

TITLE PAGE

**ACCESS TO AGE-APPROPRIATE ESSENTIAL MEDICINES: A RETROSPECTIVE SURVEY OF
COMPOUNDING OF MEDICINES FOR CHILDREN IN HOSPITALS IN NIGERIA AND IMPLICATIONS FOR
POLICY DEVELOPMENT.**

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Key messages:

- Essential medicines for cardiovascular diseases, tuberculosis, and zinc for the management of diarrhoea were commonly compounded for children in a sample of seven hospitals in Nigeria in 2011; signifying poor access to these medicines. These medicines were found to be available in age-appropriate formulations in other countries.
- In order to improve access to medicines for young children, the regulatory agency can ensure that age-appropriate medicines available outside Nigeria are granted expedited import status, or accelerated product registration. The inclusion of age-appropriate formulations for children in the country's essential medicines list, and the local manufacturing of these medicines would improve access in the long-term.
- There is need for the establishment of national guidelines for better quality and safer compounding. A formulary for compounded products should also be produced.

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Conflict of interest

None.

Ethical approval

Ethical approval was obtained from the Health Research and Ethics Committee at LUTH (ADH/DCST/HREC/459), the Lagos State Government Health Services Commission (HSC/378/Vol IV/16) for GHI and MSCH and from the FCT Health Research Ethics Committee (FHREC/2012/01/02/14-3-12) for ADH and MDH. Due to the fact that data was collected from pharmacy records and did not include sensitive personal information, the pharmacy departments at NDUTH and UBTH did not require application for ethical approval. For these two, verbal permission was obtained from the Chief Pharmacist-in-charge/ Deputy director, Pharmacy, before data collection.

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ABSTRACT

Policies to improve access to medicines for children in Nigeria do not include compounding source of medicines. Compounding is often applied as a last resort in health institutions to provide age-appropriate formulations of medicines usually for oral use in young children; but it bears some risk. Some countries have adopted policies aimed at reducing the risk based on available data. There is not much data for Nigeria. This retrospective study examined compounding records from January to December 2011 in a sample of seven hospitals to describe what medicines for oral use were commonly compounded in Nigeria. It then determined if these medicines were commercially available in forms suitable for use in children in selected countries – the United Kingdom, United States, and India. The study found that out of 2845 items compounded, over 65 % were medicines for cardiovascular conditions, diarrhoea, or tuberculosis. The main reason (96 %, n=2399) for compounding was the unavailability of age-appropriate formulations. Medicines were almost all compounded using simple syrup, vitamin C or vitamin B syrups as suspending vehicles. Final products were all oral liquids. Comprehensive stability testing was not reported for the products. Almost all of the commonly compounded medicines were found to be commercially available in dosage forms suitable for use in children in the selected countries. These medicines were all listed in the World Health Organization Essential Medicines List for children as well as in the current edition of the Essential Medicines List of Nigeria. The fact that they were compounded highlights the need for improved access to age-appropriate dosage forms for children in Nigeria. The study recommends policy expansion through a three-pronged approach to improving access: improve supply through facilitated importation/ accelerated product registration, or by in-country manufacturing; rational drug use including therapeutic substitution and establishment of a national formulary for compounding.

INTRODUCTION

In September 2015, the successor programme to the Millennium Development Goals (MDGs), the Sustainable Development Goals or SDGs, which charts a new global development agenda for the next 15 years was adopted (United Nations, 2015a). One of the eight goals of the MDGs – MDG 4 – was the reduction of under-5 mortality by two-thirds based on 1990 figures, with improving access to medicines for children being one of the ways to achieving this goal (United Nations, 2015b). However, in 2014 it was recognized that Nigeria was not on track to achieving MDG 4, at least not until 2022 (Umar and Osinusi, 2014). As the world looks beyond 2015, more effort is needed to ensure that Nigeria achieves sustainable access to medicines for children.

