

Equivalence in active pharmaceutical ingredient of generic antihypertensive medicines available in Nigeria (EQUIMEDS): A case for further surveillance

Julie Redfern,^{1*} Harparkash Kaur² Rufus Adesoji Adedoyin,³ Sandra Ofori,⁴ Raghupathy Anchala,⁵ Vamadevan S Ajay,⁶ Luciano De Andrade,⁷ Jose Zelaya,⁸ Dina Balabanova,⁹ Mahmoud Umar Sani¹⁰

¹University of Sydney, Westmead Applied Research Centre, Faculty of Medicine and Health, NSW, AUSTRALIA (julie.redfern@sydney.edu.au)

²Department of Clinical Research, London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT, UK (harparkash.kaur@lshtm.ac.uk)

³Department of Medical Rehabilitation, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, NIGERIA (radedoyi@yahoo.com)

⁴Department of Internal Medicine, University of Port Harcourt and University of Port Harcourt Teaching Hospital, Rivers state, NIGERIA (sandra.ofori@uniport.edu.ng)

⁵Chest Research Foundation, Pune, India (docraghu8@gmail.com)

⁶Public Health Foundation of India (PHFI), 4th Floor, Plot No-47, Sector-44, Gurgaon, Haryana, INDIA – 122002 (ajay.vs@phfi.org)

⁷Department of Medicine, State University of Maringa, 1590, Mandacaru avenue, Block S05 - Room 10 - University Hospital. ZIP CODE: 87080-000 - Maringá-PR / BRAZIL (luc.and1973@gmail.com)

⁸Peruvian Society of Hypertension; Jr.Sagitario A-30 Lt-45.Urb.Sagitario.Surco.Lima, PERU (joselucianozelaya@gmail.com)

⁹Department of Global Health & Development London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, ENGLAND (Dina.Balabanova@lshtm.ac.uk)

¹⁰Department of Medicine, Bayero University Kano & Aminu Kano Teaching Hospital; PMB 3452, Kano 700223, Kano State, NIGERIA (musani.med@buk.edu.ng)

***Corresponding author**

Professor Julie Redfern

The University at Westmead Hospital

PO Box 154 Westmead NSW 2145

T: +61 (02) 8890 9214

E: julie.redfern@sydney.edu.au

KEY WORDS: hypertension, medications, substandard medicines, cardiovascular disease, quality of medicines, prevention

HIGHLIGHTS

- Management of hypertension can largely be achieved through availability of and adherence to qualitative evidence-based medicines. There is very little research examining the quality of anti-hypertensive medicines available in the retail market of low- and middle-income countries (LMICs).
- In total, 361 samples of Amlodipine and Lisinopril were collected from 22 pharmacies and their stated active pharmaceutical ingredient (SAPI) measured.
- More than a quarter of some commonly prescribed anti-hypertensive medicines available in Nigeria appear to be of substandard quality (samples had more or less SAPI, than stated in the United States Pharmacopeia specified tolerance, limits range).
- The proportion of substandard quality was not statistically different for Amlodipine and Lisinopril, however, significantly more samples purchased in rural compared to urban outlets were of substandard quality.
- No falsified samples (containing zero SAPI) of either Amlodipine or Lisinopril were detected.
- Enhanced quality assurance processes in LMICs such as Nigeria are needed to support effective hypertension management.

ABBREVIATIONS

ACE Inhibitors, angiotensin-converting enzyme inhibitors

API, active pharmaceutical ingredient

ARBs, angiotensin receptor blockers

BP, blood pressure

CVD, cardiovascular disease

HPLC, high performance liquid chromatography

HPLC-PDA, high-performance liquid chromatography with photodiode array detection

LGAs, local government areas

LSHTM, London School of Hygiene and Tropical medicine

NAFDAC, National Agency Food and Drug Administration and Control

SAPI, stated active pharmaceutical ingredient

US, United States

USP, United States Pharmacopeia

WHF, World Heart Federation

WHO, World Health Organization

ABSTRACT

Background: Widespread access to good quality antihypertensive medicines is a critical component for reducing premature cardiovascular disease (CVD) mortality. Poor quality medicines pose serious health concerns however, there remains a knowledge gap about the quality of cardiovascular medicines available in low- and middle-income countries (LMICs). The aim of this study was to determine the quality of generic antihypertensive medicines available in the retail market of a developing country.

