Evaluating the Quality of Anti-Hypertensive Drugs in Lagos State, Nigeria

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background

As the burden of non-communicable diseases grows, access safe to medical therapy is increasing in importance. The aim of this study was to develop a methodology for evaluating the quality of anti-hypertensive drugs and to examine whether this prevalence varies by socio-economic variables.

Methods

Through a cross-sectional survey study design, 6 local government areas(LGA) in Lagos State, Nigeria were sampled. A list of all registered pharmacies in the state, derived from the Pharmacists Council of Nigeria, was used in the sampling process. A mystery shopper randomly purchased 102 samples (14 brands) of the antihypertensive nifedipine from 17 pharmacies in each of the six LGA in Lagos State. Definitive drug quality was assessed through High Performance Lipid Chromatography (HPLC). The quality assessment comprised two main domains; the level of active pharmaceutical ingredients (API) was used to identify falsely labelled drugs whereas the amounts of impurities revealed substandard drug samples. Good quality drugs met specifications for both API and impurities.

Results

Of the 102 drug samples collected, 30(29.3%) were falsely labelled, 76 (74.51%)

were substandard and 24 (23.53%) were good quality. Seventy-eight (76%) drug samples

did not meet both quality standards. Of the falsely labelled drugs ,17(56.67%) emanated

from LGA categorized as low social economic status or hard-to-reach and 40(52.63%) of

the substandard drug samples emanated from high social economic status LGA. Most of

the good quality drug samples, 14(58.33%), were from low social economic status LGA

Eighteen (60%) of the falsely labeled drug samples,37(48.68%) of the substandard

samples and 15(62.5%) of the good quality drug samples were from manufacturers

based in Asia. The average price of falsely labelled drugs was 375.67 Nigerian

Naira(NGN), substandard drugs was 383.33 NGN and 375.67 NGN for good quality

drugs. For drug samples that were falsely labelled and substandard, there was no

association by LGA Socio-economic status (P=0.39) and region of manufacturer (P=0.24),

but there was a trend for a difference by price (P=0.06)

Conclusion

We found a high prevalence of falsely labelled and substandard drug samples

with only 24(23.53%) having good quality. To treat non-communicable diseases, we

need efforts to monitor and assure drug quality for populations.

Dedication

I dedicate this work to my family, your unwavering love and wisdom inspires me to aim

for the stars, Dr. Moses Kinuthia for your invaluable insight and to Dr. Kevin Schulman

for always steering me in the right direction.

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1. Introduction

1.1 Background

Poor quality drugs are a global pandemic posing a great threat to global health and

international trade (1). Although the deleterious consequences of adulterated drugs

have been outlined in an extensive range of literary platforms, efforts to control the

illicit trade of poor quality drugs are lagging.(2) The issue of poor quality medicines

is complex, as the effects are experienced in all sectors, ranging from industry to

public health, where the latter bears the largest burden.(1)(3) This phenomenon

might be easily termed as a paradox since not much effort is being placed on

curbing the vice, especially in the African market where the prevalence of illicit

drug traders is increasing rapidly.(2) The widespread growth in the number of

illegal manufacturers in the pharmaceutical industry has been attributed to

multiple factors, such as globalization (which has enabled easy transportation of

pharmaceutical products), increased internet connectivity (which has aided access

of the global market space), and the fact that the poor-quality drug market has low

risks and high rewards.(1)(2) This proliferation in fraudulent dealings in the

pharmaceutical industry can be termed as a contemporary reality due to its

enormous penetration and grip in markets globally.(4) Although once considered a

problem affecting only low-income and developing countries, all countries in the

world are now touched by this problem. Health systems continue to be embarrassed, mortality rates due to various curable and irremediable ailments continue to skyrocket, and the economic burden continues to worsen.(1)(4)

Following the first cross-border convention on substandard drugs in April 1992, a meeting organized by the WHO and the International Federation of Pharmaceutical Manufacturers Associations, a definition of counterfeit medicines was agreed upon. "A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and or source. Counterfeiting applies to both branded and generic products. Counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."(4) In 2012,the World Health Organization (WHO) described poor quality medicines under the clause Substandard, Spurious, Falsely Labelled, Falsified and Counterfeit (SSFFC).This expansive description delineates just how complex the issue of drug quality is.(6)(3) Other organizations, such as the United States Food and Drug Administration (FDA), have defined substandard medicines as those that are either contaminated, contain the wrong or no active ingredient, stolen or diverted products, expired, adulterated or unapproved products.(7)The WHO recently agreed, in May 2017, to replace the SSFFC term with 'Substandard and falsified

medical products,' following a request presented to the Director General during the Seventieth World Health Assembly.(8) In this paper, the term *falsely labelled* will be used to refer to drugs that had lower amounts of the active pharmaceutical ingredient (API) than what was labelled, the term *substandard* will be used to refer to drugs that were found to have high levels of impurities, and good quality drug samples are those that meet set expectations for both label amount (API) and purity. Drugs described as poor quality are those that were identified to be substandard and falsely labelled.

Different countries have varying interpretation of these similar terms, which easily results in poor cooperation due to the confusion encountered. To ensure a better understanding of the magnitude of the problem, a proper, succinct clarification of the definition of poor quality drugs is warranted. The term substandard is used to delineate drugs which do not attain the quality specifications outlined in national standards. These standards, which are based on internationally recognized pharmacopeias such as the U.S Pharmacopeia and the British Pharmacopeia, recognized by most commonwealth nations. Falsified products represent drugs that have a distorted representation of their identity, source or both. An adulterated product with licit packaging is considered falsified, and so is a good-quality product with distorted packaging. A falsely labeled drug is

one that contains a different element or different quantities of an active

pharmaceutical agent from what is outlined on its label. The terms *spurious* and

counterfeit define drug products which are not what they purport to be.(3)(5)

Evidently, a massive overlap and heterogeneity in the various terms used to

describe poor quality drugs exists. A falsely labelled drug is also substandard since

it does not meet national or international specifications. A falsified drug is often

falsely labelled and, of course, substandard. It is evident that using the WHO's

SSFFC definition compounds the already dire situation. Fortunately, to deter

further confusion, the WHO recently agreed to replace the SSFFC term with

'Substandard and falsified medical products,' following a request presented to the

Director General during the Seventieth World Health Assembly.(8)

In a bid to assess the scope, scale and harm due to poor quality medical

products, the WHO launched a global surveillance and monitoring system in 2013,

aimed at motivating member states to report SSFFC incidents in a regulated and

structured manner.(9) Other organizations, such as the U.S.'s FDA, take the

problem of non-authentic medical products seriously, as evidenced by its Global

Strategic Framework for SSFFC medical products.(10) Some of the proposed

methods for aiding in reducing the prevalence of adulterated drugs entail raising

awareness through outreach campaigns, increasing resources allotted to regulatory

agencies, which will in turn lead to protected supply chains and prompt

identification, international collaboration in policy formulation, and prosecution of

drug counterfeiters . Developing robust data through thorough research, ensuring

drugs meet all quality standards, and providing incentives to motivate legitimate

manufacturers to provide quality medicines will go a long way in eradicating

substandard and falsely labelled medicines.