Within fifteen years from 2000 when the original MDGs were formulated, a number of policies and initiatives were announced to improve access to medicines for children. One such initiative was the Essential Medicines List for children up to 12 years (EMLc) produced by the World Health Organization (WHO) in 2007 (Briane, 2007). This list was built on the framework of the Essential Medicines List introduced by the WHO in 1977 and was intended to serve as a template formulary for developing countries to guide the selection of medicines for paediatric conditions of public health importance. The aim of the EMLc which is reviewed biennially is that health facilities should have these medicines at all times: these medicines should be accessible (Sitanshu, et al., 2010; WHO, 2011a). Access is a multidimensional concept covering physical availability, geographical access, affordability, acceptability, and quality (WHO, 2011b). Age-appropriate medicines are defined as medicines which are safe, matched to age or ability, and can deliver the intended dose in a way that is acceptable to the patient (Nunn, 2011). In the context of this paper, however, an age-appropriate medicine refers to any medicine suitable for administration to children under the age of 5 years. For physiological reasons, these children usually cannot safely swallow traditional tablets and capsules, and so are conventionally prescribed liquid formulations (Bowles et al., 2010). Though not specifically mentioned in the 2000 agenda, age-appropriateness of medicines for children has since

become a necessary consideration in the development of children's medicines; leading the WHO in 2008 to recommend Flexible Solid Oral Dosage (FSOD) forms such as dispersible tablets as the most preferred (or age-appropriate medicines) for children (WHO, 2011c).

Children have historically suffered poor access to age-appropriate medicines for a variety of reasons mainly due to poor financial returns on developing medicines for children, and ethical concerns (U.S. Food and Drug Administration, 2011). Consequently, there is a high incidence of off-label and unlicensed use of medicines in children. In 2005, it was estimated that between 45 to 60 % of medicines prescribed for children up to 12 years in Europe, were used off-label and unlicensed (EMA, 2010). Medicines are used off-label when they are used in doses, or for indications, or administered in ways other than contained in their marketing authorization; unlicensed medicines are medicines such as 'specials' (a UK term to describe medicines without a Marketing Authorization but which are produced to GMP standards under the terms of a manufacturing licence issued by the regulatory authority) or compounded products for which no marketing authorization exists (Turner and Choonara, 1997; Turner, et al., 1999; Neubert, et al., 2008).

Compounding, also known as extemporaneous preparation or dispensing, has been defined as 'the technique applied by pharmacists to produce medicines from active pharmaceutical ingredients (APIs) or using authorized medicines when no commercially available, authorized, age-appropriate or adequate dosage form exists' (WHO, 2014a). It often involves crushing tablets or dispersing the contents of capsules in a suspending vehicle. Though recommended as a last resort, it is a common practice in hospitals and pharmacies in many parts of the world (Kairuz et al., 2007; Carvalho, et al., 2008; Giam and McLachlan, 2008; Magalhães, et al., 2015). Although necessary, compounding is not without its risks. Indeed, it is recognized as one of the most hazardous activities performed by pharmacists in hospitals or community pharmacies; with unlicensed medicines more likely to lead to an adverse effect than licensed medicines (Lowey and Jackson, 2008; EMA, 2004; Bellis et al., 2013).

In many countries in the developed world, there is information on compounded products and practices that have informed policies aimed at improving the quality and safety of compounding. For example, in the United Kingdom (UK) the Handbook of Extemporaneous Preparation setting out compounding standards and detailing validated methods for the preparation of 50 commonly compounded medicines in UK hospitals was produced in 2010 (Jackson and Lowey, 2010). In addition, the UK pharmacy regulator, the General Pharmaceutical Council, in 2014 produced guidance for compounding that sets out five principles to be followed to ensure standards and to provide quality assurance for compounded products (General Pharmaceutical Council, 2015). Broader concerns about safety have led to regulations. For example, the United States, through the Drug Quality and Security Act of 2013, and the European Union, through the Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients, have produced guidelines to regulate compounding practice (Council of Europe, 2014; Minghetti et al., 2014; FDA 2015). In contrast, there is lack of information reported publicly for compounding in developing countries, especially in Africa; only one personal communication for some Anglophone countries is reported (Nunn et al., 2012).

