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Quality of antiepileptic drugs in sub-Saharan Africa: A study in Gabon, Kenya, and Madagascar

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Summary

Objective—Epilepsy is a major public health issue in low- and middle-income countries, where the availability and accessibility of quality treatment remain important issues, the severity of which may be aggravated by poor quality antiepileptic drugs (AEDs). The primary objective of this study was to measure the quality of AEDs in rural and urban areas in 3 African countries.

Methods—This cross-sectional study was carried out in Gabon, Kenya, and Madagascar. Both official and unofficial supply chains in urban and rural areas were investigated. Samples of oral AEDs were collected in areas where a patient could buy or obtain them. Pharmacological analytical procedures and Medicine Quality Assessment Reporting Guidelines were used to assess quality.

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Disclosure

The authors declare that they have no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Results—In total, 102 batches, representing 3782 units of AEDs, were sampled. Overall, 32.3% of the tablets were of poor quality, but no significant difference was observed across sites: 26.5% in Gabon, 37.0% in Kenya, and 34.1% in Madagascar ($P = .7$). The highest proportions of substandard medications were found in the carbamazepine (38.7%; 95% confidence interval [CI] 21.8-57.8) and phenytoin (83.3%; 95% CI 35.8-99.5) batches, which were mainly flawed by their failure to dissolve. Sodium valproate was the AED with the poorest quality (32.1%; 95% CI 15.8-42.3). The phenobarbital (94.1%; 95% CI 80.3-99.2) and diazepam (100.0%) batches were of better quality. The prevalence of substandard quality medications increased in samples supplied by public facilities (odds ratio [OR] 9.9; 95% CI 1.2-84.1; $P < .04$) and manufacturers located in China (OR 119.8; 95% CI 8.7-1651.9; $P < .001$). The prevalence of AEDs of bad quality increased when they were stored improperly (OR 5.4; 95% CI 1.2-24.1; $P < .03$).

Significance—No counterfeiting was observed. However, inadequate AED storage conditions are likely to lead to ineffective and possibly dangerous AEDs, even when good-quality AEDs are initially imported.

Keywords

antiepileptic drugs; developing countries; drug quality; epilepsy

1 Introduction

Epilepsy is a chronic neurologic disorder affecting more than 70 million people worldwide. Nearly 80% of people with epilepsy live in low- and middle-income countries (LMICs).¹ Primary health care is limited in LMICs, where the availability and accessibility of antiepileptic drugs (AEDs) remain important issues.² This is particularly relevant in rural areas. Poor-quality AEDs aggravate this problem, but few studies have examined this issue. Two studies have shown that the proportions of poor-quality drugs (“genuine drug products that do not meet the quality specifications set for them”) ranged from 14% (for phenobarbital in Mauritania) to about 65% (for major AEDs in Viet-nam).^{3,4} A recent counterfeiting (“deliberately and fraudulently mislabeled, may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging”) alert has been issued for phenobarbital in Guinea-Bissau and Nigeria.⁵

Consistent drug quality is ensured by the performance of stability studies and the establishment of an expiration date under specific storage conditions. These studies consider the influence of environmental factors (temperature, relative humidity [RH], and light) and the duration of storage in the area where the drug is supplied. The World Health Organization (WHO) provides guidelines for storing pharmaceutical products in tropical areas.⁶ The WHO proposed categorizing tropical areas into the following climate zones: (1) dry and hot climates (stability at 30°C and 35% RH); (2) hot and humid climates (30°C and 65% RH); and (3) hot and very humid climates (30°C and 75% RH). Storage outside these limits is unfavorable and may damage the quality of the medicines, leading them to be ineffective or dangerous. In many LMICs, a common practice is to unpack supplied tablets/capsules with only primary packaging (eg, blister packs). Even aluminum blisters are not completely effective at protecting drugs stored under inadequate conditions.^{7,8} Previous

studies on the quality of AEDs have focused on 1 country,^{3,4} and differing methods of analysis and sampling have complicated comparisons of results. To our knowledge, differences in AED quality between urban and rural areas have not been investigated. Thus, the primary objective of this study was to measure the quality of AEDs provided through various supply chains, including official and illegal AED dispensary structures. The secondary objective was to identify the variables (climatic, storage, and manufacturing origin) associated with AED quality. An ancillary study was also performed to assess the specific role of the climatic conditions representative of sub-Saharan Africa on the quality of AEDs.

2 Methods

2.1 Settings

This was a multicenter study carried out in 3 countries (Gabon, Kenya, and Madagascar) using identical data and sample collection protocols. Both rural and urban AED dispensary structures were included, and efforts were made to collect samples from both formal and informal structures. The structures were classified as public facilities (eg, public hospitals), registered private for-profit facilities (eg, private pharmacies, clinics, supermarkets), and informal facilities and facilities outside the approved distribution chain (eg, kiosks, street sellers, street markets, grocery shops).

2.2 Inclusion criteria

All drugs belonging to the N03 Anatomical Therapeutic Chemical group (antiepileptic) in the WHO Collaborating Center for Drug Statistics Methodology classification system and registered in the 19th WHO essential medicines list were considered. Only solid oral pharmaceutical forms were collected, and the packaging, when present, was also collected.