1.2 Global supply Chain

Of the various postulated solutions to this vice and germane to this paper is a

collection of robust data from research. Various products and raw materials are

required in the development of medicines. These are often sourced from varying

locations and industrial sectors. Following the completion of the manufacturing

process, drugs move from one country to another through diverse conduits to the

end consumer. These processes outline just how complex the global supply chain is.

A country such as the United States, whose drug supply chain is one of the safest in

the world, imports about 40% of the drugs and nearly 80% of the active

pharmaceutical ingredients.(11) Countries with weak regulatory mechanisms, such

as most low and middle income countries, are thus faced with a great burden with

regard to eradication of illicit drugs. To safeguard the integrity of the supply chain,

countries should evaluate drugs at different stages for robust data on quality.

Assessment of drugs at the manufacturer, distributor and retailer levels all yield reliable data to contribute toward the formulation and implementation of policies and frameworks to stop the presence of poor quality drugs in our markets. To protect public health and promote access to quality and affordable goods, frequent testing is critical. In most developed countries, such as the United States, drugs are dispensed from pharmacy stores, most of which belong to national chains. They are also often housed in convenience or retails stores.(12) This means that drugs are routinely sourced from wholesalers rather than manufacturers. **Figure 1** is an illustration of the supply chain in most developed nations.
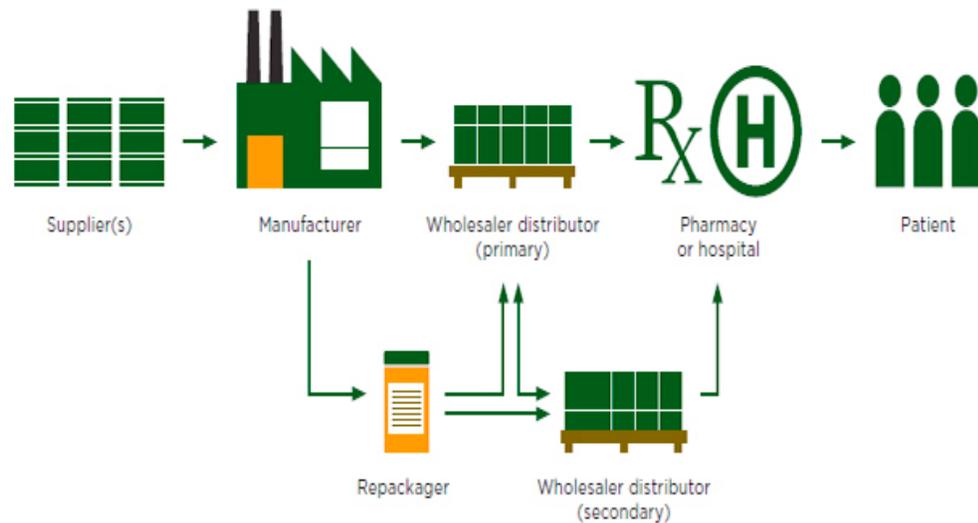
Figure 1: Supply chain framework in high income countries

(Source; FDA, 2011b)

In most low and middle-income nations, the supply chain has a similar backbone composed of manufacturer, wholesaler, distributor and pharmacy or hospital, but often this framework is compounded by extensive fragmentation. Overall, the sectors in the pharmaceutical industry in low and middle income nations can be broadly divided into public and private. These two sectors, which are often not siloed, co-exist with other sectors, such as non-governmental organizations (NGOs), which frequently channel most of the donated medicines into the supply chain system. Another high-level fragmentation of the pharmaceutical industry in low and middle income countries is based on geographical regions. National, regional, district and sub-district and rural subdivisions exist in the supply chain.(12)

Most of the drugs consumed in low and middle income countries are not locally manufactured.(13) The pharmaceutical industry is thus controlled by international firms at the manufacturer or wholesale levels, and drugs produced locally are often controlled by the private sector. Multiple wholesalers, sub-wholesalers, distributors, private and publicly-owned pharmacies exist in these nations, which is a different organizational structure from the pharmaceutical

sectors in developed nations. The segmentation and fragmentation in the supply chain, illustrated in **Figure 2**, are often so severe that endless loopholes are created for criminals involved in the sub-standard medicine trade.(12)
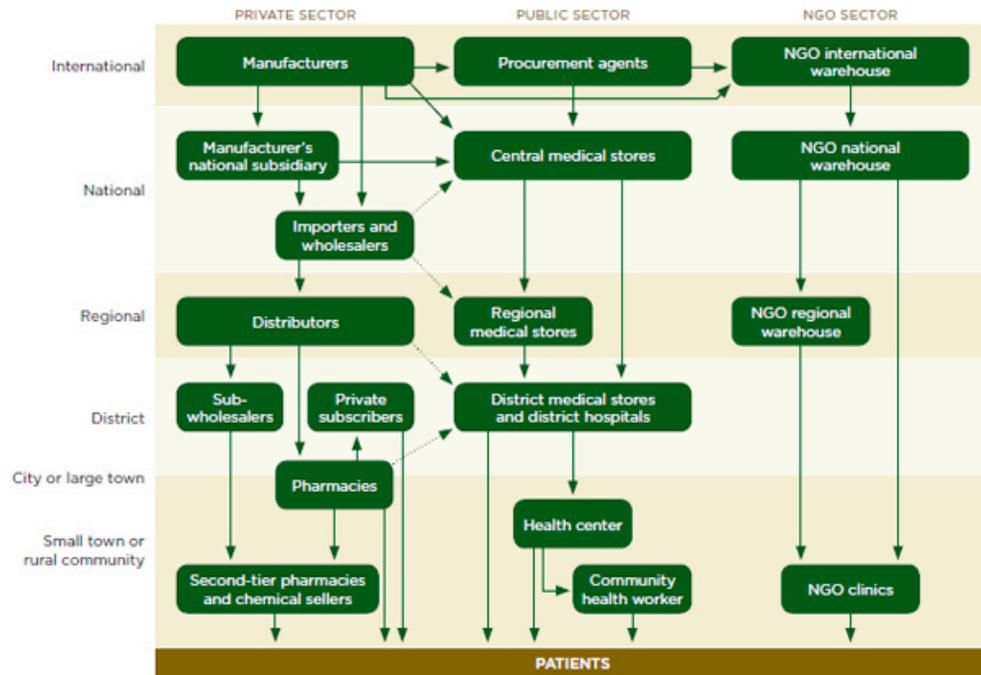
Figure 2: Supply chain framework in low and middle income countries

(Source; Yadav et. al.,)(12)

The wholesale market has commonly been the mainstay for large-scale batch testing of drugs to control or criminalize counterfeit drug manufacturers. Batch testing at the manufacturer level before disbursement to wholesalers or repackaging firms is vital in controlling the problem of substandard drugs. Recently, initiatives such as the Global Pharma Health Fund Minilabs rapid test kits have been available

for use at any stage of the supply chain, and even more frequently at the stages closest to the end consumer. These minilabs protect the last mile of the supply chain, which is frequently plagued by criminals who continue to take advantage of the failing distribution chains. The last mile in this case metaphorically represents the final processes in the supply chain before medicines reach their end destination. Collection of robust data is evidently a stronghold when evaluating the quality of drugs in different supply chain systems.