Nigeria, with an estimated 169 million people in 2012, of which about 30 million ($\approx 18\%$) are young children, is the most populous country in Africa (UNICEF, 2014). As in other developing countries, almost a decade after the MDGs were formulated, paediatric access to essential medicines in Nigeria remained low (Robertson et al., 2009). In recognition of this, the Nigerian government initiated plans and policies to improve access to essential medicines. Two of these are the Essential Medicines Scale-up Plan which was introduced in 2011 (Federal Ministry of Health, National Primary Health Care Development Agency, 2011), and the Save One Million Lives (SOML) Initiative launched in 2012 (WHO, 2012). A key focus of both programmes was the scaling up of access to essential medicines.

In Nigeria, while there is paucity of information on the extent of unlicensed and off-label medicine use in children, the available literature suggests that the situation might not be so different. A study

carried out in a tertiary hospital and a primary health care facility in Nigeria puts the proportion of off-label and unlicensed medicine use in both institutions at 41.9 %, with compounding forming the bulk of the unlicensed medicines (Okechukwu and Agbomo, 2009).

Thus far, there is only one published study on medicines compounded in one tertiary hospital in Nigeria (Aghahowa et al., 2013). The medicines compounded, compounding practices and the reasons for compounding in other hospitals in different parts of the country is not known. Thus, there is a lack of comprehensive data to guide policy aimed at improving compounding.

The aim of this study was to provide information on compounded medicines and practices in a sample of hospitals in Nigeria, and to check the commercial availability of the commonly compounded medicines in suitable dosage forms in selected countries. By providing data on compounding, and availability, this study hopes to provide a basis for policy developments that would improve compounding practice, or paediatric access to age-appropriate medicines, in Nigeria. The importance of this work lies in the fact that it is the first attempt to provide comprehensive information of compounding in seven selected hospitals with a 50% geographical spread (three out of six geopolitical zones) in Nigeria. As such, the information it provides can be considered sufficient to guide compounding policy, at least in the short-to-medium term.

METHODS

Study Design

The study was a retrospective descriptive survey to identify compounded products and practices in a sample of seven hospitals in three out of the six geopolitical zones of Nigeria. These hospitals were spread across four states in these three geographical zones as shown in Figure 1.

Locations

Hospitals surveyed were selected both purposively and based on convenience. Criteria for selection included:

- Presence of a children's unit (out-patient, in-patient, or emergency wards),
- Record of compounding,
- Presence of qualified pharmacists.

The hospitals were also selected to ensure a wide coverage. In each of the three zones sampled, the hospital chosen were either among the foremost, or had large patient turnouts, or was a paediatric specialist hospital. Researchers' work experiences with several of these hospitals also influenced their choice. The locations were approved by the authors' institutions.

Study instrument

Medicines for oral use compounded from January to December 2011 were extracted from pharmacy records using a semi-structured questionnaire summarized in Table 1. The questionnaire design was based on elements adapted from a similar questionnaire for African countries used by the Commonwealth Pharmacists Association (unpublished). This questionnaire was vetted by a consultant pharmacist with considerable practice experience, and was piloted in one of the locations for validation. Questionnaires were mostly completed by the researchers (in five locations) from records in the 'Compounding Book' of the hospitals. In the other two locations, they were completed by the responsible pharmacists in charge of compounding. Characteristics of medicines compounded: active pharmaceutical ingredient (API), starting material, final dosage form, compounding or suspending vehicle, and reasons for compounding were noted.

The therapeutic categories of the 10 most commonly compounded medicines were then identified using the Anatomical Therapeutic Chemical (ATC) classification system and also from the EMLc, 3rd edition (WHO, 2011a). Information was then entered into a Microsoft Excel database to aid analysis.

Data was collected in February and June of 2012, and January and October of 2013 during field trips to the country.

Statistical analysis

Data was analysed using Microsoft Excel 2013 and presented in terms of descriptive statistics – percentages.