2.3 Endpoints

Each pharmaceutical product produced by manufacturers has to comply with the quality standards and specifications required by the territory of use at release and throughout its product shelf-life. These standards include only 2 categories: good quality (all tests satisfied) and bad quality (the results of at least 1 test do not meet the relevant specification). The following standard tests are used to categorize each product: mass uniformity, homogeneity of appearance and organoleptic features, identification and assay of the active ingredient (AI), impurity screening, dissolution test, and a friability test (only for uncoated tablets). We designed several subcategories to increase precision according to the type of issue identified and developed a degree-of-quality scale (Figure 1). When the correct AI was not detected, the sample was considered counterfeit. When the issue identified concerned the quality of the content (quantity of active ingredient, presence or not of an impurity), the sample was considered “substandard with poor quality content.” When the issue concerned the performance features, including the absorption and distribution phases of a drug, the sample was considered “substandard with poor pharmaceutical technical features.”

At times, due to an availability issue in LMICs, there was not a sufficient number of units (tablets/capsules) to perform all analytical tests; therefore analyses were prioritized as

follows: (1) identification and assay of the AI and screening of impurities; (2) dissolution/disintegration; and (3) friability. If the sample complied with all tests performed, the sample was classified in the “good-quality-with-caution” category.

The overall raw quality result was dichotomized into the 2 main categories of good (combining categories of good quality with caution and good quality) (Figure 1) and poor quality (both substandard categories and bad quality).

The WHO guidelines were used to assess the quality of the packaging and the quality of the patient leaflet.^{9,10} Data on climatic conditions were recorded daily during the month prior the sampling phase by the climate and research department of Météo-France. Data on storage conditions were collected for each delivery structure through a questionnaire completed by the investigator. These data were compared to a reference mentioned in the WHO guidelines.⁶

2.4 Sampling method

Public and private systems from the official supply chain in the urban and rural settings of the included countries were considered. Facilities from all health levels (primary level [center of primary health care, primary point of contact for patients with a health professional], secondary [district referral hospital, the first-level hospital of a district or a defined geographic area containing a defined population], and tertiary [general and specialized hospitals]) were investigated. Due to the difficulty of identifying the number and location of informal providers, we used a convenience sampling design for these systems in urban and rural settings (kiosks, street sellers, street markets, and grocery stores) based on information from people familiar with the setting.

2.4.1 Urban setting—A study area was considered urban when it was a developed location and autonomous in terms of health services. The political and/or economic capital of the country served as the urban study area. All hospitals (secondary and/or tertiary) and other types of public facilities (dispensaries and depots) where a drug was supplied to a patient were sampled in the public system. All hospitals (clinics) able to provide a drug supply for outpatients were investigated in the private system. A random selection of 6 pharmacies from a list of official and registered facilities was sampled.

2.4.2 Rural settings—A study area was considered rural when it was located outside a city or metropolitan district and was underdeveloped in terms of infrastructure and specialized services. All accessible facilities dispensing AEDs were investigated in rural areas.

Sampling comprised 2 stages performed on the same day by 2 investigators (*A* and *B*). Stage 1 consisted of collecting the AED, which was performed by investigator *A* posing as a patient. At this stage, the seller/owner of the facilities was unaware that the purchase was for a study. In stage 2, data on the variables of interest were collected by investigator *B* using a structured questionnaire.

The sampling of informal structures was performed by investigator A, who posed as a patient without a prescription and asked the seller if “they have something to treat epilepsy, such as carbamazepine, sodium valproate, phenytoin, phenobarbital, or whatever you have to treat this disease.”

A sample (statistical unit) corresponded to an item collected at a specific collection site, and each unit (tablets/capsules) of a sample was from the same manufacturing batch. This meant that the same product (same name, AI, strength, and batch and produced by the same manufacturer) collected from 2 different sites represented 2 different samples.

Samples were purchased by box. A quantity of 100 units per sample was purchased when AEDs were sold in bulk or a refill formulation. When this quantity was not achievable (due to an availability issue or ethical considerations related to avoiding zero stock), a minimum of 20 units per sample was purchased.

2.5 Analytical testing

All analyses were performed in France in a WHO prequalified laboratory. All samples were considered for analysis. Assays were performed by high-performance liquid chromatography (HPLC, Alliance, 2695, Waters, Milford, MA, USA) with diode array detection (DAD, Waters 2996). Pharmacopoeias (British, BP 2015; American USP38 and 39; International Pharmacopoeia 5th edition) were used as references for all samples. The manufacturer’s analytical procedure was used for the sodium valproate film-coated scored, modified-release tablets. Standardized pharmaceutical tests (mass uniformity, dissolution, disintegration, and friability) were performed according to the European Pharmacopoeia, 8th edition, 2014. Unknown impurities were identified using high-resolution mass spectrometry with a liquid chromatography/quadrupole Orbitrap mass spectrometer, tandem mass spectrometry (Thermo Fisher Scientific, Scoresby, Australia), and/or 1/2-dimensional nuclear magnetic resonance (NMR Bruker Avance 500MHz, Bruker BioSpin GmbH, Rheinstetten, Germany).¹¹

Samples included in the ancillary study were those with out-of-specification (OOS) parameters: deviation(s) of parameters compared to predetermined compendial acceptance criteria on an AI assay and/or on a dissolution test. Samples and authorized drugs for export used as reference products were exposed to stress conditions for 3 months: (1) 45°C + 75.0% RH; and (2) 45°C + 99.9% RH in a climatic chamber (Memmert HP108, Schwabach, Germany) with and without primary packaging. AI assays (HPLC-DAD; Thermo Scientific Dionex Ultimate 3000, Thermo Fisher Scientific), dissolution, disintegration tests, and chemical stability (studied by total attenuated reflection-Fourier transform infrared spectroscopy [ATR-FTIR, Spectrum 65 FT-IR module ATR, Perkin Elmer, Villepinte, France] and differential scanning calorimetry [DSC 822, Mettler Toledo Greifensee, Switzerland]) were performed at T0 (baseline) and at 1- (T1) and 3- (T3) month intervals.