Methods: Samples of the two most commonly prescribed classes of anti-hypertensive medicines were collected from three states in three different geopolitical zones in Nigeria following a semi-random sampling framework. Medicine samples were purchased by mystery shoppers from 22 pharmacy outlets from six local government areas across the three states. Medicine quality was determined by measuring the amount of stated active pharmaceutical ingredient using high-performance liquid chromatography with photodiode array detection and classified according to their compliance to the specified pharmacopeia tolerance, limits for each antihypertensive.

Results: Amlodipine and Lisinopril were identified as the most commonly prescribed anti-hypertensive drugs in Nigeria. In total, 361 samples from 22 pharmacies were collected and tested. In total, 24.6% of Amlodipine and 31.9% of Lisinopril samples were of substandard quality and significantly more samples purchased in rural (59/161, 36.7%) compared to urban (32/200, 16%) outlets were found to be of substandard quality ($p < 0.001$). No falsified samples of either Amlodipine or Lisinopril were detected. There was large variation in price paid for the antihypertensive medicines (range ₦150-9750). Of the 24 pharmacy outlets surveyed, 46% stated that patients did not always require a prescription and 21% had previously reported a medicine as falsified or substandard.

Conclusion: More than a quarter of some commonly prescribed anti-hypertensive medicines available in Nigeria may be of substandard quality. Enhanced quality assurance processes in LMICs, such as Nigeria, are needed to support optimum management.

INTRODUCTION

Elevated blood pressure (BP), often termed hypertension, is one of the most important public health problems worldwide affecting one billion people three quarters of which live in the low income and middle income countries (LMICs).¹ High BP is also the leading cause of cardiovascular disease (CVD) and is responsible for 13% of deaths globally.^{2,3} In most individuals, adequate management and control of BP is associated with a reduction in deaths and disability from a number of conditions including cerebrovascular, cardiovascular, and renal disease.⁴ Therefore, prevention and optimal management of high BP in the general population is paramount to the achievement of the World Heart Federation (WHF) goal of reducing premature CVD mortality by 25% by the year 2025 and widespread access to good quality antihypertensive medicines is a critical component for achieving the goal.⁵

The last decade has seen increasing attention focused on the quality of medicines available, especially antimalarials, and it has emerged that the availability of substandard medicines is widespread.⁶ This is a crucial public health problem in developing countries. In these countries, half of the medicines for major diseases such as malaria have been found to be substandard in quality and often have little or no active ingredient.⁷ Substandard medicines are defined as medicines that are produced with inadequate attention to good manufacturing practices and may have contents or dissolution times that are outside the pharmacopeia specifications of acceptance limits range.⁷⁻¹¹ Substandard generic medicines are a major contributor¹² and have been shown to constitute 40-50% of all medicine supplies in Nigeria,¹³ one-third of all antibiotics and anti-malarial medicines in Nigeria and Thailand and 9% of medicines in India.¹⁴ Substandard generic medicines share a huge market as estimated by WHO at more than US\$35 billion which represents more than 15% of the pharmaceutical market worldwide.¹⁵

The US Pharmacopoeia (USP) medicine quality and information program listed anti-hypertensive medicines among a class of possible substandard medicines in the African region.¹⁵ A study carried out in Philippines found that the antihypertensive medicine Adalat (Nifedipine) was one of the top five substandard medications.¹⁶ However, there is currently very little research being done to assess the quality of generic antihypertensive medicines. Importantly, given that people with high BP often require lifelong adherence to indicated medicines, the problem of substandard anti-hypertensive medicines is potentially a serious public health issue. Importantly, poor quality medicines can directly impact on the health of patients if their effectiveness is reduced and this may contribute to ongoing and worsening disease which in turn leads to an increase in population health and economic burden.¹³ Therefore, the aim of this study was to determine the quality of generic antihypertensive medicines available in the retail market of Nigeria. Retailers at selected pharmacies were also surveyed for their opinions regarding falsified and substandard medicines in their local area.

MATERIALS AND METHODS

An observational study design was adopted. The methodology is detailed elsewhere and was based on published guidelines and recommendations.^{17,18} Ethical approval was obtained from the relevant Nigerian state-based ethics committees (Aminu Kano Teaching Hospital Ethics Committee, Ethical Board of University of Port Harcourt Teaching Hospital, Obafemi Awolowo University Teaching Hospital Ethics and Research Committee). This study does not involve individual patient data and hence written, informed consent was not required.