Availability of compounded medicines

Compendia for the UK, United States (US), India, and Nigeria – the electronic Medicines Compendium (Datapharm, 2012), DailyMed (U.S National Library of Medicine), National Formulary of India (Indian Pharmacopoeia Commission, 2011), and the Essential Medicines Index, EMDEX (Lindo, 2011) respectively – were then checked for commercial availability of the frequently compounded medicines. The WHO EMLc (WHO, 2011a) and the current, 5th, edition of the Nigerian Essential Medicines List (NEML) (Federal Ministry of Health, Nigeria, 2010) was also checked for inclusion of the commonly compounded medicines.

RESULTS

Compounding practices: documentation, procedures, starting material, final product, length of dispensing, suspending vehicle, containers and dosing devices

All hospitals had a compounding register (the ‘compounding book’) where compounding records are entered. An entry would include prescription information – name of patient, age, body weight, medicine(s) and treatment duration; starting materials, formula, and calculation for compounding. This entry is double-checked by a senior pharmacist. The compounding and supervisory pharmacists both sign the record. The reporting format was basically the same in all locations. In most of the hospitals surveyed, these records date back several years. Records for 2011 were chosen to establish

a baseline for comparison among locations and to provide a “snapshot” of compounding in the country.

The compounding is usually carried out in a designated space in the pharmacy; this is usually an area away from where routine dispensing takes place, a separate room or compounding laboratory.

Formulae for compounding were mostly empirically derived, that is based on the pharmacist’s expert knowledge and not on validated evidence. Products were compounded on a named-patient basis.

The starting material for compounding was usually a tablet or capsule, apart from vitamin D where this was a liquid. In all cases, the final product was a liquid oral medicine ranging in volume from 10 – 200 ml. All products were intended for use in a child. The majority, 85 % (2111/2472), of compounded products were dispensed for more than 7 days (usually 14 or 28 days). The length of dispensing corresponded to the ‘duration’ of treatment as recorded on the prescription sheet. The suspending vehicles were simple syrup BP, vitamin B complex syrup, vitamin C syrup, and water in a few cases. For some hospitals, a small amount (5-10 ml) of water was used to mix the crushed tablet or capsule content before incorporation in the syrup.

Some hospitals used amber-coloured glass bottles for dispensing the compounded products, while some used transparent plastic bottles. In some hospitals, both glass and plastic bottles were used as containers for dispensed products. Dosing devices were not routinely dispensed with the products; pharmacists sometimes advised on what dosing device might be suitable, and patients procured these separately, as the case may be.

Medicines compounded: APIs and therapeutic categories

There were a total of 2845 compounded items comprising several different APIs. The number of APIs ranged from two for MDH to 32 for UBTH. The bulk of the compounding, 71 % (2011/2845), took

place in two tertiary hospitals – UBTH and LUTH. The number of APIs and the three most frequently compounded in each hospital are shown in Table 2.

Compounded medicines varied with the level of health institution, and with each hospital. In the tertiary hospitals, cardiovascular medicines were the most commonly compounded: 54 % (602/1115) in LUTH and 43 % (386/896) in UBTH; except in NDUTH where nervous system medicines – chlorpromazine, classified as a psycholeptic, which was used clinically for the control of seizures in epilepsy and neonatal tetanus, and pyridoxine (classified as a vitamin but used clinically for the prevention of nervous system toxicity associated with the use of isoniazid) – were the most frequently compounded. With the secondary health institutions, therapeutic category varied with the hospital. MSCH compounded mostly antimycobacterials, or anti-TB medicines; ADH mostly the mineral supplement zinc (as zinc sulfate which is used to provide zinc supplementation in the management of diarrhoea), and MDH mostly the anti-malarial quinine. GHI was different from the other secondary health facilities in compounding mostly medicines for cardiovascular conditions as in LUTH and UBTH (Table 2).