Data cleaning and the processing of variables were performed using Stata version 14.1 (StataCorp, College Station, TX, USA). Data were stored on secure servers at Limoges University. Proportions, means, standard deviations, and 95% confidence intervals (CIs) were used for the descriptive analysis. The chi-square and Fisher’s exact tests (when

appropriate) were used for inferential analyses. Bivariate and multivariate analyses were performed using multinomial logistic regression (the dependent variable was a nominal variable with 5 categories) to quantify the strength of the association between the independent variables and the dependent variable (drug quality). The final model was obtained by backward stepwise regression. The independent variables included in the initial model of the multivariate analysis were those with a $P < .25$ in the bivariate analysis. The significance level was fixed at 5% in the final model.

This study received approval from the ethics boards of the 3 African countries that participated in this study as part of their ongoing epilepsy studies. All samples shipped to France received authorization for importation from the French National Security Agency of Medicines and were declared to customs. The MEDQUARG (Medicine Quality Assessment Reporting Guidelines) statement was used as a guide to report this study.¹²

3 Results

In total, 102 batches of AEDs were sampled, representing 3782 units (Table 1).

3.1 Gabon

Only the urban area (Libreville) was evaluated due to the inaccessibility of the rural study area during field operations. Thirty-four batches were sampled. The main public hospital did not have any AEDs. Several of the 19 different unofficial points of sale were investigated, but none sold AEDs. One (5%) had proposed a combination of ibuprofen-caffeine-paracetamol to treat epilepsy.

3.2 Kenya

Twenty-seven batches were collected. The urban area was Mombasa, where 22 batches were sampled. The rural area was the district of Kilifi, where 5 batches were collected.

3.3 Madagascar

Forty-one batches were sampled. The urban area was Antananarivo, where 24 batches were collected. The rural area was the region of Bongolava, where 16 batches were collected.

3.4 Results of the quality

Overall, 32.3% (95% CI 23.4-42.3) of the AEDs were of poor quality, but no significant difference was observed across sites: 26.5% in Gabon, 37.0% in Kenya, and 34.1% in Madagascar; $P = .7$; Table 2. No counterfeit drugs were found in the present study.

The carbamazepine (CBZ) (38.7% [95% CI 21.8-57.8]) and phenytoin (PHY) (83.3% [95% CI 35.8-99.5]) batches had the highest proportion of substandard quality samples, mainly due to failure to dissolve. The batch of sodium valproate (VPA) had the poorest quality, with failed tests for both the content and the pharmacotechnical categories (32.1%; 95% CI 15.8-52.3). The phenobarbital (PB) (94.1%; 95% CI 80.3-99.3) and diazepam (DZ) (100.0%) batches were of better quality (Table 2).

The good-quality AEDs were from Africa (Senegal, Madagascar, and Kenya) (90.0%), the European Union (EU) (64.6%), India (38.1%), or China (23.1%). Substandard AEDs were found in 5% of samples in Africa, in 9.5% of samples in India, in 12.5% of samples in the EU, and in 76.9% of samples in China. Bad-quality AEDs were not found in any of the samples from Africa or China and in 14.3% of the samples from India and 22.9% of the samples from the EU. Samples categorized as good with caution due to insufficient units for complete analyses accounted for 5.0% of samples manufactured in Africa and 38.1% of samples manufactured in India.

In each study area, the average RH was above the threshold of 65% recommended by the WHO (each country belonged to WHO category IV A [30°C/65% RH]), ranging from 70% ($\pm 5.4\%$) in Madagascar to 80% ($\pm 14.5\%$) in Kenya and 85% ($\pm 9.7\%$) in Gabon. The temperature threshold of 30°C was surpassed only in Gabon and Kenya, where it exceeded the daytime maximum (Gabon: 31.7 [± 2.2]; Kenya: 27.7 [± 4.9] in Mombasa and 28.0 [± 5.0] in Kilifi).

VPA (32.1%) had the worst quality of samples exposed to over 65% RH. PHY (83.3%) and CBZ (38.7%) had the poorest dissolution properties.

All samples sold from Gabon conformed to primary and secondary packaging standards. The AEDs in 100% of samples from Kenya and 24% of samples from Madagascar were sold without secondary packaging. In Kenya, 22% (6) of the samples were sold without any packaging.

In Gabon, 100% (34) of the samples were sold with an appropriate leaflet in French. In Kenya, none of the samples was sold with a leaflet. In Madagascar, 58% of the samples were sold with an appropriate patient leaflet in French.

