A review on drug quality surveillance in West Africa

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ABSTRACT

Background: Comprehensive and concerted drug quality surveillance has been recognised as a panacea towards ensuring that safe and effective drugs are in circulation.

Objectives: This review chronicles the efforts at ensuring good quality drugs within the West African sub-region. It also discusses the efforts of International donor agencies and National Drug Regulatory Agencies at combating the menace of substandard, spurious, falsely-labeled, falsified and counterfeit (SSFFC) medicines.

Methods: Literature searches were conducted on all reports detailing efforts within the various countries in the sub-region. The expectations of various donor agencies and international organizations were reviewed from available reports. Efforts by the various National Agencies were also studied using information on their websites. Based on the available records, the recurring challenges were identified and solutions proffered.

Results: Several publications in scientific journals were found addressing the quality of circulating drugs within West Africa. The reports spanned close to fifteen years. Majority of the reports on antibacterial agents focused more on antimicrobial resistance rather than on the quality of the agents. The efforts of the donors are commendable as they have been providing avenues in terms of technical training and provision of reference standards. Several challenges against effective drug quality are still prevalent in the sub-region.

Conclusion: It is imperative to note that the battle against circulation of SSFFCs is far from being won. Every stakeholder in the drug distribution chain must arise to the responsibilities of eliminating them.

Keywords: Drug quality, Surveillance, West Africa, Counterfeit medicines, Challenges

Un examen de la surveillance de la qualité des médicaments en Afrique de l'Ouest

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Résumé

Contexte: On admet qu'une surveillance complète et concertée de la qualité des médicaments est une panacée pour s'assurer que des médicaments sûrs et efficaces sont en circulation.

Objectifs: Cet article fait état des efforts visant à garantir des médicaments de bonne qualité dans la sous-région de l'Afrique de l'Ouest. Il traite également des efforts déployés par les organismes donateurs internationaux et les organismes nationaux de réglementation des médicaments dans la lutte contre la menace de médicaments de qualité inférieure, faux, faussement étiquetés, falsifiés et contrefaits (SSFFC).

Méthodes: Des recherches sur la littérature ont été effectuées sur tous les rapports détaillant les efforts dans les différents pays de la sous-région. Les attentes de divers organismes donateurs et organisations internationales ont été examinées à partir des rapports disponibles. Les efforts des différentes agences nationales ont également été étudiés à l'aide d'informations disponibles sur leurs sites Web. Compte tenu des enregistrements disponibles, les défis récurrents ont été identifiés et des solutions proposées.

Résultats: On a découvert que plusieurs publications dans des revues scientifiques traitent de la qualité des médicaments en circulation en Afrique de l'Ouest. Les rapports couvrent une période de près de quinze ans. La majorité des rapports sur les agents antibactériens ont davantage porté sur la résistance aux antimicrobiens plutôt que sur la qualité des agents. Les efforts des donateurs sont louables, étant donné qu'ils fournissent des possibilités en matière de formation technique et de fourniture de normes de référence. Plusieurs défis contre la qualité efficace des médicaments sont encore fréquents dans la sous-région.

Conclusion: il est impératif de noter que la bataille contre la circulation des SSFFC est loin d'être gagnée. Tous les intervenants de la chaîne de distribution de médicaments doivent être à la hauteur des responsabilités pour les éliminer.

Mots-clés: Qualité des médicaments, surveillance, Afrique de l'Ouest, médicaments contrefaits, défis

INTRODUCTION

The quality of pharmaceutical products is the end result of several and multifaceted factors. The procedures to establish that a comprehensive quality assurance programme exist for medicines comprise of such procedures as; to ensure that only medicine products that meet current standards for quality are procured, procedures to verify that shipped goods meet the specifications and procedures to monitor and maintain the quality of pharmaceuticals from the moment they are received until the medicine is finally consumed by the end-user.[1]

Pharmaceutical quality assurance has been described as the sum of all activities and responsibilities required to ensure that the medicine that reaches the patient is safe, effective, and acceptable to the patient while pharmaceutical quality control is the process concerned with medicine sampling, specifications, and testing, and with the organization's release procedures that ensure that the necessary tests are carried out and that the materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.[2]

Attaining and maintaining quality of drug products require several efforts from all and sundry, from government, manufacturers, drug regulatory agencies, distributors, professionals who handle drugs and, of course, to the patients. The overall quality of medicines is ensured by the technical and managerial activities of the quality system. In this regard, the sourcing of the active pharmaceutical ingredients, excipients as well as procedures and processes adopted must be regularly evaluated, validated and documented. Even when product quality is guaranteed at manufacture and release stages, it behooves an excellent system to carry out post-marketing surveillance throughout the shelf-life of the products.

More often than not the quality of pharmaceutical products goes beyond just end-stage testing and in-process controls. There are other factors outside the terrains of the manufacturing outfits. One of such significant factors is the storage of the products throughout its shelf-life. It is a legal requirement that appropriate storage conditions must be prescribed and inscribed prominently by the manufacturers on product packs. This is more so that it has been generally recognised that apart from the raw materials used in product formulation, impurities introduced during inappropriate storage can lead to introduction of unexpected quality defects and untoward side effects.

It is based on the backdrop of the foregoing that effective surveillance must be put in place at all the levels of the drug distribution chain.