Overall, 10 APIs made up the bulk (75.6 %, 2151/2845) of compounding across hospitals. These were, in decreasing order of number of preparations made: zinc and furosemide (same total number of preparations), rifampicin, isoniazid, digoxin, hydrochlorothiazide, spironolactone, vitamin D, propranolol, and pyrazinamide (Table 3). These 10 APIs belonged to three ATC main groups: cardiovascular system, anti-infectives for systemic use, and alimentary tract and metabolism. The cardiovascular medicines indicated for heart diseases and/or oedema – furosemide, digoxin, spironolactone, hydrochlorothiazide, and propranolol (see footnote in Table 3) – were the most frequently compounded, making up almost 50 % (47.6 %, 1023/2151). These were followed by anti-infectives for systemic use, or anti-tuberculosis (anti-TB) medicines – rifampicin, isoniazid, and pyrazinamide (27.8 %, 598/2151). The alimentary tract and metabolism class – constituted largely

(81.7 %, 433/530) of zinc sulfate and vitamin D indicated for the treatment of rickets – made up the remaining 24.6 % (530/2151) (Figure 2).

Reasons for compounding

In almost every case (96 %, 2309/2399) where a reason was provided, the lack of an age-appropriate formulation was the reason given for compounding (Figure 3).

Availability of commonly compounded medicines in a sample of countries

Apart from spironolactone, all commonly-compounded APIs were commercially available in suitable dosage forms in the selected countries (Table 4). All were listed in both the WHO EMLc and the NEML; though the EMLc contained a greater proportion in age-appropriate dosage forms (Table 5).

DISCUSSION

The need for a national compounding protocol to ensure safety, efficacy and quality

These results indicate the need for a national compounding protocol to harmonise compounding practice in the country, as has been carried out in other countries. While there were **compounding registers** in all the hospitals surveyed, there is a need to harmonise reporting styles. Some locations included the label in the record, but some did not. The process of risk evaluation to include substitution with a licensed suitable product if available is not systematically recorded. Even though the study was limited to one calendar year, records for the entire year were incomplete in several locations. Documentation of compounding records should be brought into line with the WHO recommendations (WHO, 2014a).

There is the need to match dispensing length with documented stability studies, or based on recommendations; but this seems not to be the practice. Only one hospital reported some physical stability studies. With no detailed studies, the stability of the compounded medicines are not known; and there might be microbial, physical and chemical stability issues. Most of the compounded medicines were dispensed for the same length of time as the treatment duration in the prescription sheet. For chronic conditions, this length of dispensing corresponded to the period the patient would usually return to the hospital for checks/evaluation. Thus, the length of dispensing, or 'assigned' shelf-life, was based on convenience. Jackson and Lowey (2010) recommends dispensing compounded products for no more than 7 days, or 2-3 days for potent medicines with narrow margins between clinical doses and toxicity (or inefficacy). Similarly, the WHO points-to-consider document on compounding recommends dispensing for 2-3 days, with refrigeration, when there are no added preservatives; or, alternatively, the addition of simple syrup beyond 65 % w/w which might help preserve the products such that they can be dispensed for longer than 3 days (WHO, 2014a). The use of the syrup-based suspending vehicles in the hospitals surveyed might have been based on this understanding. However, research is needed to provide evidence that the preservative systems in these syrups remain effective over the length of dispensing; especially where water is used for mixing the tablet or capsule before suspending in the syrup (Ghulam et al., 2007). In the absence of detailed chemical, microbiological and physical stability studies, it is necessary from the point of view of efficacy and safety, that hospitals review all information available and consider implementation of the recommendation of dispensing compounded products for only 2 – 3 days; or a maximum of 7 days. This should begin with those medicines of NTI such as digoxin.

As a rule, suitable dosing devices should be dispensed with the compounded product. Dosing devices most likely to be used by end-users, where an oral syringe was not dispensed with the product, would include graduated spoons or measuring cups supplied with other medicines the child might have been prescribed, or household spoons. With household spoons, the dose administered to the child might be inaccurate because of the wide variation in the measured volume of medicines with

this uncalibrated device (Falagas, *et al.*, 2010). For medicines with NTI such as digoxin, variations from the prescribed or intended volume as a result of inaccuracy of the dosing device would mean that the child receives a sub-therapeutic or a toxic dose. With such medicines, routinely providing the patient with an oral syringe or graduated medicine spoon which are more accurate than the common household spoon would minimise this risk (Shonna, *et al.*, 2010; Beckett, *et al.*, 2012).

