100% (n=1)	55.6% (n=5)
	Substandard	38.2 (n=21)	39.1 (n=9)	50% (n=1)	0	41.4% (n=7)	0	0	44.4% (n=4)
	Falsified	0	0	0	0	0	0	0	0
Artemether/lumefantrine tablets§ (n=218)	Acceptable	25.7% (n=56)	40.9% (n=38)	0	0	16.7% (n=14)	16.7% (n=2)	0	13.3% (n=2)
	Substandard	48.2%(n=105)	51.6% (n=48)	71.4% (n=5)	66.7% (n=2)	47.6% (n=40)	33.3% (n=4)	50.0% (n=2)	26.7% (n=4)
	Falsified	26.1 (n=57)	7.5% (n=7)	28.6% (n=2)	33.3% (n=1)	35.7% (n=30)	50.0% (n=6)	50.0% (n=2)	60.0% (n=9)
Sulfadoxine/pyrimethamine tablets (n=45)	Acceptable	13.3% (n=6)	30% (n=3)	0	33.3% (n=1)	4.5% (n=1)	0	0	20% (n=1)
	Substandard	48.9% (n=22)	40% (n=4)	75% (n=3)	33.3% (n=1)	54.5% (n=12)	0	0	40% (n=2)
	Falsified	37.8% (n=17)	30% (n=3)	25% (n=1)	33.3% (n=1)	40.9 (n=9)	100% (n=1)	0	40% (n=2)
Quinine tablets (n=8)	Acceptable	0	0	0	0	0	0	0	0
	Substandard	87.5% (n=7)	100% (n=4)	100% (n=2)	0	100% (n=1)	0	0	0
	Falsified	12.5% (n=1)	0	0	0	0	0	0	100% (n=1)
Quinine injections¶ (n=4)	Acceptable	0	0	0	0	0	0	0	0
	Substandard	100% (n=3)	100% (n=2)	100% (n=1)	0	0	0	0	0
	Falsified	0	0	0	0	100% (n=1)	0	0	0
Quinine syrup (n=16)	Acceptable	0	0	0	0	0	0	0	0
	Substandard	0	O	0	0	0	0	0	0
	Falsified	!00% (n=16)	100% (n=10)	100% (n=2)	0	100% (n=2)	0	0	100% (n=2)

Continued

Table 1 Continued

Formulation	Classification	Overall in EG	Districts of Bioko Island (outlets visited)			Districts of Rui Muni mainland (outlets visited)			
			Malabo (n=133)	Baney (n=14)	Luba (n=4)	Bata (n=106)	Ebibeyín (n=13)	Evinayong (n=8)	Mongomo (n=12)

According to the case management guidelines of EG.
All treatments are free in public health facilities.
*First-line antimalarial (complicated).
†Second-line antimalarial (uncomplicated).
‡Second-line antimalarial (complicated).
§First-line antimalarial (uncomplicated).
¶Third-line antimalarial (complicated).
EG, Equatorial Guinea.

of AS plus SP (n=5) purchased in both locations were all of acceptable quality.

Artemether injections

Artemether injections purchased on Bioko Island (n=25) were either of acceptable quality (60.0%, n=15), from Malabo (60.9%, n=14) and Baney (50.0%, n=1), or substandard (40.0%, n=10), from Malabo (39.1%, n=9) and Baney (50.0%, n=1). Of the samples (n=30) purchased on the mainland, 63.3% (n=19) were of acceptable quality from Bata (58.8%, n=10), Mongomo (55.6%, n=5), Ebebiyín (100.0%, n=3) and Evinayong (100.0%, n=1). No falsified samples were found in either location.

Quality of artemether/lumefantrine tablets

The currently recommended first-line malaria treatment, artemether/lumefantrine (AM/LUM) tablets, constituted the largest number (n=218) of ACTs purchased. About half were purchased on Bioko Island (n=103), with 10.7% (n=11) being falsified, 52.4% (n=54) substandard and 36.9% (n=38) of acceptable quality. An equivalent number of AM/LUM tablets (n=115) were purchased from the mainland, with 43.5% (n=50) found to be falsified, 40.9% (n=47) substandard and 15.6% (n=18) of acceptable quality. The falsified tablets of Coartem 20/120, AM/LUM contained batch F2261 (online supplemental picture 1) which did not dissolve in solvent, and visual examination of the packages (n=22) revealed the AMFM logo. All bar one packet (bought in Malabo) of this batch were bought on the mainland (Bata, Mongomo and Ebebiyín). This batch was found in our previous studies in Enugu, Nigeria,[20] and another on Bioko Island,[14] and forensic analysis detected the muscle relaxant chlorzoxazone and a polymer of sugar alcohol instead of the stated API.[14] Most of the falsified Coartem samples for the present investigation were purchased from pharmacies in Bata and other cities on the mainland.