The West African sub-region has been laden over the last few decades with the problems of substandard, spurious, falsely-labeled, falsified and counterfeit (SSFFC) medicines. This region shares this burden alongside the entire African Continent, Asia and South America. The factors promoting the circulation of these products are myriad and several efforts have been put in place at International, Regional and National levels to fight the menace. A counterfeit product is deliberately and fraudulently mislabeled with respect to source and/or identity. Counterfeiting can apply to both generic and branded products. Counterfeit products may include: products with the correct ingredients, with the wrong ingredients, without ingredients, with incorrect quantities of active ingredients, with fake packaging.[3]

Several efforts have been put in place to control the circulation of falsified products. One of the major mechanism by which drug products can be certified to be safe, effective and of the right quality is through efficient and well-coordinated surveillance. This review article chronicles some of the efforts being put in place by National Regulatory agencies as well as supports of international organizations. It also reviews available data on quality of medicines used in the management of major life-threatening conditions. The need to surmount some of the observed challenges is outlined.

Expectations and Supports of International Agencies

The importance attached to the use of drugs and the essence of their relevance has led to the prescription of stringent requirements by many organizations involved in drugs and drug products. This section discusses the various expectations on drug and drug product quality. The stringent requirements set up by these international organizations are expected to be adapted and adopted by both regional and national drug regulatory agencies.

Some of the agencies that have documented such requirements on product qualities include the World Health Organization (WHO), US Agency for International Development (USAID), US Food and Drug Administration (USFDA), United States Pharmacopoeia (USP) and International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The collective efforts of these international agencies have led to the design of guidelines for instituting and maintaining drug product quality all over the world and in particular across low-resources economies, the

category where majority of countries within the West African Sub-region belongs.
Some of the expectations and efforts of these agencies are briefly outlined in the following paragraphs.

World Health Organization (WHO)
The WHO is increasingly recognising that there are present in circulation, drug products of questionable quality. It therefore, through regular bulletins and drug information publications, educates health communities across the world on quality, safety and efficacy of drug products. According to WHO's drug information publication in 2014 [4], the WHO's role in combating unsafe medicines is described as providing information and creating awareness, to develop and promote norms and standards for medicines quality assurance, and to provide technical support to build regulatory capacity in Member States.[5] *Apart from this and* beyond fulfilling its normative role, WHO also offers practical support for example through its prequalification of quality control laboratories programme and its External Quality Assurance Assessment Scheme (EQAAS). The WHO also provides a unique forum bringing together Member State governments in the interest of public health. WHO's globally supported Surveillance and Rapid Alert System for SSFFC Medical Products has collected over 200 case reports resulting in five international drug alerts since 2012. As part of its standard-setting role the WHO is providing guidance on the use of laboratory techniques to identify suspect products circulating in countries. A range of spectroscopic, chromatographic and other methods have been suggested to detect SSFFC products. Hand-held devices have been developed for use at ports of entry or in remote areas, such as the FDA's Counterfeit Detection Device CD-3 which can be used to screen tablets, packaging and even documents. The WHO has as far back as 2006 launched a taskforce to fight counterfeit drugs codenamed The International Medical Products Anti-counterfeiting Taskforce (IMPACT).[6]

One other major support provided by the WHO is the regular surveillance of products through its six accredited laboratories across various regions of the world in 2014. The report of one of such surveys [6] revealed how substandard, spurious, falsely labeled, falsified and counterfeit medicines are detected in these countries. In the West African Sub-region, Ghana participated in the survey programme. Apart from the current initiatives of the WHO, this apex international agency has been recognised for instituting guidelines that have imparted positively on drug product quality.

The problems bedeviling the manufacturing, distribution and quality surveillance of drug products in West Africa are many and varied. The political instability, depressed economy, lack of adequate enforcement of rules and regulations, importation by unauthorized personnel, inadequate personnel and training have continued to prevent the circulation of safe, quality and efficacious products. Thus, countries within the sub-region have immensely benefited from the contributions of the WHO to quality assurance and quality control of drugs and drug products. Some of the publications of WHO in this regard include; notification of quality requirements, setting up of a code of good manufacturing practices for pharmaceutical products, basic test programme, provision of guidelines on selection of essential medicines, provision of guidelines on stability and WHO certification scheme among others.

The last two guidelines have had dramatic positive impacts on the quality and safety of medicines circulating in the sub-region. With the publication of the guidelines on stability of pharmaceuticals, manufacturers and agencies can now design and implement stability studies on products. This becomes necessary as majority of products are manufactured in climes different from the tropical climate of West Africa. Instances of instabilities will obviously be prevalent but for the opportunity to test and prescribe adequate local storage conditions using the WHO guideline on stability studies. In addition, the WHO Certification Scheme has provided a good mechanism for importing countries with inadequate or limited facilities to evaluate the quality of drug product right from the country of origin of such products.

US Agency for International Development (USAID)
The USAID has proven itself as one of the reliable development partners in ensuring adequate drug product quality in low-income countries. USAID regularly supports the efforts in providing quality surveillance of drug products across the world. Through collaborations with United States Pharmacopoeia, USAID has provided grants for ensuring drug product quality. One of such supports is *The Promoting the Quality of Medicines (PQM) program* that combats the proliferation of falsified and substandard medicines. Funded by the U.S. Agency for International Development (USAID), PQM is the successor to the Drug Quality and Information (DQI) program, implemented by the United States Pharmacopoeial Convention (USP). By providing technical assistance to developing

countries, PQM achieves three main goals; builds local capacity in medical quality-assurance systems, increases the supply of medicines to USAID health programs and ensures the quality and safety of medicines globally.[7] The reports presented for the first quarter of 2016 by the PQM program are presented in Tables 1 and 2. The partnership between USAID and USP has been in existence for well over 25 years. [8] The programmes involved in this partnership and the timelines are; Rational Pharmaceutical Management (RPM) project (1992-2000); Drug Quality and Information (DQI) programme (2000-2008) and Promoting the Quality of Medicines (PQM) program (2009-2019).