The multinomial logistic regression determined that the prevalence of substandard quality AEDs was increased in those supplied by public facilities (OR 9.9; 95% CI 1.2-84.1; $P < .04$) and those manufactured in China (OR 119.8; 95% CI 8.7-1651.9; $P < .001$). The prevalence of bad-quality AEDs increased when the drugs were exposed to an uncontrolled atmosphere (OR 5.4; 95% CI 1.2-24.1; $P < .03$). No difference in AED quality was observed between urban and rural sites. Furthermore, AED quality was not associated with the presence or absence of packaging, exposure to dust or moisture, or origin in an informal structure.

3.5 Environmental factors

3.5.1 Carbamazepine—Analyses were performed on 8 batches of 200-mg CBZ manufactured in China and India and compared to a reference sample manufactured in the EU and purchased directly from the factory without an intermediary.

Influence on content features: Assays of the AI were successful for all samples, and no chemical degradation was observed among T0, T1, and T3. ATR-FTIR spectrum and DSC thermograms at T0 for all samples showed the presence of the anhydrous polymorphic form

III of CBZ. A dihydrate polymorphic form was detected in samples from China and India at T1 and T3 but not in the reference product.

Influence on pharmacotechnical features: Breaks in the coating shell of tablets without packaging and red/brown spots on uncoated tablets with and without packaging were observed. Figure 2 highlights the dissolution profiles of the reference product and 5 samples that failed the dissolution test (3 samples manufactured in India were not assessed for dissolution because of a lack of quantity). The dissolution profile was unsatisfactory in all samples from India and China. At 20 minutes, the average dissolution rate ranged from -31.2% (± 14.0 ; max: -48.6) of the lowest limit of the acceptance criteria threshold for samples exposed to 75% RH during 3 months to -98.5% at 99.9% RH. The final proportion of AI released at 60 minutes ranged from 3.2% to 73.3% for all batches (United State Pharmacopeia min. 75%).

3.5.2 Sodium valproate—Analyses were performed on 14 batches of 200-mg VPA and 10 batches of 500-mg VPA enteric-coated (manufactured in the EU and India) and compared to a reference sample manufactured in the EU and purchased directly from the factory without an intermediary.

Influence on content features: Assays of AIs were successful in all samples, and no chemical degradation products were observed at T0, T1, and T3.

Influence on pharmacotechnical features: After 2 days without packaging, the pill coating of all samples cracked and melted at 45°C and 75.0% RH. All VPA samples were enteric-coated; hence, the disintegration test was performed under 2 conditions (acidic: hydrochloric acid solution, 0.1 mol/L; buffer: pH 6.8 ± 0.5). The results showed a loss of enteric resistance in 200-mg VPA after only 10 days of exposure.

3.5.3 Phenytoin—Analyses on PHY with OOS samples were not possible due to lack of sufficient samples gathered at the sites.

4 Discussion

This study revealed that nearly one-third (32.3%) of AEDs sampled in 3 sub-Saharan African countries were of poor quality. The overall substandard prevalence was estimated to be 22.6% (corresponding to the sum of poor-quality plus substandard-with-poor-pharmacotechnical features). In contrast to Otte⁵ in Guinea Bissau and Nigeria, no counterfeit samples were detected, probably because the size of the AED market in Africa renders it unimportant and because of the stigma and underdiagnosis of epilepsy in these countries. The quality of available, affordable, and accessible drugs, which relates to their efficacy and safety, should be considered when measuring the treatment gap. Indeed, an AED that is ineffective due to its poor quality is almost worse than an unavailable or inaccessible efficient AED. Poor-quality AEDs likely exacerbate the already high treatment gap found in many sub-Saharan African countries, where traditional, alternative treatments for epilepsy are often present. Long-term exposure to poor-quality AEDs may result in a

lack of confidence in biomedical pharmaceuticals, potentially causing a reduction in adherence and leading a person with epilepsy to turn to alternative treatments.

The PB batch had the best quality, with no poor-quality drugs and only 5.9% with substandard quality. This was less than the proportion of 13.7% found by Laroche³ in Mauritania in 2005, who found primarily underdosed samples. AEDs manufactured locally in Africa had better quality than AEDs manufactured in China and India. These results support the local production of AEDs and efforts to dispel locally held beliefs that drugs manufactured in the EU are of higher quality (resulting in the fraudulent labeling of drugs produced locally as manufactured in the EU).

In several instances, AED quality was satisfactory for the AI assay; however, the tablet properties that condition the *in vivo* behavior (release of correct amount of the active ingredient, correct kinetics, and correct site in the gastrointestinal tract) are also important. CBZ and VPA had the most issues in this regard. In Gabon, with its equatorial monsoon climate (Köppen-Geiger classification¹³), the VPA samples were unsealed, although sold with the primary packaging and polypropylene tube with a desiccant. We found the highest proportion of poor-quality samples in Kenya (tropical savannah climate). Unpacking was a common practice in Kenya and might be the main cause for deterioration. Exposure to the atmosphere diminishes quality, probably by accelerating oxidation and/or overexposure to humidity. Madagascar has a warm temperate climate with a dry winter, and sampling was performed during winter.