Samples of non-ACAs, sulfadoxine/pyrimethamine

Only 23.5% (n=4) of SP tablets purchased on Bioko Island and 7.1% (n=2) from the mainland were found to be of acceptable quality. Fewer samples of SP (n=17) were purchased on Bioko Island, of which 47.1% (n=8) were substandard and 29.4% (n=5) were falsified, while 50.0% (n=14) samples from the mainland (n=28) were substandard and 42.9% (n=12) falsified.

Quality of quinine formulations

Majority of quinine syrups (n=16) were purchased on Bioko Island (100.0%, n=12) and the rest on Rio Muni Mainland (100.0%, n=4); all were found to be falsified. These samples did not contain detectable levels of quinine but contained a brown sediment in an unidentified green sticky liquid resembling an adhesive. Colour of the samples stated to be quinine syrup varied from green to yellow/brown (online supplemental picture 2). Quinine tablets (100.0%, n=6) from the island and half of

those from the mainland (50.0%, n=1) were substandard. Samples of injections (n=4) purchased from the island (100.0% n=3) were substandard, and the only one sample from the mainland was falsified.

Antimalarial quality and purchase price

A detailed analysis of the data related to the cost of formulations during our survey did not reveal any association between medicine price and quality across the various antimalarial formulations. For example, the price paid in the national currency of EG - Central African CFA franc (CFA), for artemether/lumefantrine (the first-line treatment), was similar for acceptable quality (1000-7500 CFA), substandard (1000-8000 CFA), and falsified products (1000-6000 CFA). This pattern was consistent across most antimalarial formulations.

Quality of artesunate tablets, also bore no relation to the price paid as we found acceptable quality products were priced between 3000-5000 CFA, while substandard or falsified versions were available across a wider price range (1500-5000 CFA), suggesting that price cannot be used as a reliable indicator of quality for this formulation. Interestingly, substandard formulations of injectable artesunate, were actually priced higher (2500-3000 CFA) than acceptable quality versions (1500-2000 CFA), challenging the assumption that higher prices correlate with better quality. Hence, consumers cannot rely on price as a proxy for quality when purchasing antimalarials in EG.

Dissolution analyses

Assessing the bioavailability of medicines can only be carried out if published authorised pharmacopoeia monographs for dissolution testing can be followed. Hence, tablets of ACAs (AS, AS+SP, AS/AQ, AS+MF, AM and AM/LUM) could not be analysed for bioavailability. Only a select number of samples (SP, n=12; and quinine, n=8) that had been classified as acceptable or substandard quality following content analyses were subjected to dissolution testing. These consisted of SP (n=3, acceptable quality) and substandard (n=9) while all tablets of quinine had been found to be substandard (n=8). Summarised results (online supplemental table 5) give detail of brand name, outlet type, district where purchased, country of manufacture, batch number, expiry date and content analyses (stated API %), as well as compliance with pharmacopoeia tolerance limits. Most SP samples analysed for bioavailability met the pharmacopoeia tolerance limits, bar the two that were grossly substandard (% stated API below 30). While all samples of quinine tablets (n=8) were substandard (% stated API 31.3–70.3), six did meet the pharmacopoeia tolerance limits for dissolution but three did not (stated APIs 31.3% and 80.3%).

DISCUSSION

Poor-quality antimalarial medications pose a severe health risk to consumers, with studies documenting the impact of SF medicines on public health.[1 14 21–24] Concern exists that substandard antimalarials could lead to drug resistance through underdosing, though this association remains unproven.[25 26] Addressing this issue is imperative as problems regarding drug resistance and SF antimalarials[21 27] remain pervasive in malaria-endemic regions. A recent meta-analysis found global SF antimalarial prevalence of 19.1%, highest in Africa (18.7%) and Asia (13.7%).[28] Identifying SF antimalarials in malaria-endemic countries is essential to addressing this impediment in malaria control. Our multicounty study of over 10 000 ACAs from six countries (Rwanda, Cambodia, Ghana-Kintampo, Tanzania, Nigeria and EG) provides comprehensive evidence on prevalence. Substandard medicines were found in all countries, while falsified samples appeared in Nigeria (Enugu state (1%), Ilorin city (0.8%)) and EG (Bioko Island (7.4%)).[21] This follow-up study was informed by these investigations, which highlighted the need for routine monitoring using representative sampling to quantify ineffective medicines.