1.3 Methods of detection of falsely labelled and substandard drugs

Various methods have been employed in studies aimed at evaluating the quality of drugs. The number of studies conducted in developing countries is limited and a majority of these systemic evaluations are focused on antimalarial and antibiotics.(13)(14)(15) Additionally, these appraisals are often carried out through quantitative, methods. with very few applying qualitative approaches.(16)

The sampling methods executed are often not well outlined in some studies, and when they are indicated, it is often through randomization and convenient sampling. The latter process involves getting samples for the study without any precise guidelines, which results in bias.(17) It is likely that some investigators unintentionally or deliberately prefer to employ sampling strategies that

underestimate the prevalence of poor quality drugs in instances where they are concerned about potentially causing embarrassment. Inversely, investigators overestimate their findings when funding or publishing opportunities are at stake. Due to the difficulties encountered in getting country-specific estimates of the amount of poor quality drugs present, decisions on appropriate sampling size are often not comprehensive and exhaustive.(17) For example, in a well-defined geographical area, it is likely that one facility is responsible for supplying a majority of poor quality drugs, or twenty facilities are responsible for a fairly small proportion of the poor quality drugs encountered in the same region. Having pre-existing data on the proportion of medicine outlets likely to dispense unsafe medical products would be critical in mapping distribution and weighting for a statistically robust sample size.

An example of an objective sampling technique employed in studies evaluating the quality of drugs is the Lot Quality Assurance Sampling (LQAS). This method relies on randomizations is which batches or lots of goods are tested instead of individual items. However, this method has a higher risk of both Type 1 and 2 errors.(17) Other standardized methods, such as the Medicine Quality Assessment Reporting Guideline (MEDQUARG), an algorithm of how medicine surveys should be conducted, have been used in select studies.(18)(17)

Most studies stratify the sources of their samples based on geographical and socioeconomic variables. A majority of studies collected their products from formal facilities, such as pharmacies, hospitals, drugs stores, distribution centers and wholesalers. Informal avenues, such as open air markets, private individuals, unregistered drugs stores and online resources, have also been sampled.(17)

Different methods have been used to assess drug quality in various countries. High performance liquid chromatography (HPLC) is the gold standard in identifying the content of drugs because small deviations in the content of API or amounts of impurities can be detected. Other biochemical testing methods include thin layer chromatography, color reactions and disintegration tests, such as the Minilab Global Pharma Health Fund test. Near-infrared spectroscopy and Raman spectroscopy, which are fast and easy to perform, have been used to differentiate between products containing the same API. Other newer technologies include drug samples laden with biodegradable barcode and QR codes.(19)

1.4 The cross-sectional study of drugs in Lagos State, Nigeria

This study focuses on the pharmaceutical market in Nigeria. With the earliest case of counterfeit drugs in the country being reported in 1968, data on how widespread the problem is remains unknown.(20) This study is aimed at establishing

the prevalence of poor quality anti-hypertensive drugs in Lagos State, Nigeria, and to examine whether this prevalence varies based on an area's socio-economic status. An estimated 24% of deaths nationally emanate from non-communicable diseases in Nigeria, based on 2015 World Bank data on the number of deaths due to non-communicable diseases. With a population of over 180 million people, the country continues to face a double burden due to the high number of debilitating infectious diseases.(21) Nigeria has a large drug market, primarily due to the large population and the underutilized manufacturing capacity which has resulted in the importation of 70% of the drugs used.(22) With most unscrupulous drug manufacturers favoring the African medicines market, and with Nigeria being a major consumer of drugs from foreign international industries, the actual number of counterfeit anti-hypertensive drugs is unknown.(18) Additionally, the onsite quality surveillance methods in place have proven to be inefficient in curbing the vice. This continues to contribute to the high mortality rate and premature deaths due to hypertension in the country. People diagnosed with hypertension continue to die prematurely despite strict follow up and management because of counterfeit drugs. The country's National Agency for Food and Drug Administration and Control (NAFDAC) lacks a strong arm to regulate the manufacture and importation of most drugs, so the national pandemic persists. (20)(23) Measures, such as in-person visits and police

raids to locations notorious for the sale of counterfeit drugs, have been deemed

unsustainable.(20)

2. Methods

2.1 Study Period

Nifedipine samples were collected between May 2017 and July 2017.

2.2 Setting and selection of study areas

Lagos, the most populous state in Nigeria, is divided into 20 local

government areas (LGA), all varying in population and geographical size. Of the 20,

six LGAs were selected for the study based on the level of socioeconomic status and

how populous they are. Data from the 2006 national census(**Table: 1**), acquired from

the National Population Council of Nigeria, was considered. Three LGAs were

composed of areas considered to be of high socioeconomic status and the other three

were identified from hard-to-reach areas, also recognized as low socioeconomic

status areas.(24)LGAs were also categorized based on urbanization, structural

development and transport conditions, which were simultaneously used to reflect

socioeconomic status. Additionally, the identification of LGAs was based on a

consensus of the principal investigator from Duke Global Health Institute and the

expert opinion of Health Strategy and Delivery Foundation staff members. (25)

Table 1: Lagos state population data

LGA	1996	LGA	2006
Agege	790,333	Agege	461,743
Alimosho	522,854	Ajeromi-Ifelodun	687,316
Badagry	144,722	Alimosho	1,391,571
Epe	123,119	Amuwo-Odofin	328,975
Eti-Osa	213,199	Apapa	222,986
Ibeju/Lekki	30,259	Badagry	237,731
Ikeja	246,791	Epe	181,734
Ikorodu	224,089	Eti-Osa	283,791
Lagos Island	201,424	Ibeju/Lekki	117,793
Lagos Mainland	341,649	Ifako-Ijaye	427,737
Mushin	654,988	Ikeja	317,614
Ojo	1,256,167	Ikorodu	527,917
Oshodi/Isolo	545,777	Kosofe	682,772
Shomolu	935,789	Lagos Island	212,700
Surulere	715,859	Lagos Mainland	326,700
		Mushin	631,857
		Ojo	609,173
		Oshodi-Isolo	629,061
		Shomolu	430,569
		Surulere	502,865
TOTAL	**6,947,019**		**9,113,605**