An oral drug can produce its pharmacological effects only if it reaches the sites of action. The AI must reach the bloodstream after passing through the digestive wall. This passage and transport can be done only when the AI is dissolved. The high frequency of substandard CBZ was likely caused by various manufacturing processes and the sensitivity of the oral formulation to RH. The stress study confirmed that CBZ tablets may be unable to correctly release the AI. The modified dissolution behavior might be due to the polymorphism of CBZ.^{14,15} In 2000, Kobayashi¹⁶ showed significant differences between the areas under the curve (AUCs) of different polymorphs, with the lowest AUC for the dihydrate. Thus, the presence of the dihydrate modifies dissolution, which might disturb release of the AI in the gastrointestinal tract. In 1999, Lake¹⁷ showed *in vitro*/*in vivo* correlations of CBZ tablet dissolution data with *in vivo* pharmacokinetic data. The proportion of the AI released after 20 minutes was correlated with the C_{max} and $AUC_{0-\infty}$ of CBZ, with a correlation coefficient of .99. Our study showed that none of the batches manufactured in China and India complied with the pharmacopoeias' specifications at 20 minutes. The consequence was a bio-inequivalence between drug batches or between generic and originator drugs.

Issues concerning the coating of VPA also remain problematic. The bioavailability of enteric-coated tablets is similar to that of regular tablets.¹⁸ However, peak plasma levels occur at 1-2 hours for regular tablets compared to 3-8 hours for enteric-coated tablets.^{19,20} A loss of coating may change the absorption of VPA, with fluctuations in levels of the drug in the blood, which may ultimately impact its effectiveness and tolerability. Storage without temperature and humidity controls and unpacking are practices leading to improper and dangerous drugs, especially in hot and humid climates, such as much of sub-Saharan Africa.

The possible clinical consequences of these findings can be illustrated by the pharmacokinetic properties of disturbance and heterogeneity. Most of the older-generation AEDs are far from ideal in terms of pharmacokinetics and interaction potential (eg, PHY, CBZ, and VPA have nonlinear kinetics). Hence, substandard issues dramatically worsen the picture and are as dangerous as deliberately falsified drugs.²¹ To our knowledge, no study has assessed the quality of AEDs in Western Europe or North America. In addition, there is a scarcity of data on the stability of AEDs over time and under tropical conditions. However, several studies have found similar results reflective of medications that are unstable and potentially unsuitable for use in tropical conditions, including due to improper attitudes and supply and storage practices. A review by Johnston reported that half the generic versions of ramipril tablets were substandard after 3 months of storage under temperature-stressed conditions (40°C and 75% RH).²¹ The same result was reported with use of the generic version of tacrolimus, which was associated with a higher rate of acute kidney rejection, as well as with the use of antibiotics and antimalarial and antineoplastic agents, which failed accelerated stability tests, leading to increased morbidity and mortality.²¹

According to the pharmaceutical sector country profile published by the WHO, a marketing authorization is needed to import AEDs into each country. Local manufacturers are approved in Kenya and Madagascar but not in Gabon. Public sector procurement is both centralized and decentralized. The government pharmaceutical supply system has a central medical store at the national level and public warehouses at secondary levels of the public-sector distribution network. National guidelines on Good Distribution Practices (GDP) have been produced, but there is no licensing authority that issues GDP licenses. Hence, a list of GDP-certified wholesalers and distributors in the public and private sectors does not exist. Medicine quality control laboratories (QCL) to control finished pharmaceutical products are available in Madagascar (n = 1) and Kenya (n = 2) but not in Gabon. The QCLs adhered to the WHO Good Practices (GP) for QCL only in Kenya. The sampling of imported drugs is authorized in the 3 countries, but only the public market is monitored in Kenya and Madagascar, and the results have not been published. Findings from this study suggest the need to invest resources in monitoring several cross-sectional parts of the supply chain, including the end. Our findings suggest that storage and distribution practices are particularly critical points, especially in the context of high temperature and RH.

The main limitation of this study was its cross-sectional design, which provided only a snapshot of the situation. Indeed, the results may have differed if another time-frame were chosen. No causal inferences about the effects of variables on AED quality could be established with this type of study design. Degradation may have occurred during the period between sampling in Africa and analysis in France. To minimize the impact of this confounder, the time between the sampling phase and the analysis was reduced as much as possible. In addition, samples were cautiously packed and stored in a closed temperature-controlled location before shipment to France. Another limitation was the difficulty checking the relevance of the drug package label (if present) with regard to manufacturing origin. The number of samples in each country was small mainly due to the low availability of AEDs in the study areas. In consideration of the wide geographical dispersion of the collection sites, a multisite cluster sampling design was developed to produce as representative a sample as possible of the situation in sub-Saharan Africa. The intracluster

variance was important (high variability of AED availability, manufacturers, strengths, and batch numbers were noted between structures).