Context

Nigeria was chosen as the country in which medicines will be collected for this study based on the knowledge that it is a LMIC with a large population who suffer from high prevalence of hypertension. It is the most densely populated country in Africa and according to the

World Health Organization, in 2016 over half a million Nigerians died from non-communicable diseases, including cardiovascular diseases.¹⁹ Population research has reported that 35% of Nigerian adults had elevated blood pressures in 2008²⁰ with rates being highest amongst urban dwellers.²¹ Therefore, when combined with the large population, Nigeria contributes a substantial proportion of the total burden of hypertension in Africa.²² This increasing burden requires that health planners and implementers ensure the availability of high quality evidence-based medicines for hypertension.²³

Geographical sampling framework

The stepwise and semi-random sampling framework developed to determine which retail outlets would eventually be included in the study has been detailed in our previous publication.²⁴ The purpose and concept behind the sampling framework was to identify a combination of urban and rural locations in northern and southern states of Nigeria via a stratified and systematic approach. Firstly, three states of Nigeria (Figure 1) representing varied geopolitical areas were selected via consultation with local experts (purposive sample). Secondly, for each state, one urban and one rural local government area (LGA) was randomly selected therefore, providing a total of six LGAs across the three states (three rural and three urban). Thirdly, geographical mapping software (QGIS Geographic Information System, version 2.8.3-Wien, 2015) was used to randomly select four geographical co-ordinates in each of the selected LGAs. Using those coordinates, the pharmacy outlet nearest to each of the coordinates was identified. The total sample included 22 retail outlets (pharmacy shops) from six LGAs across three states in different geopolitical zones of Nigeria.

Identification and collection of generic hypertensive medicines

For this study, the intention was to purchase samples of the generic brand antihypertensive medicines representing the two most commonly prescribed brands. The most two commonly

prescribed antihypertensive medicines (Amlodipine and Lisinopril) prescribed in Nigeria were identified using the National Agency Food and Drug Administration and Control (NAFDAC) agencies publicly available data. A complete list of all available generic medicines for Amlodipine and Lisinopril was then obtained and a computerised random sequence was then used to randomly select 10 generic brands (where available) of each of Amlodipine and Lisinopril. Using this process, we aimed to collect approximately 20 generic medicines from each outlet for subsequent quality testing. Where less than 10 generic brands were available at an outlet, all available brands were collected.

To purchase the samples of generic medicines, a research assistant (who spoke local language) acted as a mystery shopper and visited each of the identified pharmacy outlets and systematically purchased a full box (usually 28 or 30 tablets) of each of the pre-selected generic brands for each medicine. The covert approach was used to minimise the risk that a seller might realise they are to be a part of a research project and therefore raise suspicion and minimise risk that the seller might decline to sell the required samples. In total, 361 samples of amlodipine (n= 195) and Lisinopril (n= 166) were purchased from 22 pharmacies, in three geopolitical states (Rivers, Osun and Kano).

Once purchased, each sample was retained in its point-of-purchase packaging and placed in an individual zip-lock bag together with a completed standardized data collection form. The data collection form for each sample included recording of the outlet type, date of purchase, price paid, brand name, formulation, stated active pharmaceutical ingredients, country of manufacturer, NAFDAC registration number, number of tablets per sample, batch number and expiry date were recorded on a standard data collection form. Each sample was then stored in an air-conditioned room (approximately 20°C) in a central location prior to dispatch

via international courier to the London School of Hygiene and Tropical medicine (LSHTM) in London, United Kingdom (UK) for pharmacopoeial content analysis.

Laboratory pharmacopoeial content analysis of samples

Tablets were weighed, colour of each tablet (white, off white, yellow, pale blue, shocking pink etc) and a description of their shape (round, heart shaped, oblong, hexagonal, octagonal etc) recorded prior to measuring the amount of stated active pharmaceutical (SAPI) in each tablet. For quantitative analysis by high performance liquid chromatography with photodiode array detection (HPLC-PDA), pulverised tablets were combined with the solvent (methanol: water; 1:1), sonicated and centrifuged. The supernatant, containing soluble active ingredients was then injected into the HPLC column and the amount of SAPIs present in the tablet was determined. HPLC analysis was conducted using a Dionex Ultimate 3000 system (ThermoFisher, Hemel Hempstead, UK) and separation achieved using an Acclaim 120, C₁₈, 5 µm Analytical (4.6 x 150 mm) from Fisher Scientific, Leicestershire, UK. The mobile phase of ammonium formate (10 mM, pH 2.7) and acetonitrile (v/v; 50:50 over 4.2 min) at a flow rate of 1.2 mL/min for the analysis of Amlodipine; Water and acetonitrile (v/v; 16/84 over 3.0 min) at a flow rate of 1.2 mL/min for the analysis of Lisinopril. The photo-diode array detector (UV-PDA; DAD 3000) was set at 237 nm for amlodipine and 210 nm for Lisinopril. For each sample a duplicate set of tablets were analysed twice (total number of measurements = 4) on the HPLC and a mean of the values recorded.