2.3 Sampling design and selection of samples and sample collection sites

2.3.1 Sampling design

Throughout the process of evaluating the quality of nifedipine, drug samples were collected from registered pharmacies through both simple and stratified sampling methods. Pharmacies were derived from strata of LGAs whose main inclusion factor was based on whether they were high socioeconomic status or hard-to-reach (low socioeconomic status). A second stratum was formed based on the number of facilities on each street. Seventeen pharmacies were required from each LGA and they were randomly selected from major streets in each LGA. A list of registered pharmacies from the Pharmacists Council of Nigeria outlined the precise location of each facility. Additionally, all state and federal levels hospitals present in the LGAs were automatically sampled.

2.3.2 Selection of medicines for sampling

For the evaluation of the quality of anti-hypertensives in Lagos State, nifedipine, with the preferred strength of 20mg or 30mg, was used as the drug of choice. Calcium channel antagonists are the second most commonly used anti-hypertensive drugs and their availability is widespread in Lagos State.(26)(27) Twenty milligram nifedipine drug samples were collected. If the indicated strength was not available, an alternative strength of 30mg was sampled. Only branded medicines were sampled. If multiple

branded medicines were available, the least popular brand was purchased. In most

pharmacies, however, only the two most common branded types were available. Drugs

sampled had to be well-labeled and in sealed blister packages, indicating the brand

name, expiration date, manufacturer name and address.

2.3.3 Sample collection sites

The initial step entailed getting a list of all registered pharmacies in the

abovementioned six local government areas. The Pharmacists Council of Nigeria (PCN)

Lagos State office provided a list of registered pharmacies in the state. Before conducting

the survey, a list of pharmacies from each of the six LGAs, both privately and

government owned, was compiled. The study process was deployed after the number of

facilities on major streets in each LGA was identified. Registered pharmacies were then

sampled randomly from streets around the most urbanized sections of each LGA, as

well as areas with the largest number of registered facilities. The survey investigator

involved in the sampling process was a local resident of Lagos State. He was trained on

the study sampling criteria prior to the commencement of the sampling process. The

criteria entailed presenting to the randomly selected pharmacy as a mystery shopper, by

posing as a patient or customer without identifying himself as an investigator,

presenting a drug prescription and requesting to purchase branded nifedipine 20mg or

30mg drug samples. The study surveyor was also expected to purchase the least

common nifedipine drug sample from the pharmacies. Following full payment for the drugs, a receipt indicating the cost and name of the facility was to be sought from the pharmacists. Drug prescriptions were not required for privately-owned facilities. They were needed only when we sought a drug sample from a state or federal level facility. Pharmaceutical chain stores were excluded from the sampling process. The mystery shopper purchased the least common branded nifedipine drug sample from the pharmacies. As noted, almost all facilities had branded nifedipine drugs from two major manufacturers. Following full payment for the drugs, a receipt indicating the cost and name of the facility was sought from the pharmacists.

2.3.4 Drug price, storage and transportation

All collected drug samples specifications; date of collection, buying price, pharmacy name and location, and origin of the drug were documented in a comprehensive database. Each sample was kept in its original package and was then placed in a transparent Ziploc plastic bag. A unique code, derived from the sampling date, LGA, cost and numerical value on the sample record list, was assigned to each drug sample. This code was printed on adhesive labels which were adhered to the sample's Ziploc plastic packaging. Samples were stored securely in a conducive environment with temperatures below 25 degrees Celsius. Upon completion of the sampling process, the samples were divided into six packages based on the LGA they

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originated from. The six packages were further secured using bubble wrap for protection from mechanical stress. The drugs were then transported via courier services to an FDA-registered laboratory in North Carolina, USA.

2.3.5 Drug quality measures

Nifedipine drug samples were assessed for quality at Campbell University College of Pharmacy and Health Sciences laboratory in North Carolina using High Performance Liquid Chromatography (HPLC). Prior to the laboratory analysis, the drug samples were visually inspected and examined for abnormalities such as broken blister packaging and passed expiry dates.

We followed recommended international pharmacopeia guidelines to designate drug quality measures. Namely, the guideline recommends that amounts of active pharmaceutical ingredient in each nifedipine tablet should be in the 90% to 110% range, and that the amounts of impurities should be less than 2% for nifedipine nitrophenylpyridine analog and less than 0.5% for nifedipine nitrosophenylpyridine analog(28). The level of active pharmaceutical ingredients (API) was used to identify falsely labelled drugs whereas the amounts of impurities revealed substandard drug samples. Good quality drugs met both specifications for the API and impurities.

2.4 Analysis

We summarized categorical variables using counts and percentages, and continuous variables using mean (standard deviation) or median [interquartile range] depending on the distribution of the data. We compared socioeconomic characteristics of Lagos State, price of the drugs, and country of origin of drugs across drug quality measures using chi-squared tests for categorical variables and Mann-Whitney tests for continuous variables.

Logistic regression models were used to examine the association between three key predictors (Lagos State LGA socioeconomic status, price of the drug and the geographical location of drug manufacturers) and characteristics of nifedipine drug samples; both API amount and purity levels. Stata (version 14.2, StataCorp) was used for the statistical data analysis.

2.5 Ethical approval

A request for exemption from Institutional Review Board (IRB) review was sought prior to commencement of the study from Duke University School of Medicine and College of Medicine of the University of Lagos, Health Research Ethics Committee.

Further permission was sought from the U.S Food and Drug Administration for

importation of drug samples for laboratory evaluation.

3. Results

3.1 Description of samples

Lagos State Nigeria is divided into 20 Local Government Areas (LGA) of which 6 were isolated for the sampling process. 3 LGA were from a high social economic status and the other 3 were from a lower social economic status also known as hard-to-reach. The most populous LGA were identified based on the last census data sourced from the National Population Commission, Lagos State. Additional information on the socio-economic status was used to narrow down to a list of 6 LGA. These LGA are as follows:

- High socioeconomic areas: Eti Osa, Ibeju Lekki and Ikeja

- Hard-to-reach areas: Alimosho, Mushin and Ikorodu

17 pharmacies were sampled from each or the identified LGA and based on a compilation of names of pharmacies registered by the Pharmaceutical Council of Nigeria (**Table: 2**).