This study had several strengths, including its multi-country comparison, which provided a more robust picture of the AED quality situation in sub-Saharan Africa. The choice of countries included in this study was made with the aim of representing the diversity of sub-Saharan Africa, but the 3 countries that participated in this study likely do not represent the subregion. In particular, the following criteria were considered when selecting the countries for this study: socioeconomic level (Madagascar is a low-income country; Kenya is a lower-middle-income country; Gabon is an upper-middle-income country); climatic conditions (Gabon has an equatorial climate [hot and wet throughout the year]; Kenya and Madagascar have a tropical climate composed of 2 seasons: a wet season [hot and humid] and a dry season [cold and dry]); the organization of the health system (Kenya is an English-speaking country in eastern Africa; Gabon is a French-speaking country in central Africa, Madagascar is a French-speaking islandic country in eastern Africa); and the state of the trade regimes and regional economic communities according to the United Nations (Gabon belongs to the Economic Community of Central African States; Kenya belongs to the East African community, COMESA—Common Market for Eastern and SADC—Southern Africa and Southern African Development Community, the Intergovernmental Authority on Development, and the Community of Sahel-Saharan States; and Madagascar belongs to the COMESA). A standard methodology of data collection was employed, and the laboratory used for analysis was robust and followed worldwide recommended guidelines. Temperature and RH were ascertained from multiple recordings during the month prior to sampling the AEDs and were provided by the French national monitoring weather center, which collaborates with international weather monitoring centers. This approach provided a relevant picture of the atmospheric exposure of the samples.

5 Conclusion

The inadequate storage conditions, including a lack of temperature and RH controls of AEDs are likely to lead to ineffective and dangerous medications, even when good-quality AEDs are initially imported. The adverse consequences of inadequate storage are likely compounded under conditions characterized by high temperature and varying RH, such as those in much of sub-Saharan Africa. Efforts to raise awareness about the quality of AEDs in these settings are needed.

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References

1. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*. 2010; 51:883–90. [PubMed: 20067507]
2. Newton CR, Garcia HH. Epilepsy in poor regions of the world. *Lancet*. 2012; 380:1193–201. [PubMed: 23021288]
3. Laroche M-L, Traore H, Merle L, et al. Quality of phenobarbital solid-dosage forms in the urban community of Nouakchott (Mauritania). *Epilepsia*. 2005; 46:1293–6. [PubMed: 16060942]
4. Mac TL, Gaulier J-M, Le VT, et al. Quality of antiepileptic drugs in Vietnam. *Epilepsy Res*. 2008; 80:77–82. [PubMed: 18434092]
5. Otte WM, van Diessen E, van Eijsden P, et al. Counterfeit antiepileptic drugs threaten community services in Guinea-Bissau and Nigeria. *Lancet Neurol*. 2015; 14:1075–6.
6. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report. Geneva: World Health Organization; 2009. Annex 2 (WHO Technical Report series, No. 953)
7. Ballereau F, Prazuck T, Schrive I, et al. Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. *Am J Trop Med Hyg*. 1997; 57:31–6. [PubMed: 9242314]
8. Yang D, Plianbangchang P, Visavarungroj N, et al. Quality of pharmaceutical items available from drugstores in Phnom Penh, Cambodia. *Southeast Asian J Trop Med Public Health*. 2004; 35:741–7. [PubMed: 15689098]
9. Guidelines on packaging for pharmaceutical product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva: World Health Organization; 2002. Annex 9 (WHO Technical Report series, No. 902)
10. Guidance on package leaflet. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Summary of product characteristics and labelling. Geneva: World Health Organization; 2002. Annex 2 (WHO Technical Report series, No. 902)
11. Durand S, Sancelme M, Besse-Hoggan P, et al. Biodegradation pathway of mesotrione: complementarities of NMR, LC-NMR and LC-MS for qualitative and quantitative metabolic profiling. *Chemosphere*. 2010; 81:372–80. [PubMed: 20692682]
12. Newton PN, Lee SJ, Goodman C, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med*. 2009; 6:e52. [PubMed: 19320538]
13. Kottek M, Grieser J, Beck C, et al. World Map of the Köppen-Geiger climate classification updated. *Meteorol Z*. 2006; 15:259–63.
14. Krahn F-U, Mielck J-B. Relations between several polymorphic forms and the dihydrate of carbamazepine. *Pharm Acta Helv*. 1987; 2:247.
15. McMahon L-E, Timmins P, Williams A-C, et al. Characterization of dihydrates prepared from carbamazepine polymorphs. *J Pharm Sci*. 1996; 85:1064–9. [PubMed: 8897272]
16. Kobayashi Y, Ito S, Itai S, et al. Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. *Int J Pharm*. 2000; 193:137–46. [PubMed: 10606776]
17. Lake O-A, Olling M, Barends D-M. In vitro/in vivo correlations of dissolution data of carbamazepine immediate release tablets with pharmacokinetic data obtained in healthy volunteers. *Eur J Pharm Biopharm*. 1999; 48:13–9. [PubMed: 10477323]
18. Klotz U. Bioavailability of a slow-release preparation of valproic acid under steady-state conditions. *Int J Clin Pharmacol Ther Toxicol*. 1982; 20:24–6. [PubMed: 6799412]
19. Gugler R, Schell A, Eichelbaum Y, et al. Disposition of valproic acid in man. *Eur J Clin Pharmacol*. 1977; 12:125–32. [PubMed: 336377]
20. Albright P, Bruni J, Suria D. Pharmacokinetics of enteric-coated valproic acid. *Ther Drug Monit*. 1984; 6:21–3. [PubMed: 6424275]
21. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *Br J Clin Pharmacol*. 2014; 78:218–43. [PubMed: 24286459]