Table 1: USAID PQM Progress in First Year 2016 [7]

Area of Technical Assistance	Q1 FY16 Progress
Quality Control (QC) Trainings	12 training workshops held in 8 countries
Quality Management Systems (QMS)	18 labs in 13 countries assisted
Medicines Quality Monitoring (MQM)	Active PQM Supported: 14 countries (122 sentinel sites Active Country Operated: 7 countries (63 sentinel sites)
Good Manufacturing Practices (GMP)	42 companies in 14 countries assisted

Table 2: USAID PQM Accomplishments in Strengthening Medicines Quality Control [7]

Indicator	Q1 FY16 Progress
No. of laboratories provided with equipment/supplies	12
No. of laboratory instruments/equipment installed, calibrated and qualified	50
No. of PEPFAR-supported testing facilities (laboratories) that are recognised by national, regional or international standards for accreditation or have achieved a minimal acceptance level towards attainment of such accreditation	1 (Ethiopia)
No. of ARV, OI, TB, antimalarials and MCH PMS samples tested	1504 tests
No. of APIs prequalified	API: 1 Prequalified
No. of FPPs prequalified	FPP: 2 Global Fund ERPs
No. of Dossiers accepted by WHO	FPP: 2 Dossier Accepted by WHO
No. of WHO GMP inspections	FPP: 1 Successful WHO GMP Inspection

PEPFAR, President's Emergency Plan for AIDS Relief; ARV, Antiretroviral Therapy; TB, Tuberculosis; API, Active Pharmaceutical Ingredient; FPP, Finished Pharmaceutical Product; ERP, Expert Review Panel; PMS, Post-Marketing Surveillance

US Food and Drug Administration

The USFDA, an agency of the US Department of Health and Human Services, provides sound guidelines for the adequate quality monitoring of food and drug products. It has come to serve as the apex body for prescription of appropriate tests and guidelines for ensuring the quality and safety of foods and drugs. Majority of national and regional drug regulatory agencies draw inspirations from the codes set up by the USFDA.

The USFDA provides several pharmaceutical quality resources. The resources are aimed at ensuring that products are provided with the strictest quality to guarantee efficacy. Some of these resources as presented on USFDA's website are; Centre for Drug Evaluation and Regulations (CDER)'s Quality Initiative & the Office of Pharmaceutical Quality, Quality Information for Applicants: Chemistry and Manufacturing Controls (New Drug Application, Biologics License Application, Investigational New Drug, etc.), Quality Information for Manufacturers: Current Good Manufacturing Practices, Advancing Product Quality as well as Presentations on Pharmaceutical Quality Topics.9 In particular, the expectations on advancing product quality provides guidelines on Quality Metrics for Drug Manufacturing, FDA / EMA Quality by Design pilot program and Continuous Manufacturing process monitoring using new paradigm shift of Process Analytical Technology.

The USFDA equally provides guidance on current good manufacturing practices.[10]

USP

The USP has as its mission to help protect and improve the health of people around the world. In accomplishing this mission, USP creates standards and foster partnerships so as to continually work to build and reinforce a foundation that draws it closer to a world where everyone can be confident of quality in health and healthcare.

Thus, USP pursues a mission to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. The USP envisions a world in which all have access to high quality, safe, and beneficial medicines and foods. USP approaches this vision with a sense of urgency and purpose, strengthened by its cadre of dedicated expert volunteers, members, and staff, and by working collaboratively with key stakeholders across the globe.[11]

ICH

The International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is also another international agency that has contributed significantly to ensuring the quality of pharmaceuticals through provision of standard guidelines for manufacturing and evaluation of products. The harmonization achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management. 12

Previous Reports on Drug Quality Surveillance

Several commendable efforts have been made at ensuring that pharmaceutical products that circulate within the West African sub-region are subjected to quality assessments in order to make sound pronouncements on their suitability or otherwise. The scientific literatures are replete with reports of studies conducted within the region as well as reports in other parts of the world using drug products sampled within the West African sub-region. This section reviews the reports and chronicles some of these surveillance efforts with a view to assessing the seriousness attached to drug product quality.

Two particular classes of drugs have been the subject of extensive surveillance from available literature; the antimalarial and antibacterial agents. The reasons for such attention on these drugs are obvious. Majority of the countries in the sub-region still battle with the need to control malaria and various infections. The prevalence of these two medical conditions makes their respective therapeutic agents objects of counterfeiting and adequate attention will continually be needed to overcome the issue of circulation of SSFFCs in the various countries within the sub-region.

Reports on quality of antimalarial drugs

Malaria has been recognised as highly endemic in Sub-Saharan Africa. However, the 1990s witnessed a new surge in malaria due in part to increased resistance to chloroquine and sulfadoxine-pyrimethamine (SP). 13,14 Exposure to substandard antimalarial drugs has been recognised as one likely source of this trend. 15, 16, 17 Attaran *et al*[18] noted that pressure from malaria scientists prompted wholesale adoption of artemisinin-based combination therapies (ACTs) by endemic country governments and donors.