The study did not include treatment outcome and any adverse drug reaction experienced by the patients. That would have involved clinicians and other members of the healthcare team. Nigeria does not have a specific reporting procedure for compounded products; even though there is a general pharmacovigilance reporting system in operation since 2004. However, compounded products have been known to have quality and safety issues (Kairuz, *et al.*, 2007; Gudeman, *et al.*, 2013).

The commonly compounded medicines were all indicated for paediatric diseases of public health importance, signifying that they were essential medicines. Apart from prematurity and birth-related complications, the three major causes of death in children under the age of 5 in Nigeria are malaria, pneumonia, and diarrhoea: diarrhoea alone accounting for 11 % (some 95 000) deaths in 2010 (WHO, 2014b; Umar & Osinusi, 2014). The volume of compounding for zinc reflected this burden of diarrhoea. These results illustrate that as at 2011, eleven years after MDG 4 and four years to the 2015 target, access to age-appropriate medicines for one of the leading causes of mortality and morbidity in children in Nigeria was still inadequate.

However, some progress has been made. With access to zinc for the management of diarrhoea, the situation has improved since 2011. In 2014, the first dispersible tablet formulation of zinc was locally produced in Nigeria following a pre-qualification exercise by WHO (initiated and backed by the local medicines regulatory agency with the support of government) under the WHO's prequalification of medicines programme (WHOPIR, 2014; WHO, 2014c). It is believed that this local production of the age-appropriate dispersible zinc tablets would reduce the need for compounding of this medicine in

hospitals. In fact, LUTH, for example, no longer compounds zinc. For malaria, the public-private partnership – Affordable Medicine Facility – malaria Artemisinin Combination Therapies (AmFm – ACTs) – launched in 2011 under the Global Fund for Malaria, TB, and HIV/AIDS led to dispersible anti-malarial tablets suitable for use in young children being offered to the public at subsidized prices (Ajayi et al., 2013). The finding that only one hospital (MDH) had a record for extemporaneous compounding of the anti-malarial quinine may suggest that there was good access to the WHO recommended first-line artemisinin-based treatment for malaria. However, most patients with malaria would in the first instance take treatment from community pharmacies or patent medicine vendors while only very serious cases are treated at tertiary hospitals or secondary health facilities as those surveyed (Beyeler, et al. 2015). Thus, the situation with regards to access to age-appropriate anti-malarial for children cannot be determined from the survey results.

With tuberculosis, a triple-drug fixed-dose-combination (FDC) dispersible tablet formulation is currently being given out free on the directly observed treatment short-course (DOTs) programme which was introduced in 2001 (Erah and Ojieabu, 2009). The fact that anti-TB medicines were still being compounded in 2011 might be related to possible temporary logistic difficulties leading to stock-outs at the time of the survey. It is to be noted, though, that the FDC anti-TB medicines are not all age-appropriate with research being conducted to find suitable products for dosing reasons (WHO, 2015). This can be another reason for the compounding of the individual anti-TB medicines.

Thus, even though the outcomes may not yet be optimal, for the infectious and communicable diseases of diarrhoea, malaria, and tuberculosis policy interventions are in place.

However, the same cannot be said for the provision of medicines for the non-communicable cardiovascular diseases. Cardiovascular diseases have usually not been considered with the same level of priority as infectious diseases, at least in sub-Saharan Africa countries like Nigeria. However, emerging data suggest that their impact on public health is significant (Ogeng'o et al, 2013; Thomas et al., 2013). For instance, congestive cardiac failure is reported as a 'common' cause of morbidity

and mortality among Nigerian children, and accounts for between 5.8 to 9 % of paediatric emergency admissions (Oyedeji et al, 2010). The lack of age-appropriate cardiovascular medicines for children across the globe is well documented (Yeung et al., 2004; Wimmer et al., 2014). The implication of this is that in the near future, there may still be need for compounding of these medicines for the non-infectious – but increasingly of public health significance – cardiovascular diseases. There is, therefore, the need that policies are developed to meet this emergent situation; more so as the SDGs emphasises the control of NCDs.