Classification and analysis of samples

Medicine quality was determined by measuring the SAPIs using HPLC-PDA and we classified samples according to the latest World Health Assembly definitions (falsified, substandard or unregistered)²⁵ and compliance with the authorised specifications published in USP monograph for each antihypertensive. ‘Falsified’ medicines are defined as medical

products deliberately/fraudulently misrepresent their identity, composition or source.²⁵

‘Substandard’ medicines are “out of specification” and are defined as authorised medical products that fail to meet either their quality standards or their specifications, or both.²⁴

‘Unregistered’ is defined as any medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority.²⁵ Most (84%) of these generic samples collected had a NAFDAC registration number, but we were not able to verify its authenticity. For sample classification, laboratory results were expressed as a percentage of the % SAPI. The % SAPI then used to classify each sample of Amlodipine and Lisinopril as good quality (acceptable pharmaceutical quality, if compliant with USP specified tolerance, limits range 90 -110% SAPI), poor quality (substandard, if contains either less or more than the acceptable dose, <90 ->110% SAPI) and falsified (no SAPI). These acceptable ranges are based on large number of samples of dosage units (6-12 for these antihypertensives) but there is lack of consensus on what the acceptable range of % SAPI are permitted for fewer samples

Retailer surveys

To gain insight into retailer views about falsified and substandard medicines, their reporting and factors associated with potential availability we conducted qualitative surveys with retailers from the identified LGAs in each state. Surveys were administered and collected by research assistants (independent of the mystery shopper) on a different day to sample collection to avoid confusion. Each participating retailer was asked a series of 11 questions designed to explore their awareness of potential reporting along with factors impacting on availability. Basic demographic data were also collected such as the number of years of pharmacy experience, whether a script was always needed, whether the outlet had air-conditioning and the gender of the respondent. Results were summarised in a spreadsheet prior to analysis.

Analyses

Descriptive statistics were used to compare the medicines on their physical and chemical characteristics with the reference product (medicine). Continuous variables are summarised and presented as means with standard deviations with categorical variables are summarised and presented as proportions. Rates of substandard medicines were compared for Amlodipine versus Lisinopril and urban versus rural purchase using chi-square tests with significance level set at 0.05. Survey results were summarised by proportions and themes.

RESULTS

Overview of samples collected

A total of 361 of the generic antihypertensive samples (195 Amlodipine and 166 Lisinopril) were purchased from 22 pharmacies in three geopolitical states (9 in Kano State, 8 in River State and 5 in Osun State). Two of the identified pharmacies were no longer available for sample collection and of those where samples were collected not all had 10 generic brands of Amlodipine and Lisinopril available for purchase. Hence, a total of 368 samples were purchased but of those, five were Ozatan-25 and two were Betafil and had to be subsequently excluded from analysis.

The eventual 361 samples were manufactured in a total of 12 countries as follows; India (n=203), United Kingdom (n= 68), Nigeria (n=43), China (n=24), Portugal (n=6), Pakistan (n=5), Slovenia (n=5), Malaysia (n=2), Bangladesh (n=2), Germany (n=2) and Egypt (n=1). In total, 82% (296/361) of samples had a NAFDAC registration number Kano State (113/145, 78%), Osun State (73/77 95%), Rivers State (110/139, 79%). There was a large variation in the price paid for the medicines, range ₦150-9750 (at an exchange rate of ~ ₦365 to a USD, this is approximately \$US0.41 - \$US26.86), mean price was ₦888.74 (\pm 897.43) By state, price paid also varied as follows Kano mean ₦644.95 (\pm 505.05) and range ₦200-3000; Osun

mean price ₦908.42 (± 1277.60) and range ₦150-9750 and; Rivers State mean price ₦1130.07 (± 892.89) and range ₦300-4500.