Our analyses of 637 antimalarials revealed alarming rates in EG: 31.2% substandard and 28.3% falsified, compromising treatment efficacy and malaria control. Regional differences were evident, with Bioko Island showing more acceptable quality medicines (42.2%) than mainland (38.8%), though both faced substantial quality issues. These findings contrast with our previous study, which found 91.0% acceptable-quality ACAs, 1.6% substandard (1.6%) and 7.4% falsified medicines.[14] This deteriorating trend necessitates immediate policy reinforcement and robust regulatory action.

These results reflect our mystery client sampling approach, which provided robust estimates in previous studies on Bioko Island and in Enugu, Nigeria.[6 14 21] This method reduces sampling bias as outlets, unaware of the survey's aim, sell what they have without hiding products of questionable quality, treating surveyors as typical patients.

Despite free antimalarials in public health facilities, patients often choose private sector treatment due to shorter wait times and perceived better service. The private pharmaceutical sector operates with minimal oversight. EG's Medicines Regulatory Authority lacks sufficient capacity and resources, allowing poor-quality medicines to proliferate through unregulated supply chains. This regulatory gap remains unaddressed since our previous study, with no policy changes targeting pharmaceutical quality between 2013 and 2018. EG's geographical position, with porous mainland borders and sea access, facilitates the importation of unregulated pharmaceuticals, while falsified products with previously reported batch numbers indicate regional trafficking networks.[14 20 29]

Regulatory presence is more concentrated on Bioko Island near government institutions. This creates some deterrent against pharmaceutical fraud, while mainland areas have less oversight. The regions also differ in outlet types, with more informal vendors on the mainland vs established pharmacies on Bioko Island, influencing

product supply chains. Since 2004. the Bioko Island malaria Elimination Project (BIMEP) has operated on Bioko Island with substantail investment in healthcare infrastructure, creating greater awareness about treatment quality, while the mainland has received significantly less malaria control investment. These disparities require targeted interventions for each region's specific challenges.

Higher falsification rates on the mainland compared with Bioko Island (30.9% vs 25.6%) reflect different supply chains. Bioko's capital city, Malabo, has more formalised importation channels through controlled ports of entry. In contrast, mainland regions border Cameroon and Gabon, enabling informal cross-border trade with minimal pharmaceutical inspection. The continued availability of AS monotherapy tablets, despite treatment guideline recommendations against them, highlights the disconnect between official policies and market realities driven by consumer demand.

In 2007, WHO Member States adopted World Health Assembly resolution 60.18, which recommended discontinuing oral artemisinin-based monotherapy manufacture and distribution due to drug resistance risks.[30] Only rectal formulations for pre-referral and injectables for severe malaria should be used. Despite this, AS monotherapy tablets (n=62) remained available on Bioko Island in 2013 (37.1% falsified).[14] In our current study, primarily in Malabo (from 34 pharmacies), with 63.9% (n=46) containing no stated API. This contradicts both WHO and updated NMCP guidelines.

Antimalarials endorsed in EG since 2005 include AS plus SP and amodiaquine, with AM/LUM recently adopted as the first-line treatment for uncomplicated malaria. Concerningly, 28.0% (n=61) of these first-line treatment samples purchased from mainland districts were falsified. Many contained the batch F2261, originally reported as falsified in Angola[29] and bearing the AMFm logo; the same batch identified in our previous studies on Bioko Island and in Enugu, Nigeria.[14 20] No falsified samples were detected among other ACTs (AS-mefloquine, AS-amodiaquine or AS-SP).

In malaria-endemic Africa, intermittent preventive treatment with SP (SP-IPTp) is recommended for pregnant women in their first or second pregnancy, starting in the second trimester with monthly doses, ensuring that at least three doses are received. Evidence from malaria-endemic countries indicates that SP-IPTp is associated with reduced maternal parasitaemia, reduced low birthweight infants and increased mean birth weight.[31] Our findings show concerning SP quality. Of 17 samples from Bioko Island, 47.1% were substandard and 29.4% falsified. Mainland samples (n=28) showed even worse quality with 50.0% substandard and 42.9% falsified, with only two samples meeting acceptable quality.