Table: 2 Number of registered pharmacies in Lagos State LGA

LGA	NUMBER OF REGISTERED PHARMACIES
Alimosho	123
Mushin	63
Eti-Osa	90
Ikeja	128
Ikorodu	88
Ibeju Lekki	35

3.2 Description of samples

We collected samples of the calcium channel antagonist, nifedipine from various pharmacies in six local government areas in Lagos State. In Nigeria, as is in most parts of the world, the management of hypertension entails various drug combinations. (27) In monotherapy treatment regimens, thiazide diuretics and calcium channel blockers have been proven to be efficacious particularly among black people.(26) In polytherapy, calcium channel antagonists, beta blockers and diuretics are the most commonly used drugs in Nigeria.(27)

Seventeen pharmacies were sampled from each of the six LGA and based on a compilation of names of pharmacies registered by the Pharmaceutical Council of Nigeria (**Table 2**). A total of 102 drug samples of nifedipine were collected from public and privately-owned pharmacies in Lagos State. Of these samples, 101 (99.02%) were from privately-owned pharmacies. All the sampled pharmacies were registered with the Pharmaceutical Council of Nigeria. Drug prescriptions were not required for privately-owned facilities and were needed only when we sought a drug sample from a state or federal level facility. A total of 14 different branded drugs were collected from the six LGAs in Lagos State with each sample packet ranging between 15 to 30 tablets. In most pharmacies, however, only two most common branded types were available. The

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dosage of branded nifedipine drugs that were collected was 20 mg (n=94; 92.16%) and 30

mg (n=8; 7.8%). None of the drugs collected were expired at the time of purchase, and all

samples were in blister packages except for one sample that was packed in a transparent

resalable plastic bag.

The commonest dosage of branded nifedipine drugs that were collected was

20mg comprising 92.16% of the samples. Nifedipine drug samples indicated to contain

30mg of the active pharmaceutical ingredient comprised 7.84% of the total drug

samples. None of the drugs collected were found to be expired at the time of purchase

and all samples were in blister packages except for one sample that was packed in a

transparent resalable plastic bag.

3.2.1 Compliance with specifications

We evaluated the drugs through High Performance Liquid Chromatography

(HPLC) and the results provided outlined the amount of active pharmaceutical

ingredient found and amount of impurities found. Relevant international pharmacopeia

outline that amounts of active pharmaceutical ingredient should be in to 90% -110%

range and amounts of impurities should be less than 2% for nifedipine

nitrophenylpyridine analog and less than 0.5% for nifedipine nitrosophenylpyridine

analog.(28) The laboratory analysis was preceded by the initial physical and visual

examination. All the drugs passed the pre-laboratory screening tests and were all

evaluated through the HPLC test.Based on the international pharmacopeial standards

29.41% of the drugs collected were falsely labelled whereby, the percentage amount

found of the active pharmaceutical ingredient fell below the FDA and USP the 90%

lower limit. Thirty (29.4%) samples of the drugs collected were falsely labelled whereby,

their percentage amount of API fell below the FDA and USP 90% lower limit. (**Table

3**)One drug sample had amounts of active pharmaceutical ingredient exceeding the

expected 110% upper limit: it contained 27mg of nifedipine API, which contradicted the

20mg amount labelled on the sample's blister packaging.

Table 3: Percentage of poor quality drugs based on % amount found by LGA and social economic status

SES	LGA	QUALITY CATEGORIES			
		FALSELY LABELLED (<90% OR >110%)		GOOD (>90%- <110%)	
		n	%	n	%
HIGH SOCIAL ECONOMIC STATUS	ETI-OSA	1	5.88	16	94.12
	IBEJU-LEKKI	1	5.88	16	94.12
	IKEJA	11	64.71	6	35.29
HARD-TO-REACH	ALIMOSHO	7	41.18	10	58.82
	IKORODU	8	47.06	9	52.94
	MUSHIN	2	11.76	15	88.24
TOTAL		30	29.41	72	70.59

Nifedipine nitrophenylpyridine analog constituted the only impurity found in the nifedipine tablets. It was found in amounts exceeding the 2.0% specification in 76 (74.51%) of drug samples collected (**Table 4**). Of the 102 samples collected, 24 (23.53%) complied with both tolerance limits; 72 (70.59%) met the active pharmaceutical ingredient standards; and 26 (25.49%) met the drug purity standards. Nifedipine nitrophenylpyridine analog impurities which constitutes the two major impurities found in nifedipine tablets, was found in amounts exceeding the 2.0% specification in 74.51% of drug samples collected. This was the only impurity found.

Table 4: Percentage of poor quality drugs based on % purity found by LGA and social economic status

SES	LGA	QUALITY CATEGORIES			
		SUBSTANDARD (<98%)		**GOOD (>98%)**	
		n	**%**	**n**	**%**
HIGH SOCIAL ECONOMIC STATUS	ETI-OSA	7	41.18	10	58.82
	IBEJU-LEKKI	16	94.12	1	5.88
	IKEJA	17	100	0	o
HARD-TO-REACH	ALIMOSHO	16	94.12	1	5.88
	IKORODU	14	82.35	3	17.65
	MUSHIN	6	35.29	11	64.71
TOTAL		**76**	**74.51**	**26**	**25.49**

Of the 30 falsely labelled drugs 56.67% emanated from LGA categorized as low social economic status or hard-to-reach.76 drugs samples were found to be substandard based on the amount of impurities found, 40 of them were from high social economic status

LGA. Out of the 76 samples, 6 drug samples from Ikeja, a LGA categorized as a high social economic status area, were found to have impurities in quantities exceeding 10% which is an extreme deviation from the 2% limit.

3.2.2 Country of origin and manufacturers

The drug samples analyzed in this study came from 6 different countries based on their labels: India, Israel, Nigeria, Switzerland, Germany, and Slovenia. These countries were grouped into continents and as indicated in the **table 5**. Almost half of the drugs collected were reported to come from Asia; 50 (49.01%). Thirty-nine (38.3%) of the drug samples were manufactured in Africa and came from manufacturers based in Nigeria. We could not establish the precise location of manufactures of 6(5.9%) of the drug samples collected.

Table 5: Percentage of places of manufacturer in each LGA

Places of drug's manufacturer	Alimosho	Eti-Osa	Ibeju-Lekki	Mushin	Ikeja	Ikorodu	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Asia	10 (58.8)	4 (23.5)	10 (58.8)	9 (52.9)	8 (47.1)	9 (52.9)	50 (49.0)
Europe	3 (17.6)	0 (0)	0 (0)	2 (11.8)	1 (5.9)	1 (5.9)	7 (6.9)
Africa	4 (23.5)	13 (76.5)	7 (41.2)	4 (23.5)	7 (41.2)	4 (23.5)	39 (38.2)
Unknown	0	0 (0)	0 (0)	2 (11.8)	1 (5.9)	3 (17.6)	6 (5.9)

Most of the falsely labelled drugs were from Asia which was the indicated source of most the drug samples; 18(60%) were from manufacturers based in Asia,7(23.33%) were from Africa and 5(16.67%) were from Europe and unknown locations (**Table 6**).