Medicine quality

Overall, 260 (72.0%) samples of antihypertensive were found to be compliant with the USP specified tolerance, limits range and hence classified as acceptable quality (will deliver the therapeutic dose) and 101 (28.0%) did not comply with the pharmacopeia specified tolerance, limits and hence classified as substandard (Table 1). That proportion of substandard quality was not statistically different for Amlodipine (48/195, 24.6%) and Lisinopril (53/166, 31.9%). However, significantly more samples purchased in rural (59/161, 36.7%) compared to urban (32/200, 16%) outlets were found to be of substandard quality ($p < 0.001$). Substandard quality samples were manufactured in India (n=50), UK (n=23), Nigeria (n=15), China (n=6) and Portugal (n=1).

TABLE 1: Quality of amlodipine and Lisinopril per state range

State	Antihypertensive	Total	Substandard	Acceptable quality
Osun	Amlodipine, n (%)	37	4 (10.8)	33 (89.2)
	Lisinopril, n (%)	40	22 (55.0)	18 (45.0)
Rivers	Amlodipine, n (%)	80	37 (46.2)	43 (53.8)
	Lisinopril, n (%)	59	6 (10.2)	53 (89.8)
Kano	Amlodipine, n (%)	78	7 (9.0)	71 (91.0)
	Lisinopril, n (%)	67	25 (37.)	42 (62.7)
Total, n (%)		361	101 (28.0)	260 (72.0)

No falsified samples of Amlodipine or Lisinopril were found as all samples had measurable amounts of SAPIs. The lowest SAPI amount detected was 50.6% (one sample of Amlodipine

from Rivers State). Numerous substandard samples had SAPI's that did not comply with the USP specified tolerance, limits range outside of 90-110% (Table 2).

TABLE 2: Range % SAPI outside USP specified tolerance, limits range

State	Antihypertensive	Total	Substandard	Range % SAPI outside
				tolerance limits
Osun	Amlodipine	37	4 (10.8 %)	71.1 - 82.2
	Lisinopril	40	22 (55.0 %)	77.5 - 130.0
Rivers	Amlodipine	80	37 (46.2 %)	50.6 - 156.1
	Lisinopril	59	6 (10.2 %)	84.1 - 170.0
Kano	Amlodipine	78	7 (9.0 %)	69.2 - 147.3
	Lisinopril	67	25 (37.3%)	58.6 - 89.2

The majority of samples of both antihypertensives that did not comply with the specified tolerance, limits range were past their expiry date at the time of laboratory analysis. Total of 32 (31.7%) substandard samples (20 lisinopril from Osun; 4 amlodipine from Kano; 6 amlodipine and 2 lisinopril from Rivers) had an SAPI greater than 110%. Most (305/361, 84%) of the collected samples had a NAFDAC registration number indicating that they were registered to be sold in Nigeria and 22% (22/101) of the samples determined to be substandard also had a NAFDAC registration number.

Pharmacy outlet survey

Provider surveys were collected from a total of 24 pharmacy outlets (13 urban and 11 rural). The majority of those completing the survey, 71% were men and they had an average of 12.3 (\pm 9.10) years of experience. In 46% of the pharmacies, patients did not always need a prescription and only 29% (n=7) stored their medicines in an air-conditioned space. The

majority (16/22, 73%) of pharmacy providers stated that all patients paid for their medicines without insurance and 87% stated that the price difference between innovator and generic medicines was a hindrance to patients. In total 83% of those surveyed said they were aware of surveillance programs to check for falsified and substandard medicines, 87% claimed they knew how to report falsified and substandard medicines but only 21% had ever reported such an issue. In total, 46% reported that they had had reason to stock or sell medicines without a NAFDAC registration number.

Only 21% of outlets surveyed claimed to be aware of any policy or treatment guideline providing information about which generic medicines are used in the treatment of hypertension and when asked if such a guideline should be available, the majority agreed. When asked an open question about what contributes to the potential proliferation of substandard and falsified medicines in Nigeria, survey respondents' factors identified included (i) high costs of medicines; (ii) corruption and high government tariffs; (iii) poor regulation, lack of monitoring/surveillance and minimal enforcement; (iv) porous borders and (v) poverty, unemployment and overpopulation.