Key Points

- The burden of epilepsy in low- and middle-income countries is still high; availability and accessibility of antiepileptic drugs (AEDs) are critical, and complicated by poor drug quality
- The analysis of 3782 AEDs gathered from 3 sub-Saharan African countries, revealed that 32.3% of AEDs were of poor quality
- Improper storage without temperature and humidity control and unpacking practices generate improper and possibly dangerous drugs

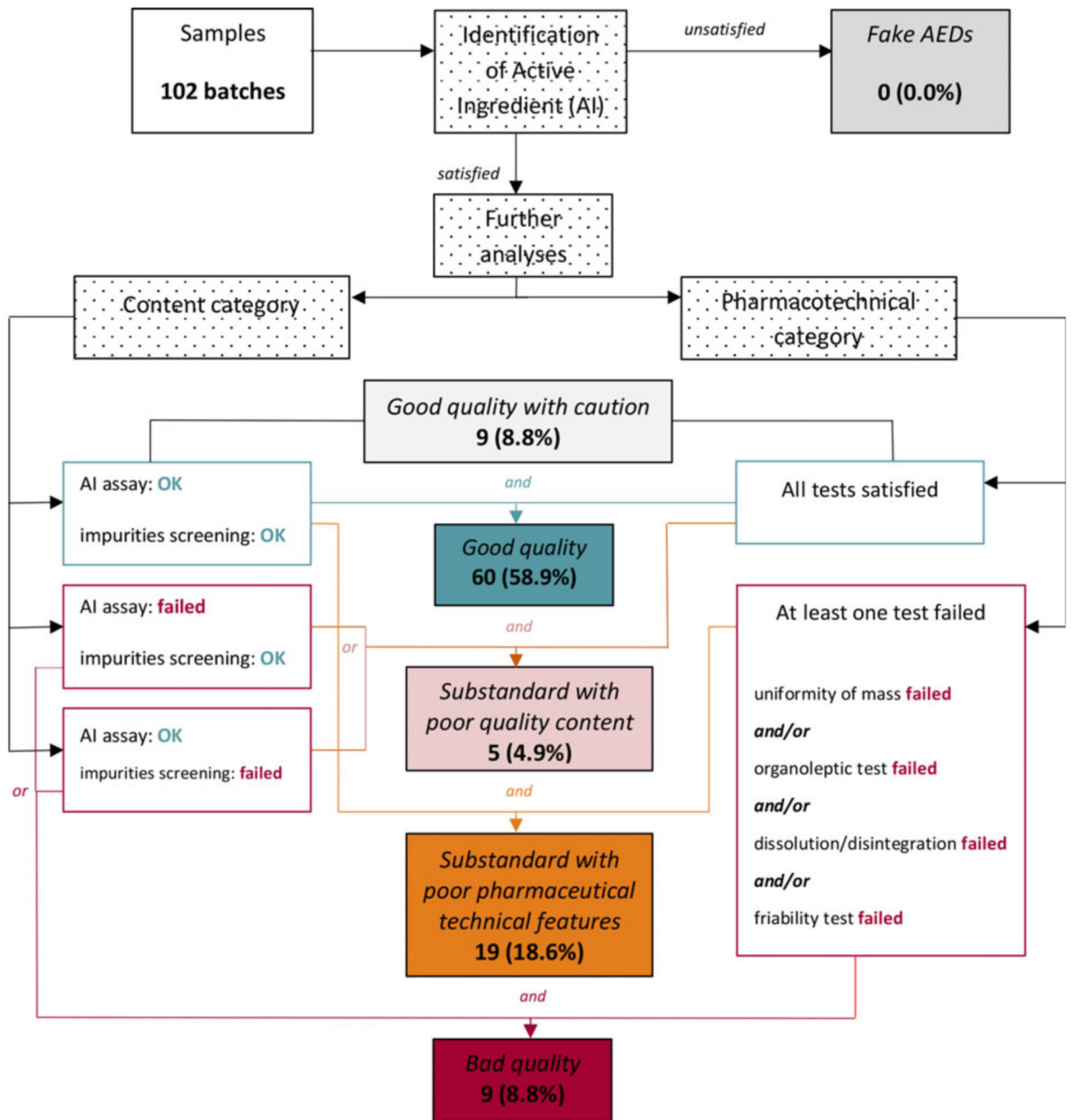


Figure 1.
Quality degree scale

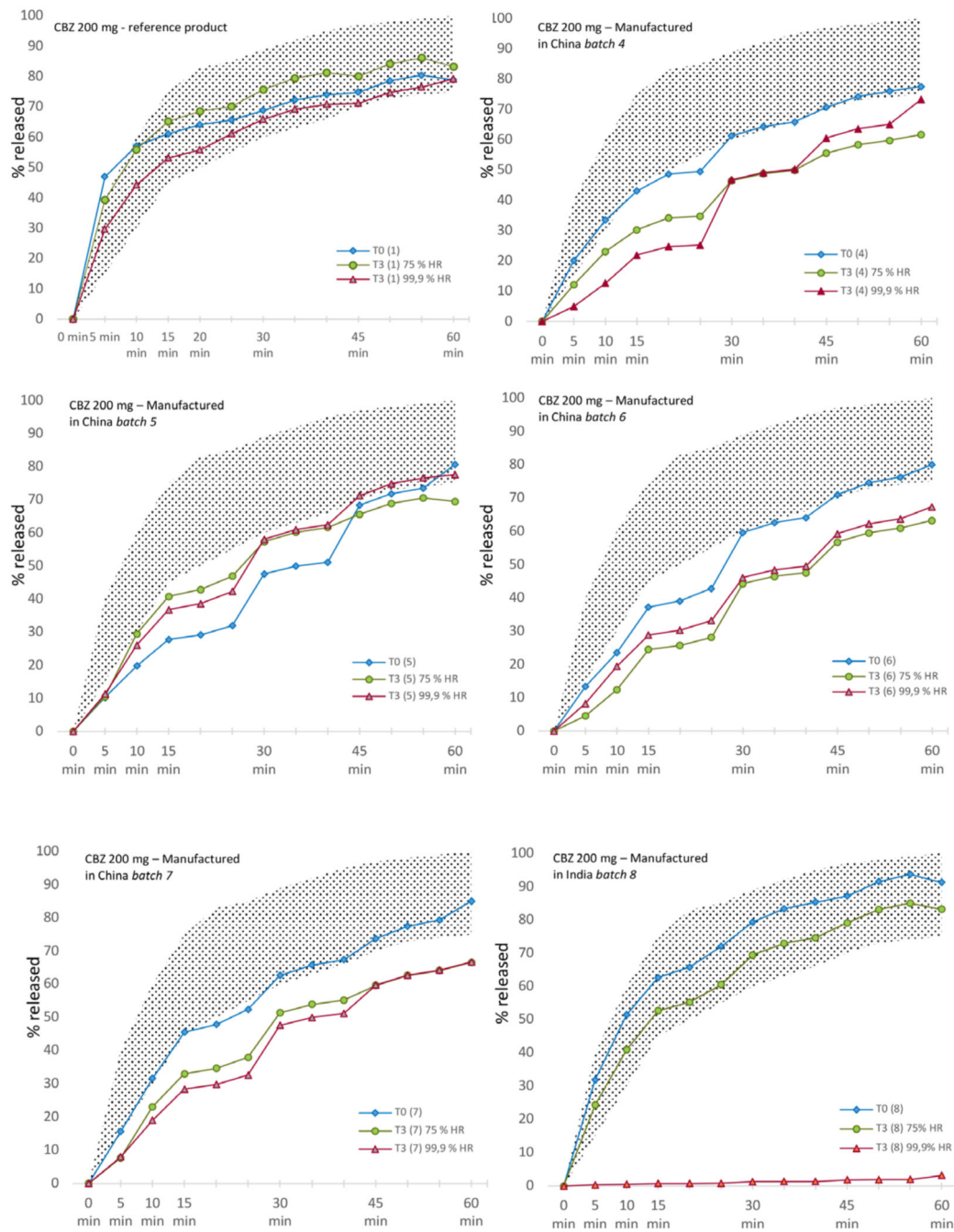


Figure 2. Dissolution profiles of sample of carbamazepine (CBZ) 200 mg at T0, T3 exposed to 45°C and 75% relative humidity (RH), T3 exposed to 45°C and 99.9% RH

Table 1
Description of the sampling by type of delivery structure investigated

	Type of outlets	CBZ		VPA		PHY		PB		DZ		Total		%
		N batches	N tablets	N batches	N tablets	N batches	N tablets	N batches	N tablets	N batches	N tablets	N batches	N tablets	
Public	Public hospital	2	120	3	80	1	10	3	100			9	310	9
	Primary health center							3	100			3	100	3
Private	Private hospital	2	40	2	40	1	20	2	40			7	140	7
	Pharmacy	20	790	19	670	3	99	19	840	3	90	64	2489	63