Quinine is an effective medicine for the treatment of complicated malaria and is recommended in parenteral form as the third-line option in EG, but the formulations (tablets, injections and syrups) available on the Island and mainland are of very poor quality, substandard or falsified. The syrups did not contain the stated API but resembled an adhesive and contained brownish sediments. All sales of this antimalarial should be withdrawn immediately. Bioavailability determinations of SP and quinine were carried out; however, general conclusions cannot be reached given the small sample size, but the results are presented as other researchers have also found inconsistencies between content and dissolution testing.

Most falsified antimalarials were purchased from pharmacies across both regions, with only one-third officially registered with the Ministry of Health. This highlights challenges in monitoring drug quality where regulation is weak. Survey challenges include lack of sampling frames, outlet turnover, provider apprehension and staff safety concerns. Since many patients obtain antimalarials from unregulated providers, conducting a thorough census of all medicine outlets before quality surveys is essential to capture the complete medicine supply landscape.

Economic factors likely influence the distribution of poor-quality medicines across EG. The mainland, which is generally less economically developed than Bioko Island, which hosts the capital city and petroleum industry, presents different market dynamics for pharmaceuticals. On Bioko Island, the BIMEP has ensured antimalarials free access to antimalarials through public health facilities. In contrast, patients in more remote mainland areas often face additional costs such as transportation lost income due to travel time, which may lead them to purchase medicines that are more accessible, though potentially lower quality and from local vendors. Private sector prices for antimalarials varied substantially across outlets and regions, with higher prices in urban centres not consistently reflecting better quality. In some cases, expensive products were found to be falsified, highlighting the inadequacy of price as an indicator of quality and the importance of systematic quality assurance mechanisms.

EG's recently established reference laboratory in Baney District offers an opportunity to strengthen pharmaceutical quality assurance.[32] This facility could serve as a central hub for ensuring compliance with pharmacopoeia standards through routine testing of imported medicines. Collaborating with customs authorities and the Ministry of Health and Social Welfare (MOHSW) would enable systematic quality checks at points of entry, ensuring that only approved, high-quality medicines are distributed within the country.

Introducing a fee-for-service model for pharmaceutical importers and distributors would help sustain the operations of the reference laboratory while maintaining affordability for public health programmes. Integrating customs inspections with in-country testing would also streamline the detection and prevention of falsified or substandard drugs, reducing their circulation in the marketplace and supporting the efficacy of malaria control efforts.

Furthermore, this model could position the laboratory to expand its scope to other essential medicines,

addressing broader public health challenges while fostering long-term capacity building. Combining these efforts with targeted public awareness campaigns and low-cost screening devices would reinforce the regulatory framework and improve adherence to pharmaceutical standards nationwide.

Package appearance inspection alone has proven inadequate for detecting falsified medicines. This study demonstrates the need for integrating low-cost medicine screening devices into regulatory processes to enable systematic quality assessment of medicines. These screening tools would serve as an initial filter to identify products requiring confirmation through pharmacopeial methods, using equipment such as the HPLC system, which is regarded as the 'gold standard'. This two-tier approach would enhance detection efficiency while optimising the use of advanced analytical resources.

Limitations of the study

Limited funding for resources, expertise and equipment poses a significant challenge to monitoring antimalarial quality, especially in resource-constrained settings like EG. In spite of this limitation, the findings from this study support increased surveillance and regulatory action by the MOHSW. In order to assure medicine quality and protect the public's health, a review and revision of the national policy standards for the authorisation and approval of medicine use and importation is strongly recommended. Increased regulation of medicine quality at pharmacies and informal medicine outlets is needed.

CONCLUSION

The prevalence of SF antimalarials in EG has increased from 9% in 2013 to 59.5% in 2018. Most falsified samples were purchased from pharmacies across both regions, with mainland areas showing higher rates than Bioko Island. The continued availability of AS monotherapy tablets and widespread poor-quality medicines undermines national malaria control efforts, potentially contributing to drug resistance. This comprehensive follow-up study expands our understanding by including mainland regions and analysing non-artemisinin antimalarials, providing critical evidence for targeted interventions. Urgent regulatory reform is needed to strengthen medicine quality monitoring,[33] particularly in the private sector where most patients seek treatment despite free options in public facilities.

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