DISCUSSION

This is one of the first studies to explore the quality of generic antihypertensive medicines in an African country, namely Nigeria. The results showed that more than a quarter of the samples analysed for content were of substandard quality but there were no falsified samples identified. Substandard medicines can lead to under dosing and overdosing. Overdosing on anti-hypertensives requires consumption of several times (up to 5 times) the therapeutic range. However, patients can experience side effects such as headaches, dizziness and palpitations on even taking double the required dose. Hence, taking a tablet which contains more than USP specified tolerance, limits range of SAPI may not in itself be enough to cause

an “overdose”. Moreover, many anti-hypertensive medicines have varying strengths (e.g. the strength of lisinopril varies from 5mg to 40 mg), so at present data is lacking on whether a dose of greater than the specified tolerance, limits range of SAPI for a 5mg tablet for example can be harmful to a particular patient. Both medicines analysed in this study, do not have a narrow therapeutic index so clinically, more harm will be done by having lower doses than the reverse.

The study also highlighted there is significant variation in cost of the generic antihypertensive medicines and that substandard quality medicines were more commonly collected from outlets located in rural areas. In addition, surveys of pharmacy retailers showed that many commonly do not require a prescription for patients to purchase antihypertensive medicines but that the majority were aware of surveillance programs aimed at falsified and substandard medicines. Also, most retailers knew how to report substandard medicines but only around 20% had ever done so.

Blood pressure lowering is one of the priority areas identified for action by the WHF if the target of a 25% reduction in premature CVD mortality by 2025 is to be achieved.²⁶ Therefore, understanding the quality of available antihypertensive medicines is also vital. Nigeria is a LMIC that is responsible for the greatest hypertension burden in Africa due to the combination of prevalence and population.¹⁹ It is therefore anticipated that a representative sample from the three chosen Nigerian states is highly relevant and potentially generalisable across Africa and other developing countries. Whilst this research offers an initial step and suggests there is a high prevalence of substandard quality medicines, greater surveillance is needed. It is anticipated that the results will attract attention to the issue of substandard antihypertensive medicines and sensitise policy-makers, national drug regulatory authorities and governments so as to facilitate debate among health providers, national Cardiology

societies/associations and civil society organisations. Ultimately, improving medicine quality and associated surveillance will reduce the disease burden and improve health at a population level.

Whilst the public health and criminal issues associated with falsified medicines has gained increasing attention in recent years, the potential effects of substandard medicines cannot be underestimated and is emerging as a major health concern. A recent report highlights that substandard medicines are also reaching patients because of poor manufacturing and quality-control practices in the production of genuine medicines (either innovator or generic).²⁷ In their review, Johnston and Holt (2014) found 29 studies where substandard quality medicines were identified and in some cases all the sampled antibiotics or antimalarials were found to contain API concentrations outside the quality limits range.²⁷ One small study tested the quality of antihypertensive medicines in Rwanda and found 20% of samples were substandard at the time of purchase.²⁸ Whilst the focus of the Rwandan study was on storage facilities, it found similar results to the present study in terms of substandard quality antihypertensives in Africa. Another African study tested 1185 samples from across 10 sub-Saharan African countries and found that among the generic medicines, 24% were of substandard quality.²⁹ In terms of storage, we found only 29% of outlets surveyed stored their medicines in air-conditioned spaces and given the average Nigerian climate, it is likely to indicate that this may have impacted on medicine quality, stability and expiry.²⁷ Overall, the problem of substandard quality antihypertensive medicines has now been reported across several independent studies and hence requires urgent attention.

Given the prevalence of substandard antihypertensive medicines and the potential public health impact, the concept of improving the situation presents both challenges and opportunities. Johnston and Holt (2014) state that “a concerted effort is required on the part

of governments, medicine manufacturers, charities and healthcare providers to ensure that only medicines of acceptable quality reach the patient.”²⁷ In the present study, we found that most retailers were aware of potential surveillance programs but very few had ever report substandard of falsified medicines. Therefore, perhaps programs are there but more publicity, random checking and reinforcement is required to inform retailers and enable them to have the knowledge and skills to understand when and how to report substandard medicines and why it is important for public health within their country. Another important step is to continue to collect systematic data and gain a detailed and objective understanding of the problem across the supply chain including from manufacture to retail.²⁷ Overall, more research and surveillance will help sensitize policy makers, national drug regulatory authorities and key regional and national governments as well as facilitate discussion and debate among health providers, national cardiology societies/associations and civil society representatives.²³