In a six country study by Bates *et al*[13], a range of antimalarial drugs were procured from private pharmacies in urban and peri-urban areas in the major cities of six African countries, situated in the part of that continent and the world that is most highly endemic for malaria with Ghana and Nigeria being two of the study sites. Semi-quantitative thin-layer chromatography (TLC) and dissolution rates testing were used to measure active pharmaceutical ingredient content against internationally acceptable standards. The Global Pharma Health Fund e.V. Minilab® was used to run semi-quantitative thin-layer chromatography (TLC) where drugs were adjudged to have passed if it meets the 80% of drug content without any upper boundary being set. 35% of all samples tested failed either or both tests, and were substandard. Further, 33% of treatments collected were artemisinin monotherapies, most of which (78%) were manufactured in disregard of an appeal by the World Health Organisation (WHO) to withdraw these clinically inappropriate medicines from the market. The high persistence of substandard drugs and clinically inappropriate artemisinin monotherapies in the private sector risks patient safety and, through drug resistance, places the future of malaria treatment at risk globally.[13]

However, in more a comprehensive laboratory-based study of the quality of SP combination drugs available in the Nigerian market in 2003, the quality and physicochemical equivalence of eight different brands were assessed. The assessment included the evaluation of uniformity of weight, friability, crushing strength,

disintegration and dissolution tests as well as chemical assay of the tablets. In the study, all the eight brands of the tablets passed the British Pharmacopoeia (BP) standards for uniformity of weight, disintegration and crushing strength. Three of the eight brands failed the friability test. One of the brands did not comply with the standard assay of content of active ingredients while another brand did not comply with the USP specifications for dissolution test for SP tablets. There were no significant differences in the amounts of pyrimethamine and sulfadoxine released from the different brands. [19]

Artemisinin-based combination therapies (ACTs) are currently recommended by the World Health Organisation (WHO) as first-line treatment for falciparum malaria. The use of good quality medication for effective malaria control and treatment cannot be overemphasized. [20] This has led to the need to control substandard, degraded and falsified ACTs which pose a threat to malaria patients [21] and may accelerate the spread of drug resistance. [22] Falsified monotherapies and ACTs have also been reported in Africa, where there is a high burden of potentially fatal falciparum malaria. 23, 24 With 48 million clinical episodes and 180,000 deaths per year, Nigeria is the single most heavily malaria-burdened country in the world. Malaria accounts for 60% of outpatient visits, 30% of hospitalizations under five years of age, and 11% of maternal deaths. In 2005 Nigeria adopted the ACT artemether/ lumefantrine as the first-line treatment for uncomplicated malaria at public health facilities, and subsequently added artesunate/amodiaquine. [23] In Southeast Nigeria in 2008, 27% of non-ACT antimalarial drugs (60 out of 225) did not meet the United States Pharmacopoeia (USP) quality specifications for dissolution testing. 25 In the study by Kaur et al. (2015), content analysis of 3024 samples purchased from 421 outlets in Enugu, Nigeria using convenience (n=200), mystery (n=1,919) and overt (n=905) approaches, showed overall 90.8% Artemisinin containing antimalarials to be of acceptable quality, 6.8% substandard, 1.3% degraded and 1.2% falsified. Convenience sampling yielded a significantly higher prevalence of poor quality ACAs, but was not evident by the mystery and overt sampling strategies both of which yielded results that were comparable between each other. Artesunate (n=135; 4 falsified) and dihydroartemisinin (n=14) monotherapy tablets, not recommended by WHO, were also identified. [23]

In a 2004 survey published by WHO [4], which included participants from Ghana, 6% of 417 products suspected to be SSFFCs actually tested positive to be SSFFCs.

The pharmaceutical equivalence studies of some commercial samples of artesunate and amodiaquine tablets conducted in south-west Nigeria in 2009 revealed that thirteen generic brands of artesunate (87 %) and four amodiaquine brands (80 %) investigated were imported. Two brands of the imported artesunate brands were found to contain undetectable amount of artesunate while another 8 samples contained overages. All the amodiaquine brands passed the assay test as stipulated by United States Pharmacopoeia (USP) for amodiaquine tablets while tablet disintegration time of amodiaquine products ranged from 5.8 – 20.7 min. All but one artesunate sample passed the disintegration test too. A majority of the artesunate brands tested had significantly different dissolution profiles ($p < 0.05$). Four (80 %) of the amodiaquine tablet brands tested had similar dissolution profiles and percent drug released within 30 min ($p > 0.05$). One amodiaquine brand demonstrated poor dissolution profile as it did not meet minimum dissolution requirements within 30 min. [26]

In a 2007 survey of available literature, Amin and Kokwaro reviewed several publications that reported the antimalarial drug quality in Africa using the MESH PUBMED database. 27 The search conducted by the authors yielded 21 relevant peer-reviewed articles and three reports on the quality of antimalarial drugs in Africa. The literature was varied in the quality and breadth of data presented, with most bioavailability studies poorly designed and executed. The review highlights the common finding in drug quality studies that; most antimalarial products pass the basic tests for pharmaceutical dosage forms, such as the uniformity of weight for tablets, most antimalarial drugs pass the content test and in vitro product dissolution is the main problem area where most drugs fail to meet required pharmacopoeial specifications, especially with regard to SP products. In addition, there are worryingly high quality failure rates for artemisinin monotherapies such as dihydroartemisinin (DHA); for instance all five DHA sampled products in one study in Nairobi, Kenya, were reported to have failed the requisite tests. [27]

Bassat *et al*.[28] presented a comprehensive review of some of the surveillance efforts on the quality of antimalarial medicines in some African countries. [28] The estimates of the prevalence of poor-quality medicines have been found to vary according to the

sampling and analytical methods used, and reliable, comparable data were reported to be sparse. [28] In 2008, the WHO coordinated a survey of the quality of artemisinin-based combination therapy (ACT) and SP medicines in six sub-Saharan African countries that had received WHO support to strengthen regulatory controls. [28, 29] Overall, 76 of 267 samples (28.5 %) failed to comply with WHO specifications. Extreme deviations from the specifications, likely to be associated with negative health outcomes, were found in 11.6 % of samples. In 2009, a parallel study of 197 samples was conducted collaboratively by the WHO and the United States Pharmacopeia Drug Quality and Information Program, in which 44 % of samples from Senegal failed quality control tests. [28] In a summary of reported data between 2010 and 2011 in Ghana and Togo, 132 artemisinin-containing medicines were reportedly sampled. Only one sample lacked an Active Pharmaceutical Ingredient (API) while for combination products: 83.7 % (had drug content outside 90–110 % API) and for monotherapy, 57.9 % were found to substandard. [30]