Table 6: Number of poor quality drugs based on % found, % purity and places of drug's manufacturer per LGA

PLACES OF DRUG'S MANUFACTURER	LGA						
	ALIMOSHO n (n % Found, n %Purity)	MUSHIN	ETI-OSA	IKEJA	IKORODU	IBEJU-LEKKI	TOTAL N (%of 102) (n % Found, n %Purity)
Asia	10(6,10)	2(0,2)	1(1,1)	8(6,8)	7(4,7)	9(1,9)	38 (37.25%) (18,37)
Europe	2(0,2)	1(1,0)	0(0,0)	1(1,1)	1(1,1)	0(0,0)	5 (4.9%) (3,4)
Africa	4(1,4)	3(0,3)	6 (0,6)	7(3,7)	4(3,4)	7(0,7)	31(30.39%) (7,31)
Unknown	0(0,0)	1(1,1)	0(0,0)	1(1,1)	2(0,2)	0(0,0)	4 (3.92%) (2,4)

Substandard drugs were mainly manufactured in Asia where 37 (48.68%) of drug samples collected failed to meet purity standards. The second commonest origin of substandard drug samples was Africa with 31(40.79%) substandard drug samples. All samples indicated to have been manufactured in unknown locations and Europe, except 1, were substandard. Good quality drugs samples came from Asia 15 (62.5%), 8(33.33%) were sourced from Africa and 4(16.67%) were from Europe and unknown regions.

3.2.3 Price of drugs compared to poor quality

The prices of drugs samples collected varied in the different LGA but were all below 2 US dollars.1 US dollar is equivalent to 368 Nigerian Naira-(NGN). The mean price was 380.30 NGN. Good quality drugs had a higher mean price of 431.74 NGN than poor quality drugs 365.12 NGN (**Table 7**). The highest LGA price average come from a low social economic status LGA, which also had the least number of poor quality drugs. The second highest priced drugs were from a high socio-economic status LGA whose drugs samples failed to meet drug quality standards. The two lowest price averages were from areas characterized as being both low and high social economic status and both had poor quality drug samples amounting to over 80% of their samples. Overall, the mean price was higher in high socio-economic status LGA [m= 382.80 NGN, sd=0.65(233.36)] than in lower socio-economic status LGA [m= 377.84 NGN, sd=0.81(297.51)]

Table 7: Number of poor quality drugs per LGA and Average Price

LGA	NUMBER OF POOR QUALITY DRUGS	AVERAGE PRICE IN USD (Nigerian Naira)	SES
Ibeju Lekki	16 (94.12%)	0.85 (290)	HIGH
Ikeja	17 (100%)	1.36 (462)	
Eti-Osa	8 (47.06%)	1.17 (398)	
Alimosho	16 (94.12%)	0.87 (295)	LOW
Ikorodu	14 (83.35%)	0.83 (282)	
Mushin	7(41.18%)	1.62 (550)	

3.2.4 Predictors of drug quality

Among the drug samples that met specifications for purity and amount of active pharmaceutical ingredients(API), only 24 (23.63%) met both specifications. Forty eight (47.06%) samples met specifications for API but not for purity and only 2(1.96%) met purity standards and failed to satisfy the API standards. The samples that met the API amount standards and those that met the purity standards were significantly different (P<0.05). The API amount standards did not differ by LGA socio-economic status (P=0.35), price (P=0.43), and region of manufacturer (P=0.89). Similarly, API purity standards of the drug samples did not differ by LGA Socio-economic status (P=0.39) and region of manufacturer (P=0.24), but there was a trend for a difference by price of the drug samples (P=0.06).

Among drugs that failed to meet quality specifications, low socio-economic status LGA were less likely to have low quality drugs than high socio-economic status LGA: correlation coefficient (β) -0.08 (95% CI -0.24 to 0.09).The price of drugs was associated with the quality of the drug. As the price increased, the less likely that the drugs would be of low quality: β -0.05 (95% CI -0.16 to 0.07). A linear regression of region of manufacturer against low quality drugs revealed that compared to drugs from Africa, drugs from Asia, Europe, and those whose origins were unknown, were not

significantly different; Asia β- -0.34 (CI -0.22 to 0.15), Europe β- -0.08 (CI -0.43 to 0.27),

Unknown β- -0.12 (CI -0.50 to 0.25)

4. Discussion

Falsely labelled and substandard drugs continue to become widespread globally

posing great threat to the health of patients and the integrity of the pharmaceutical

sector. The negative effects of these poor-quality drugs have been identified to transcend

the poor individual health outcomes as they are at risk of causing household,

community and national financial deterioration. Additionally, these drugs threaten

national and global health security and continue to contribute to short life expectancy

for both children and adults.

4.1 Discussion of Findings

Our report represents the first study of antihypertensive drugs in Lagos State,

Nigeria whose main aim is to evaluate the prevalence of falsely labelled/ substandard

drugs and the association with social-economic status. This report is also a

representation of the first study leveraging pre-existing geographical civil divisions of

Lagos State, Nigeria in its sampling process for the evaluation of antihypertensive drugs.

Of the 102 samples collected, only 24 samples of nifedipine (23.53%) met expected

standards following biochemical analysis (**Table 8**).

Falsely labelled drugs which were drugs that failed to meet standards set for the amount of active pharmaceutical ingredient, were identified in 30 (29.42%) samples. The proportion of substandard drugs, which are drugs containing high levels of impurities, comprised 76 (74.51%) of the samples.

Table 8: Number of good quality drugs meeting all expected purity and amount standards

LGA	NUMBER OF SAMPLES	PERCENTAGE	SES	TOTAL
ETI-OSA	9	52.94	HIGH	10
IBEJI LEKKI	1	5.88		(41.67%)
IKEJA	0	0		
ALIMOSHO	1	5.88	LOW	14
IKORODU	3	17.65		(58.33%)
MUSHIN	10	58.82		
TOTAL	24	23.53	-	-

The frequency of falsely labelled and substandard drugs differed by socioeconomic status. A higher proportion of falsely labelled drugs were from hard-to-reach or low socioeconomic status LGA. These are drugs that were mislabeled and the amounts of API found differed from the labelled dose. The inverse was observed in the proportion of substandard drugs. A higher proportion of drugs with high levels of impurities came from high socioeconomic areas. Contrary to our expectations, a higher number of drugs that met all the purity and API amount standards were from areas of low socioeconomic status. Overall, the number of good quality drugs was found to be

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higher in lower socioeconomic areas as compared to the high socioeconomic areas. Although most drugs in this study met the set standards for amounts of API, the levels of impurities in the samples collected contributed to the large number poor quality drugs. For example, a majority of samples had amounts of API within the normal range of 90%- 110% but most of these samples had impurities exceeding the 2% mark. Several factors have been identified to cause the high levels of impurities in the nifedipine drug samples. These include poor manufacturing processes whereby impure substances are used in the drug manufacturing technique, unacceptable quality control and assurance, wrong storage and low quality packaging.