For this research we limited the sample collection to three states of Nigeria because of the extent of hypertension in Nigeria and for practical reasons. However, extensive preliminary sampling processes were employed to a balance between generalisable and random collection. It should also be noted that despite rapid collection, attention to detail in terms of storage and analysis, some samples were past their expiry date at the time of laboratory analysis. The knowledge base is sparse on whether substandard medicines only result from poor manufacturing practices or may be due to improper storage or the exact length of time on the shelf, that exceeds the stated expiry date for each SAPI. The only study on the effect of storage of medicines under tropical conditions is for the first line innovator antimalarial medicines and not for generics.³⁰ Stability of the innovator antimalarial medicines (Coartem[®] ; artemether/lumefantrine and Winthrop[®]; artesunate/amodiaquine) was evaluated in tropical climates by ageing the samples on-site in Ghana and in a stability chamber at LSHTM over a

period of four years and, removing samples from each site at regular intervals and measuring the SAPIs. Loss of SAPIs in these “naturally aged” samples was 0 to 7% over 3 years (~12 months beyond the stated expiry) and remained within the USP specified tolerance limits for each of those antimalarials.³⁰ In addition, this research was limited to generic medicines only and future research should also include innovator medicines. Despite this, the proliferation of generic medicines encouraged by national policies, makes this an essential group to understand and interrogate. Finally, the surveys conducted were limited to a relatively small number of retail outlets although these represented both rural and urban outlets and hence the results are considered highly generalisable.

CONCLUSIONS

More than a quarter of some commonly prescribed anti-hypertensive medicines available in Nigeria appear to be of substandard quality. However, no falsified samples of Amlodipine or Lisinopril were found. Provider surveys indicated that the majority of retailers were aware of surveillance programs to check for falsified and substandard medicines but that very few had ever made a prior report and there was a reported lack of awareness of guidelines. This study suggests that the quality of antihypertensive medications available in Nigeria is suboptimal and therefore public health management of hypertension could be negatively impacted. Our findings underscore the vital need for national authorities to track the scale of ineffective medicines that jeopardise treatment of life-threatening diseases through routine monitoring of medicine quality with robust laboratory techniques in place to analyse them on a regular basis.

Figure legend/s

FIGURE 1: Map showing the three states of Nigeria where EQUIMEDS was conducted

Competing interests

None to declare.

Funding

This research is funded by a World Heart Federation Emerging Leader Program pilot funding grant.

Author contributions

All authors conceived and developed this research as a collaborative group during international workshop and subsequent meetings through the World Heart Federation Emerging Leader Program. RA, SO, MS are leading the Nigerian component and HK developed HPLC methods and led the sample analysis process. JR, RA, AV, LD, FZ and DB provided leadership regarding sampling, data collection, sample size and geographical mapping. All authors have reviewed and approved the final manuscript.

Acknowledgements

We thank the World Heart Federation Emerging Leader Program leads, Committee and all participants who supported and peer reviewed the content of this research. In particular we thank Mark Huffman and Pablo Perel for their support and enthusiasm.

REFERENCES

- [1]. Ibrahim MM, Damasceno A (2012) Hypertension in developing countries. *Lancet* 380: 611–619.
- [2]. World Health Organization (2009) Global health risks: Mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization.
- [3]. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, et al. (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380: 2224–2260.
- [4]. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
- [5]. Beran D, Perrin C, Billo N, Yudkin JS. Improving global access to medicines for non-communicable diseases. *Lancet Glob Health* 2014;2(10):e561-562.
- [6]. Kaur H, Clarke S, Lalani M, Phanouvong S, Guérin P et al. Fake anti-malarials: Start with the facts: meeting report summary. *Malar J* 2016; 15:86.
- [7]. Attaran A1, Barry D, Basheer S, Bate R, Benton D, Chauvin J, Garrett L, Kickbusch I, Kohler JC, Midha K, Newton PN, Nishtar S, Orhii P, McKee M. How to achieve international action on falsified and substandard medicines. *Br Med J* 2012;345:e7381.
- [8]. Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. The global threat of counterfeit drugs: why industry and governments must communicate the dangers. *PLoS Med* 2005;2: e100.
- [9]. Newton PN, McGready R, Fernandez F, Green MD, Sunjio M, Bruneton C, et al. Manslaughter by fake artesunate in Asia—will Africa be next? *PLoS Med* 2006;3:e197.
- [10]. Newton PN, Green MD, Fernández FM, Day NP, White NJ. Counterfeit anti-infective drugs. *Lancet Infect Dis* 2006; 6:602-13.