In another general surveillance effort spanning the period of 10 years (2003-2013), in a publicly available medicines quality database (MQDB), the U.S. Pharmacopoeial Convention (USP) reports results of data collected from medicines quality monitoring activities spanning the period of 2003–2013 in 17 countries of Africa, Asia, and South America. The MQDB contains information on 15,063 samples collected and tested using Minilab® screening methods and/or pharmacopoeial methods. Approximately 71% of the samples reported came from Asia, 23% from Africa, and 6% from South America. The samples collected and tested include mainly antibiotic, antimalarial, and anti-tuberculosis medicines. A total of 848 samples, representing 5.6% of total samples, failed the quality test. The failure proportion per region was 11.5%, 10.4%, and 2.9% for South America, Africa, and Asia, respectively. Eighty-one counterfeit medicines were reported, 86.4% of which were found in Asia and 13.6% in Africa. [31] In this reported survey, Ghana and Liberia participated in the programme.

Quality surveillance on Antimicrobials

Majority of the surveillance efforts on antibiotics have focused on the documentation of antimicrobial resistance (AMR) and efforts at generating baseline data within the West Africa sub-region. While AMR may result from multiple causative factors, one angle to the emergence obviously will be the quality of the medicines and the strict adherence to recommended regimens. Thus, a loophole in the documentation of AMR is the lack of evaluation of the quality of majority of the drugs. This section presents some of the published data on surveillance efforts on antimicrobial agents.

Antimicrobial drug resistance has become such a global concern that it was the focus of the 2011 World Health Day sponsored by the World Health Organization (WHO). Although antimicrobial drug resistance is well mapped and tightly monitored in some well-resourced countries, such processes do not exist in under-resourced countries. An increasing body of evidence reveals accelerating rates of antimicrobial drug resistance in these countries. Resistance has been noted to arise in the absence of any surveillance and threatens the achievement of the Millennium Goals for Development in terms of reduction of maternal and infant deaths (www.un.org/millenniumgoals/). The problem is even more pressing because, in a globalized world, microorganisms and their resistance genes travel faster and farther than ever before, and the pipeline of new drugs is faltering. [32]

As at 2015, Opintan *et al.* [33] noted that data on AMR in Ghana are limited, and monitoring of AMR is nonexistent. The study therefore sought to generate baseline data on AMR, and to assess the readiness of Ghana in laboratory-based surveillance. Biomedical scientists in laboratories across Ghana with capacity to perform bacteriological culture were selected and trained. In-house standard operating protocols were used to perform microbiological investigations on clinical specimens. Additional microbiological tests and data analyses were performed at a centralized laboratory. Surveillance data were stored and analyzed using WHONET program files. A total of 24 laboratories participated in the training, and 1,598 data sets were included in the final analysis. Majority of the bacterial species were isolated from outpatients (963 isolates; 60.3%). Urine (617 isolates; 38.6%) was the most common clinical specimen cultured, compared to blood (100 isolates; 6.3%). Ten of 18 laboratories performed blood culture. Bacteria isolated included *Escherichia coli (27.5%), Pseudomonas spp.* (14.0%), Staphylococcus aureus (11.5%), Streptococcus spp. (2.3%), and Salmonella enterica serovar Typhi (0.6%). Most of the isolates were multidrug-resistant, and over 80% of them were extended-spectrum beta-lactamases-producing. Minimum inhibitory concentration levels at 50% and at 90% for ciprofloxacin, ceftriaxone, and amikacin on selected

multidrug-resistant bacteria species ranged between 2 ìg/mL and > 256 ìg/mL. A range of clinical bacterial isolates were resistant to important commonly used antimicrobials in the country, necessitating an effective surveillance to continuously monitor AMR in Ghana.

Recognising that tuberculosis (TB) is becoming a worldwide threat, in 2008, a new research network, the West African Network of Excellence for Tuberculosis, AIDS and Malaria (WANETAM), was founded, comprising nine study sites from eight West African countries (Burkina Faso, The Gambia, Ghana, Guinea-Bissau, Mali, Nigeria, Senegal and Togo). The goal was to establish Good Clinical Laboratory Practice (GCLP) principles and build capacity in standardized smear microscopy and mycobacterial culture across partnering laboratories to generate the first comprehensive West African drug-resistance data. [34] Following GCLP and laboratory training sessions, TB isolates were collected at sentinel referral sites between year 2009 – 2013 and tested for first- and second-line drug resistance. From the analysis of 974 isolates, an unexpectedly high prevalence of multi-drug-resistant (MDR) strains was found in new (6 %) and retreatment patients (35 %) across all sentinel sites, with the highest prevalence amongst retreatment patients in Bamako, Mali (59 %) and the two Nigerian sites in Ibadan and Lagos (39 % and 66 %). In Lagos, MDR is already spreading actively amongst 32 % of new patients. Pre-extensively drug-resistant (pre-XDR) isolates are present in all sites, with Ghana showing the highest proportion (35 % of MDR). In Ghana and Togo, pre-XDR isolates are circulating amongst new patients.