Some of the compounded medicines were high risk medicines that that ought not to be compounded for reasons of efficacy and safety, both for the patient and the compounding pharmacist. For example drugs with narrow therapeutic indices (NTI) such as digoxin where there is no assurance that the intended dose would be given; with the therapeutic efficacy consequently in question, or possible toxicity with overdose. Others were anti-neoplastic medicines such as mercaptopurine (not among the top 10 compounded APIs, and thus not shown here) that require protective clothing and handling only in designated areas to avoid contact with the skin and other possible adverse effects on the compounding pharmacist. However, based on researcher's observation at the time of the study, there was no evidence that special protective measures were adopted or taken when these cytotoxic preparations were compounded. It would be necessary that where compounding of these medicines are undertaken, **dedicated areas** and **protective equipment** should be worn as recommended (WHO, 2014a).

As seen from the results, local unavailability was the main reason for compounding: this might have been due to several factors. One of these might be that in the hospitals, some of the medicines compounded might have been stocked-out during the survey period, as noted for the anti-TB medicines, suggesting logistics challenges. Another reason could be that medicines available elsewhere in suitable dosage forms had not, at the time of the survey, been registered by the local medicines regulatory agency; and so were not available in Nigeria as licensed products. This latter

reason appeared to have been the case with, for example, furosemide and digoxin. It is encouraging to note that some of these medicines that were compounded are now licensed in the country as liquid medicines, for example digoxin elixir (National Agency for Food and Drug Administration and Control, 2015).

There is no system whereby hospitals can procure medicines not available in suitable dosage form from 'specials' manufacturers as it is in UK, for example. So, medicines not available as age-appropriate dosage forms would have to be prepared as required in each hospital. While patients have to pay an additional cost for this (for the container, and in some cases, a 'compounding charge'), the amount is minimal. The alternative to this would be that the end-user either forces the child to swallow the intact dosage form, which can be unsafe, or in many instances not possible, or to manipulate the adult dosage form (WHO, 2007). Thus, by compounding, the pharmacist provides a useful and much needed service.

However, there is still the need to ensure availability of other high risks APIs such as furosemide in age-appropriate formulations. While this is available as an oral liquid in the selected countries surveyed (but not in Nigeria), this liquid has a high alcohol content (10 % w/v) necessary to solubilize the API. This high content of alcohol makes it not age-appropriate for neonates or young children. Medicines for neonates are not supposed to contain alcohol, and young children less than 5 years should not be exposed to alcohol medicines contents or more than 5% w/v (Whittaker, *et al.*, 2009). There is thus an urgent need for an age-appropriate formulation of furosemide, preferably as a dispersible tablet that could be used in low-resource settings.

While not within the scope of this work, there did seem to be at least one instance of compounding for an off-label indication with chlorpromazine. For the indications for which this medicine was used, a licensed product such as diazepam, administered intravenously, orally, or rectally (in children more than a year old) using the appropriate formulation would have been a safer alternative. This finding

suggests the need for further studies into the rational prescribing and use of medicines for paediatric conditions in Nigeria.

Implications for policy development

The country can consider a three-pronged policy approach to increasing access to age-appropriate medicines for children: increase supply, promote rational drug use and generic substitution and establish standards for compounding.