	Pharmaceutical depot	4	50					2	50			6	100	6
	Illicit point of sale	3	150	4	123	1	20	5	350			13	643	13
	Total	31	1150	28	913	6	149	34	1480	3	90	102	3782	100
Country (number of outlets investigated)														
	Gabon (26)	7	260	11	400	1	60	12	630	3	90	34	1440	33
	Kenya (18)	8	160	6	103	5	89	8	160			27	512	26
	Madagascar (31)	16	730	11	410			14	690			41	1830	40
	Total (75)	31	1150	28	913	6	149	34	1480	3	90	102	3782	100

CBZ, carbamazepine; VPA, sodium valproate; PHY, phenytoin; PB, phenobarbital; DZ, diazepam.

Table 2
Overall degree of quality by AI and by country

	Active ingredient										Country					
	CBZ		VPA		PHY		PB		DZ		Gabon		Kenya		Madagascar	
	%	N batches	%	N batches	%	N batches	%	N batches	%	N batches	%	N batches	%	N batches	%	N batches
Good quality	58.0	18	50.0	14	16.7	1	70.6	24	100.0	3	73.5	25	63.0	17	43.9	18
Substandard with poor quality content			17.9	5							14.7	5				
Substandard with poor pharmacotechnical features	38.7	12			83.3	5	5.9	2					18.5	5	34.1	14
Good quality with caution	3.3	1					23.5	8							22.0	9
Bad quality			32.1	9							11.8	4	18.5	5		
N total		31		28		6		34		3		34		27		41

CBZ, carbamazepine; VPA, sodium valproate; PHY, phenytoin; PB, phenobarbital; DZ, diazepam.