However in 2013, Adegoke and Orokotan[35] in addition to studying the success rate of the anti-tuberculosis programme in a south-west Nigerian secondary health facility carried out a pharmacopoeial quality assessment of some of the major anti-TB drugs. The drugs examined for their physicochemical properties included ethambutol HCl, isoniazid, streptomycin sulphate, rifampicin and pyrazinamide. All the drugs were obtained from the pool of donated drugs used in the directly observed treatment short courses. The drugs passed the physicochemical properties using the International Pharmacopoeial guidelines. The results thus eliminated any reason for failure as being due to poor-quality drugs. [35]

Quality Surveillance on other drug products

Literatures abound on the evaluation of the quality of some other medicines such ciprofloxacin, quinine, ibuprofen, cephalosporins and paracetamol. The focus in such publications have been on the generic substitution or otherwise of various brands using several physicochemical properties.

Reported cases of adverse drug effects and events as a result of product quality

The link between quality of medicines and safety in use cannot be overemphasized. The quality of a particular pharmaceutical product carries with it the attendant results of guaranteeing efficacy and safety upon administration.

The attributes of quality as related to medicines include; identity (confirmation of API); assay (amount of active ingredient on the label); disintegration (prerequisite for bioavailability); dissolution (guarantees higher level of assurance of bioavailability); impurities (generally related to API toxicity); uniformity (uniformity of content/dosage which reveals efficiency of GMP) sterility for injectable solutions (to exclude introduction of contaminants into the body); package and label which contains regulated information. [36] In addition to the foregoing, some other critical and relevant quality attributes are prescribed for some medicines based on their peculiar and unique usefulness e.g. vaccines.

When pharmaceutical products fail any or all of these attributes, the attendant consequences are often very grave. As chronicled by Smine in 2012 [36], some of the reported adverse effects and events related to drug product attributes in West Africa include; amodiaquine led to reported children deaths in Ghana in 2005 as a result of overdose; substandard medicines in Nigeria between 2008 and 2009 led to the death of 84 children as a result of diethylene glycol contamination and fake vaccine led to 2,500 deaths in Nigeria in 1995 [36]. While the consequences of these poor-quality medicines are not limited to West Africa, the major brunt of the effects are felt more due to some other reasons that have posed as challenges to effective drug quality surveillance in the region.

Issues of Counterfeit, fake, spurious and substandard drugs in West Africa

The quality assurance of medicines is still weak in most USAID supported countries of which the West African sub-region belongs. Some of the adduced reasons include; weak medicines regulations; lack of adequate or absence of post-marketing surveillance program; quality, safety, and efficacy poorly assessed in registration; access and affordability of medicines still highest priorities of Ministries of health in Many African

countries indicating that drug quality will still be suspect for some time to come; weak or incomplete enforcement and apparent lack of resources [36].

Drug counterfeiting poses a great danger to every society, and the less the awareness, the more it gains root into the system. The first step towards combating counterfeiting is getting people to know that it exists with all its consequent deleterious effects. [37] Some issues of SSFFC medicines have been reported in several West African countries. In Nigeria, the National drug regulatory agency (NAFDAC) has reported some of these instances to include; drugs with no active ingredient(s) e.g. having only lactose or even chalk in capsules and tablets, olive oil in specialized multivitamins capsules. Also drugs with insufficient active ingredients (e.g. 41 mg Chloroquine instead of 200 mg, 50 mg Ampicillin as against 250 mg) have been recovered from circulation. Drugs with active ingredient(s) different from what is stated on the packages e.g. Paracetamol tablets packaged and labeled as sulphadoxine/pyrimethamine combination antimalarial. Clones of fast moving drugs (these are drugs with the same quantity of active ingredients as the genuine original brand, but may not have the same efficacy) have equally been sampled in the country. Drugs without full name and address of the manufacturer and herbal preparations that are toxic, harmful, ineffective or deceitfully mixed with orthodox medicine were also severally reported. The issue of expired drugs or drugs without expiry date, or expired and re-labeled with the intention of extending their shelf-life and drugs not certified and registered by NAFDAC have all been discovered from surveys. [37]

The WHO has identified several factors facilitating illicit trades in drugs and which often lead to the emergence of SSFFCs. Some of these factors are; weak drug regulatory control and enforcement; scarcity and/or erratic supply of basic medicines; extended, relatively unregulated markets and distribution chains; price differentials; lack of effective intellectual property protection; due regard is not paid to quality assurance; there is a lot of money to be made; lifestyle medicines are wanted and thus increased demand definitely will produce the issues of counterfeiting; equipment is widely available and often can be bought by anybody without due regard for the purpose of purchase; distribution is now easy (e. g. internet and postal delivery); patients are self-prescribing (self-medication/ignorance); weak legislation and enforcement, organized crime has moved in; consumer-generated demands for inappropriate products and often without following due process of proper diagnosis; insufficient channels for effective remedies; corruption, indiscipline and lack of functional consumer's association. [38]

Issues of SSFFCs may abound for some years to come unless adequate pharmacovigilance efforts are put in place and countermeasures that have been developed are optimized and properly implemented.

Efforts at combating drug counterfeiting in West Africa

The fight against drug counterfeiting and thus maintaining quality of medicines circulating in the West Africa has received tremendous support from International donor agencies and organizations. However, the National Drug Regulatory Agencies in the various countries have equally been active in the drive towards promoting effective drug quality surveillance. This section reviews some of the efforts of these agencies in some of the countries within the sub-region.