The strong association of poor quality drugs and place of manufacturing highlights the urgent need to enforce trans-border drug monitoring and regulations. Drug manufacturers from Asia were reported as a risk factor for substandard and falsely labelled drugs as the largest proportion of drugs that failed to meet the expected standards were indicated to come from manufacturers in this continent. This is in accordance with international reports such as the World Health Organization and United Nations Office of Drugs and Crime which have implicated that Asia accounts for the largest share in the trade of poor quality medicines.(29)

4.2 Limitations

Most reports, ours included, are limited since they only provide a snapshot of the magnitude of the scale of poor quality drugs. Illegal medicine vendors are extremely flexible and innovative in how they reconstitute drugs and with the increased ease of conducting business through the internet, the amounts of poor quality drugs continue to rise almost uncontrollably. It is thus hard to get a precise measure of the scale of the existence of substandard and falsely labelled drugs in not only Lagos State but the rest of Nigeria and the globe. The study was only focused on Lagos State and is thus not generalizable to represent the rest of the country. To secure representative information, we secured population data from the National Population Commission, Lagos State as well as a list of all registered facilities in Lagos state. These had explicit limitations whereby the population data was more than 10 years old and the list of registered drugs vending facilities was not categorized according to LGA. This led heterogeneity in the LGA identified for the study. For example, Ikeja LGA was categorized as a high socioeconomic status area but had areas that would be considered as hard-to-reach. Additionally, Ikeja differed immensely socioeconomically from Eti-Osa yet they were both identified as high socio economic areas.

Randomization in the study of the prevalence of substandard or poor quality drugs is often not feasible in every market particularly informal drugs shops and

internet pharmacies. It was impossible to create an exhaustive list of all possible

pharmacies, which is a mandatory requirement for randomized sampling. Therefore,

creating a basis for calculation of risks of poor quality drugs for the whole population in

Lagos State was not actualized due to an array of reasons. The list of registered facilities

in the LGA sampled was not up-to date, exhaustive and neither did it provide precise

location details.

A literature review of studies evaluating the equality of drugs further elaborates

the difficulties faced in randomization. A systematic assessment of data published in

2007 to 2016 of prevalence and risks of counterfeit and poor quality drugs revealed that

of the 41 studies, only 17 employed random sampling in their methodology and most of

these studies had insufficient sampling strategies.(30) The randomization plan was

carried out on facilities divided according to location, types of facilities and markets

(formal, informal, public or private). This makes it difficult to identify studies that reveal

the true prevalence of poor quality drugs. The sampling process was labor intensive and

time consuming and replicating the methodology employed might not yield significant

results particularly in the evaluation of informal markets. Time and financial pressures

did not facilitate for a very large sample size of not only the formal markets but the

unregulated open air markets as well.

Nevertheless, the study had many notable strengths including the largest sample of drugs sourced from registered drugs facilities in Lagos State, the use of mystery shoppers to eliminate bias and production of strong findings that could potentially be used to formulate and implement policies geared toward the control of the illegal drug trade.

4.3 Interventions

Drug adulterating methods are becoming more advanced each day thus rendering the vice to grow and penetrate various geographical areas unequally. (31)Developing countries continue to be most affected where the number of preventable deaths continues to increase due to causes such as poor quality drugs. This study reveals that the pandemic needs stringent measures as the poor-quality drugs identified resemble genuine products and visual inspection is insufficient. Without chemical analysis, medical doctors, patients and even pharmaceutical professionals are at risk of being deceived. We suggest creating of robust countermeasures on three different fronts; Policy and legal, supply and demand fronts.

4.3.1 Policy and legal aspects

To fully disintegrate the business of poor quality drugs, it is critical that we understand its causes and organization. Globally the main reason for the rife

counterfeiting in medicine is lack of robust legislation and enforcement. For example,

many open air markets exist in Nigeria and these have been deeply rooted in the trade

of poor quality drugs.(22) Manufacturers sell to traders in these markets who in turn

distribute the drugs to other parts of West Africa and Central Africa.(22) Additionally,

more than 70% of the drugs used in the legitimate market in Nigeria are imported from

China and India, countries that are known to be major sources of poor quality

drugs.(22)A systemic approach is needed in eradicating the vice that is poor quality

drugs.

Effective regulation and implementation of policies is an exclusive mandate of

the government to the population. The government of Nigeria should empower

preexisting regulatory bodies such as the National Agency for Food and Drug Control, a

federal agency under the Federal Ministry of Health. Establishing transparency and

capacity building at the state level is also critical in stopping the trade of substandard

drugs and promoting legal enforcement. Open air medicines markets should be

abolished immediately as they continue to create a conducive environment for the trade

of poor quality medicines. The government should also tailor measures that target each

player in the supply chain as profits reaped in the trade of poor quality drugs vary not

only by location but also via the hierarchy present in most supply chains. Wholesalers

for instance reap more profit than small scale retailers. Additionally, the government

should consider providing incentives to manufactures and key pharmaceutical supply chain stakeholders to encourage good manufacturing processes and improvement of quality control measures.

Key stakeholders in the pharmaceutical industry also have a paramount role to pay in the eradication of poor quality drugs in the supply chain. Stakeholders such as drug manufacturers, wholesalers and retailers should also be actively involved in the abolishment of the illicit drugs trade. Cohesively collaborating with the government regulatory bodies and aiding private pharmaceutical enforcement bodies will certainly results in a marked reduction in the trade. A study carried out in Turkey to evaluate the quality of supply chains revealed that legal action by legitimate medical product rights holders scared away counterfeiters from producing the specific drug. Key stakeholders such as manufacturers of pharmaceutical products also have the mandate to follow international and national standards set for good manufacturing practices. This study revealed that it is highly likely that the poor-quality drugs encountered came to be because of inefficiencies in the production process. The high number of samples with low amounts of active pharmaceutical ingredient and levels impurities exceeding the set standards could have been due to use of poor quality raw materials, low quality control in the manufacturing process or inefficiencies in end product testing processes. It is thus

a mandate of the manufacturers and the government to ensure pharmaceutical products incorporated into the health supply chains meet all expected standards.