- [11]. Keoluangkhot V, Green MD, Nyadong L, et al. Impaired clinical response in a patient with uncomplicated falciparum malaria who received poor-quality and underdosed intramuscular artemether. *Am J Trop Med Hyg* 2008;78:552-5.
- [12]. World Health Organization (2015) Media centre. Available: <http://www.who.int/mediacentre/factsheets/fs275/en/>. (Accessed 2nd February 2019).
- [13]. Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open* 2013;3(8): e002923.
- [14]. Banerjee Y. Mission. Indradhanush and the counterfeit drug trade in India. *Lancet Infect Dis* 2015;15(12):1379-1380.
- [15]. Morris J, Stevens P. Counterfeit Medicines in Less Developed Countries: Problem and solutions. International Policy Network 2006.
- [16]. World Health Professions Alliance. Background Document on Counterfeit Medicines in Asia, 2011. Available at http://www.whpa.org/Background_document_Counterfeit_Medicines_in_Asia.pdf (Accessed on 2nd February 2019).
- [17]. World Health Organisation. Guidelines on the conduct of surveys of the quality of medicines. (June 2015) Available at http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidelines-on-medicines-quality-surveys-QAS15-630_30062015.pdf (Accessed 2nd February 2019).
- [18]. Newton PN, Lee SJ, Goodman C et al. Guidelines for Field Surveys of the Quality of Medicines: A Proposal. *PLoS Medicine*, 2009;6(3):e52.
- [19]. World Health Organization - Noncommunicable Diseases (NCD) Country Profiles, 2018. Available at https://www.who.int/nmh/countries/nga_en.pdf
- [20]. World Health Organisation. Nigeria: WHO statistical profile, last updated 2015. Available at <http://www.who.int/gho/countries/nga.pdf?ua=1> (Accessed 2nd February 2019).

- [21]. Adediran Olufemi Sola, Okpara Ihunanya Chinyere, Adeniyi Olasupo Stephen, Jimoh Ahmed Kayode. Hypertension prevalence in an Urban and Rural area of Nigeria. *Journal of Medicine and Medical Sciences* 2013;4(4):149-154.
- [22]. Adeloye D and Basquill. Estimating the Prevalence and Awareness Rates of Hypertension in Africa: A Systematic Analysis. *PLoS One* 2014;9(8):e104300.
- [23]. Kayima J, Wanyenze RK, Katamba A, Leontsini E, Nuwaha F. Hypertension awareness, treatment and control in Africa: a systematic review. *BMC Cardiovasc Disord* 2013; 13:54.
- [24]. Redfern J, Adedoyin RA, Ofori S, Anchala R, Vamadevan A, De Andrade L, Zelaya J, Kaur H, Balabanova D, Sani M. Physico-chemical equivalence of generic antihypertensive medicines (EQUIMEDS): protocol for a quality of medicines assessment. *BMJ Global Health* 2016;1: e000086.
- [25]. World Health Organisation. Who member state mechanism on substandard/spurious/false-labelled/falsified/counterfeit (ssffc) medical products. Appendix 3, a70/23 (2017). Available at <https://www.who.int/medicines/regulation/ssffc/definitions/en/> (Accessed 2nd February 2019).
- [26]. Adler AJ, Prabhakarany D, Bovetz P, Kazix DS, Manciak G, Mungal-Singh V, Poulter. Reducing cardiovascular mortality through prevention and management of raised blood pressure A World Heart Federation Roadmap. *Global Heart* 2015;10(2):111-122.
- [27]. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *Br J Clin Pharmacol* 2014;78(2):218–243.
- [28]. Twagirumukiza M, Cosijns A, Pringels E, Remon JP, Vervaet C, Van Bortel L. Influence of tropical climate conditions on the quality of antihypertensive drugs from Rwandan pharmacies. *Am J Trop Med Hyg* 2009; 81:776–781.

- [29]. de Terline D M, Diop BI, Bernard M et al. Substandard drugs among five common antihypertensive generic medications: an analysis from 10 African countries. *J Hypertens* 2018;36(2):395-401.
- [30]. Hall Z, Allan EL, van Schalkwyk DA, van Wyk A, Kaur H (2016) Degradation of Artemisinin-Based Combination Therapies under Tropical Conditions. *Am J Trop Med Hyg*, 94(5), 993-1001.