In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) is the apex body responsible for the issues of drug quality, safety and efficacy. Several spirited efforts have been carried out in recent years to advance the cause of eliminating SSFFCs. These include; staff re-orientation and motivation; restructuring and modernization of regulatory processes; public enlightenment campaigns; stopping the importation of fake drugs to Nigeria at source; beefing up of surveillance at all ports of entry; mopping up what is already in circulation; regular monitoring of GMP of local manufacturers; streamlining and strict enforcement of our registration guidelines. 37 In addition to all these efforts, NAFDAC also maintains functional website where drug alerts are issued regularly. Such alerts include instances of fake or counterfeit drugs, recall of products with their full graphics online as well as lists of banned restricted or controlled drugs, food and chemicals. [39]

The regulator in Sierra Leone is The Pharmacy Board. The Pharmacy Board has as its mission “implementing appropriate and workable regulatory guidelines to achieve the highest practicable standards of the practice of pharmacy by professionals, and of safety, efficacy and quality of all drugs, medical devices, cosmetics and nutritional agents locally manufactured, imported, exported, distributed, sold or used, in order to ensure the protection of public health as envisaged by the Pharmacy and Drugs Act, 2001”. [40] Some of

the efforts of the Pharmacy Board in Sierra Leone as detailed on the agency website include; report on adverse drug reaction, publications of several guidelines, publication of gazettes and issuance of public notices. There is also avenue for reporting on destruction of counterfeit, expired and substandard drugs with the latest report on May 14, 2017. [40]

In Ghana, the regulatory agency is the Ghana Food and Drug Agency (Ghana FDA). The agency equally maintains a functional website and a survey of the website revealed such activities as press releases on quality of food and drugs, report on adverse drug reactions as well as publication of registered importers of medicines. The Ghana FDA is also ISO 9001:2015 certified. [41]

In The Gambia, there is an established Food Safety and Quality Authority (FSQA). The FSQA is the sole National Competent Authority with powers of delegation mandated to officially control the safety and quality of food and animal feed whether locally produced, imported or destined for export. The work of the Authority is expected to contribute to consumer health and safety, the facilitation of trade and control of fraudulent and deceptive food marketing, labeling and advertising practices. The Authority is responsible for: the overall official control of food safety and quality. It equally ensures that food and feed comply with legal requirements, or where appropriate with approved codes of good practice. The agency carries out inspection, sampling and certification of food and feed for import and export when so required, inspects establishments, processes and products throughout the production and distribution chain also assesses laboratory services in terms of technical capacity to carry out food and feed analysis for official control. 42 The issues of drug regulation seem to have rested with the Ministry of Health and Social Welfare [43] where some drug guidelines are available on their website. However, in 2015, the government through the Ministry of Health and Social Welfare inaugurated a medicine and pharmacy regulatory/governing body, which is tasked with the responsibility of helping to safeguard the welfare of people in drug-related use in The Gambia. The governing board comprises a Medicine Control Agency and a Pharmacy Council. While the Council is aimed at controlling the sales and regulation of drugs in the country, the Agency is expected to look into the quality of drugs and medicine products to ensure authorization of any medicines that enter the country. [44] It is anticipated that this new agency will attain the status of maintaining effective drug quality monitoring. However, there are regulations governing the prohibition of some drugs by the Customs service of The Gambia. [45]

There is commendable collaboration within the region on drug quality monitoring through the West African Drug Regulatory Authority Network (WADRAN) launched in 2001. The WADRAN aims to combat counterfeit drugs on a regional level through the exchange of information and strategies between countries and the creation of regionally harmonized regulatory efforts. The regional effort was propelled by the relocation of drug counterfeiters to other West African countries after they had been removed from Nigeria. In Nigeria, the penalties for producing, importing or distributing fake drugs range from imprisonment of 3 months to 5 years, or a USD 70 to 3600 fine. Since its initiation, facilitated by the National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria, the forum has helped set regional standards and processes for drug registration in order to facilitate the entry of larger manufacturers with higher-quality products and enable facilities such as bioequivalence laboratories to be leveraged across the region. As at the 2007 data available for review; successes of the NAFDAC include; counterfeit drugs in circulation have dropped from an average of over 41% in 2001 to 16.7% in 2006; drugs not registered with NAFDAC are about 19% of all drugs on the market, as against 68% in 2001; production capacities of local pharmaceutical industries have greatly increased and their number has risen from 70 to 150 in 6 years. They now cover 40% of local pharmaceutical needs, as opposed to 25% in 2001; multinational Pharmaceutical Companies are returning to Nigeria due to the improved regulatory environment; the ban on "made-in-Nigeria" drugs has been lifted by other West African countries; between 2001 and 2007; NAFDAC carried out 110 destruction exercises of counterfeit and substandard products valued at about 150 million USD. [46]

Challenges against adequate surveillance

The demand to maintain adequate quality of drugs in circulation within the West African sub-region has been fraught with several challenges. Some of these challenges equally militate against adequate surveillance of drugs.

For the drug regulatory agencies, there has always been a dearth of highly qualified and well-motivated staff to carry on the drive for effective drug quality regulation. The need to train these human resources is also an on-

going challenge. The challenge is currently being addressed by international partners, though, but the benefits may take some time to become evident. Coupled with inadequate manpower are the meager financial resources available to prosecute some of the lofty visions and missions of the regulatory authorities within the sub-region. It is clearly evident that poor resources manifest in lack of sufficient presence on the worldwide web for some of these countries.

The medicine policies and regulations currently being adapted by majority of the countries are weak. Gone are the days of lack of adequate regulations but the challenge of effective implementation of the available regulations still persists. Worrisome is the fact the punitive measures against drug counterfeiters seems not to be enough deterrent to prospective offenders.

One other major challenge that is believed to be having effect on sound quality surveillance on drug products is the high turnover of trained staff and even the rate at which Ministers of Health are changed. Once a change occurs, there is bound to be a change in policies and the drive for implementing the policies coupled with the fact that Ministers will have their own visions and ideas of what a healthcare system should look like. This will in the long run create unstable regulations.