The end consumers also have an active role to play.(16) Moreover, patients purchase cheaper drugs from unlicensed facilities even though they are aware that they could possibly be counterfeit. Evidently the substandard and falsely labelled drug existence is driven by complex factors such as corruption and poorly performing financial sectors.(32) Government and private sector collaboration is needed in raising patient awareness. Educating the public on poor drug quality as a health problem, using the right materials for each product will be crucial in curbing the trade of counterfeit goods. More information should also be sought on what patients are willing to pay for genuine medical products.

Beyond national measures to control the epidemic of poor quality drugs, cross-border and multi sector partnerships are needed. Nigeria should collaborate with other states to facilitate multilateral cross-border investigations. Adopting and implementing regulations placed by multilateral organizations such as the World Health Assembly's International Medical Products Anti-Counterfeiting Task Force (IMPACT) and the United Nations office on drugs and crime will ensure the production and distribution of counterfeit goods is eradicated. (33)(34)

4.3.2 Interventions for the pharmaceutical supply chain

Combating the distribution of counterfeit drugs is a complex task and requires multidisciplinary efforts. Nigeria evidently is immensely affected by this illicit trade. Proper management of limited resources to secure the pharmaceutical supply chain in the country is warranted and we recommend testing drugs in various stages of the supply chain. In the introduction segment of this report, we outlined the supply chain organization in most African countries including Nigeria. Comprised of different levels, introducing various validation steps in the supply chain will aid in arrest and prosecution of parties involved in this illegal trade. These validation steps should be enacted on different levels in the supply chain such as the manufacturer, suppliers, wholesalers, repackagers, distributors, medical stores, warehouses, pharmacies or hospitals under the private sector, government, and non-governmental organizations.

This study revealed that most drugs samples collected were substandard or falsely labelled. They contained the correct active pharmaceutical ingredient but in lower amounts that failed to meet expected pharmacopeia specifications. This means that the drugs could possibly be manufactured by registered manufacturers who unfortunately are not meeting all standards set for good manufacturing practices. On the contrary, the drugs could be manufactured by illicit drugs vendors who use the right

raw materials and processes but do not adhere to good manufacturing practices

rendering their products counterfeit and weakly dosed. Nonetheless, drug testing at the

manufacturers level is invaluable and compulsory. Drug testing methods are varied and

are based on both chemical analysis and light sources used to visually assess drug

samples. At the manufacturer level, chemical analysis methods such as colorimetric

methods, liquid chromatography-mass spectrometry, near infrared spectroscopy, near

infrared chemical imaging, mid-infrared spectroscopy, Raman spectroscopy, X-ray

fluorescence, X-ray powder diffraction, Ion Mobility Spectrometry, and Isotope Ratio

Mass Spectrometry can be used.(1)(23) Although some of these methods can be time

consuming and expensive, their impact on reduction of poor patient outcomes due to

poor quality drugs is invaluable. Quicker testing methods such as Near Infrared

spectrometry, Near infrared chemical imaging can be used across all levels of the supply

chain.(19) An example of a successful time efficient testing method is the Global Pharma

Health Fund Minilab™ which is a basic thin layer chromatographic test. It is beneficial

and its impact is greatly positive due to its use as a field assay kit.

Alternate drug protection methods that manufacturers can continue to embrace

are visual and light dependent screening methods that help health professionals and

patients discriminate between real and poor quality drugs. Beyond visual comparison of

primary and secondary drug packaging, other visually qualitative analytical methods

include, tamper proof containers, holographic techniques, radio frequency identification tags, digital watermarking, bar codes, and information technological methods such as scratch cards placed on drug packaging that when scratched reveal a hidden code that can be used to confirm authenticity.(32)(35)

4.3.3 Interventions for the demand side

Developing effective and sustainable countermeasures to the illicit trade of substandard and falsely labelled drugs is often focused on the manufactures and supply chain ends leaving the patient or demand end unaddressed. To combat this problem there is a great need to understand the consumers' attitudes in their respective environments or contexts. Consumers in lower and middle income countries have different drives and motivations from end users in developed nations toward consuming poor quality drugs. Consumers in developed nations are more susceptible to poor quality drugs due to consumption of lifestyle drugs which is a contrast to those in developing nations where the significantly high demand creates a conducive environment for counterfeiters for critical drugs such as antibiotics and antimalarial.(36)(37)(38) More studies should be carried out in Nigeria and other low and middle income countries to understand the consumer perceptions and what affects their attitude toward poor quality drugs as without consumers' demand, the supply of inferior drugs would be non-existent. There are multiple postulated reasons for the

purchase and use of counterfeit drugs. The major reason for the vulnerability to poor

quality drugs is unaffordable prices.(16)Consumers in Nigeria often cannot afford

medicines in legitimate markets such as chain pharmacy stores and end up purchasing

drugs in non-legitimate stores without much consideration of the medical products'

authenticity. This is a contradiction to the common phenomena of linking high prices to

high quality and goes to illustrate just how poor consumers have no option but to

consume poor quality drugs. In addition to unaffordability other factors greatly

influencing the use of substandard and poor quality drugs is inaccessibility, no

availability and lack of knowledge about the presence of illicit drugs. The latter factor is

more pronounced and compounded by the variability in the pharmaceutical industry.

Consumers often make the assumption that generic drugs are less at risk of being

adulterated as compared to branded drugs.(16) Cultural and social factors also come

into play in influencing purchase practices among consumers. It is a common incidence

for people to trust their relatives and friends more than certified health workers thus in a

population that is not well educated, the supply of adulterated drugs cannot be halted

by exclusive health education from pharmacists and health workers.(16) Policy makers

and pharmaceutical industry stakeholders should raise awareness not only about the

presence of poor quality drugs but also educate people on ways of identifying the illicit

drugs and the appropriate channels to use reporting purposes.(39) Creation of incentives

to consumers will also encourage people to seek and purchase of legitimate drugs and

want better products.

5. Conclusion

In this study, we encountered a significant proportion of substandard and poor quality drugs in Lagos State, Nigeria. All drugs collected had the appropriate API upon biochemical analysis. The high levels of impurities, whose probable cause is lack of adequate quality assurance during manufacture, evidently make it difficult not only for patients but for retailers to identify poor quality drugs without biochemical analysis. The risk of buying a poor-quality drug from a registered facility in Lagos State does not vary based on socioeconomic variables as well as price. This is mainly due to the similarity and consistency of branded drugs and pricing among the LGA in Lagos. These results however, cannot be generalized to the informal markets or other parts of Nigeria. A collaborative effort is thus needed to eradicate substandard and falsely labelled drugs to stop premature mortalities resulting from infections non-communicable diseases.

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