The end-users, especially the patients, need adequate education. One of the challenges is that the economic power of majority of the populace in the West African region is weak. There are still economies within the region where an average family subsists on less $1 per day. Thus majority of patients will look for cheap medications and often will patronize non-professionals to the detriment of their health conditions.

The expected sound drive from pharmaceutical sectors is also very weak. One major requirement as recommended by WHO is that manufacturers put up excellent countermeasures against counterfeiting. The pharmaceutical companies must be seen to do more in this regard. Many companies find themselves existing slightly above survival level. The governance at the level of the pharmaceutical sector also requires dynamism and sound professionalism to ensure that the fight against drug counterfeiting assails. A situation when profiteering is the goal must no longer subsist.

The political will to support pharmaceutical sectors and indigenous manufacturing is still very weak. The Pharmaceutical Group of the Manufacturers' Association of Nigeria has often called on the Nigerian government to put pharmaceutical raw materials in the exclusive list that will drastically reduce the tariff of imported goods related to local manufacturing. Many of the West African states have not really seen the need for thorough home-breed manufacturing; hence the support is not there. We also have a scenario where majority of previously government-owned manufacturing outfits have folded up except those belonging to the Military in Nigeria.

Closely related to inadequate political will is the political instability in the West African sub-region. Until recently, governance has been unstable. It is hoped that with the emerging stability, the challenges facing drug regulatory agencies will end. The need to have professionals who truly understand drug related issues at the helm of the various drug regulatory agencies within the sub-region is also a major challenge. Many appointments at the top echelon of management have been politicized. This cannot augur well for the development of sound surveillance efforts.

The trickle at which support comes from donors is also a major challenge for adequate drug quality advancement within the sub-region. No doubt there has been a revolution in the support received from donor agencies, but much still need to be done to overcome these challenges especially in the area of improved and enhanced technical assistances.

The challenge of chaotic drug distribution pathway and network within the sub-region is also a major confronting factor against effective drug quality assurance. Drugs presently are profoundly treated as articles of commerce rather than life-saving devices. A general social orientation on the importance of getting appropriate medicines at the right time and at the correct quality is missing among the major drug distributors. As long as open markets, courier ferrying and other non-professional drug distribution subsist, the circulation of SSFFCs is bound to be existent. In addition to these, the challenge of maintaining appropriate storage during distribution and use of medicines is still prevalent.

One other very important challenge militating against adequate drug quality in Africa generally is the segmentation of global trade with respect to drug products. In a 2014 survey, there is a perception amongst pharmaceutical experts that some Indian manufacturers and/or their distributors segment the global medicine market into portions that are served by different quality medicines. The survey found out that drug quality is poorer among Indian-labeled drugs purchased inside African countries than among those purchased inside India or middle-income countries. Substandard drugs – non-registered in Africa and containing insufficient amounts of the active ingredient

– are the biggest driver of this quality difference. [47]

RECOMMENDATIONS

This section seeks to proffer some solutions to the myriad of challenges outlined in this review. This is not all encompassing and recommendations will continue to emerge as the challenge of maintaining adequate drug quality continues. There is a need to keep up the fight against drug counterfeiting at all levels of the systems in the region in order to improve the health status of the general populace.

There is also a need to have well-motivated law enforcement agents who will drive the fight against illegal and illicit trading in drugs as a way of improving quality. Africa has been known to be a den of drug counterfeiters because there is less risk of being caught in Africa.

The various governments need to enact laws that will restrict access to specialized medicines. The typical situation in Nigeria where holders of patent medicine licenses sell prescription only medicines calls for attention by all and sundry. A sound will to neglect all political antics for professionalism must be embraced by the governments at all levels. There is therefore the need to have accredited drug distribution and dispensing outlets in major cities, towns and villages in the countries in the West African sub-region.

More laboratories both at the government and private sectors levels to handle the modern-day sophistication of effective drug quality control are required. In addition, technical supports from equipment manufacturers are still at the weak end. Thus, there is a need to have sound technical back-up even when budget improves to equip laboratories.

The USP's Center for Pharmaceutical Advancement and Training (CePAT) facility in Ghana was established as a collaborative effort and it provides technical training for national and local regulatory authorities and officers; quality assurance and quality control professionals; manufacturers and others in the pharmaceutical industry. To date, CePAT has trained nearly 200 technicians representing 19 countries throughout Africa. [48] There is a need to increase the number of personnel trained in the sub-region especially due to the menace of counterfeiting prevalent in the region.

The provision of technical support in terms of supply of chemical reference substances being carried out by the USP needs a magnificent scale-up if the drive to improve drug quality in the region will be attained.

More researchers are equally needed to focus on drug quality surveillance for drugs circulating in the Sub-region. The issue of SSFFCs is a dynamic one and studies and surveys carried out for a long period are needed in order to forestall occurrence of adverse events as often repeated with deliberate adulteration of paediatric syrups and suspensions.

Finally, training and re-training of specialists who are skilled in drug quality surveillance must continue and this can be done as collaborative efforts among the states within the West African sub-region.

A major limitation in this write-up is the lack of presence on the worldwide web of the activities of some drug regulatory agencies in some of the West African states. This made it impossible to adequately evaluate their efforts towards proper drug quality surveillance.

CONCLUSIONS

Efforts have been intensified in very recent years to improve on the quality of medicines in circulation within West Africa. However, a lot still needs to be done on the part of government, professionals, manufacturers, distributors and the end-users in order to have drugs that are safe, effective and of appropriate quality always in circulation.

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