Firstly, policy expansion, expedited regulatory approvals, and inclusion of suitable medicines in the local EML can help to improve supply of age-appropriate medicines. The focus of public health policies with regards to access to medicines for children in Nigeria is, understandably, on infectious/communicable diseases such as diarrhoea, pneumonia, malaria, HIV/AIDs, and tuberculosis. The results from this first multi-centre survey of compounding, however, showed that medicines for the non-communicable cardiovascular diseases were being very commonly compounded in hospitals. Thus, public health policies should also focus on the provision of these medicines in age-appropriate dosage forms. A focus on the provision of age-appropriate medicines for both communicable and non-communicable paediatric diseases would be in alignment with the SDGs. SDG 3 – which effectively replaces MDGs 4,5 and 6 – aims for the complete eradication of communicable diseases in the under-5 while better managing non-communicable diseases (United Nations, 2015a). Age-appropriate dosage forms of medicines that are commonly compounded which are available in other countries should be granted expedited import status, or accelerated registration in the country, by the local drug regulatory agency, at least in the short-term. It would also be necessary to include FSOD forms in the next edition of the country's Essential Medicines List, such that these medicines can be manufactured locally in the long-term. These measures would help improve the supply of suitable cardiovascular medicines for children.

To guide policy formulation and planning, it would be useful if similar surveys as this one are conducted at fixed intervals, approximately once a year, to find out what APIs are commonly

compounded by a more representative sample of hospitals and to see if these medicines are available in suitable dosage forms elsewhere, so that necessary steps can be taken to ensure that they are made available locally. These surveys can take the form of selected hospitals in each of the six geo-political zones in the country uploading a monthly report of compounded medicines to a central coordinating Centre at the local regulatory agency. This would then form a database that can inform decisions for improving availability and geographical access to medicines for which age-appropriate commercial products exist outside the country.

There is a lack of local data on cost-benefit analysis of hospital compounding of medicines compared with procuring the commercially available medicines from countries where they are available. Regulatory restrictions may limit the ability of hospitals to make such direct procurements. The possibility of quality-qualified designated hospitals in each state providing age-appropriate medicines by compounding as a value-added service where suitable medicines are not available, or are too expensive, can be explored. Such a cost-benefit analysis could be performed in a future study.

Secondly, rational drug use policies in children should be considered. The national formulary, combined with the standard treatment guideline appropriately modified to include age-appropriate medicines for children, can be used to guide selection of use of medicines for children. Each hospital can also include therapeutic alternatives that are available in age-appropriate dosage forms in their local formulary to guide prescribers in the choice of suitable formulations to prescribe for children. Therapeutic product substitution as recommended by the WHO guideline on compounding should be encouraged. Educational strategies for pharmacists and physicians on the risks inherent in compounding and the need to ensure better medicine use in children would also help to ensure access to suitable medicines for children and to further improve patient safety.

Thirdly, quality standards for compounded products and practices should be established. For those medicines for which no suitable product exist elsewhere, and with no therapeutic alternatives, and

for which compounding is necessary, measures should be put in place to guarantee product quality. Recently, more information is becoming publicly available that can guide compounding (Jackson and Lowey, 2010; PharmInfoTech; e-drug compounding; extemp.ie; The Hospital for Sick Children, 2014). These can be used as reference sources of formulae for compounded medicines, as well as provide stability information to guide length of dispensing. The limitation might be that these sources would mainly contain products 'specific' to local needs with stability data that might not reflect storage conditions in Nigeria.

On 9 December 2014, Nigeria signed the Health Bill into law (Liebschutz, 2014). This Bill seeks, among other things, to improve the quality and standard of health care in health institutions in the country. It is imperative that a policy framework be fashioned out from this Bill to address compounding as a means of providing medicines for children when no suitable commercial formulation exists. In line with this, the Government, or the professional body of pharmacists, should organize a forum where hospital pharmacists can meet to share information on compounding best practices which would lead to the formulation of a national guidance document. This forum should also be tasked with the production of a national formulary of compounded medicines. These would help to ensure quality and standards of medicines compounded for children in hospitals in Nigeria as a means of ensuring paediatric public health.

Limitations

A main limitation of this study is its retrospective nature. Compounded products, and practices, might have changed in these institutions. Indeed, as earlier noted, dispersible zinc tablets are now locally available. What this study showed though was that in many cases where medicines were compounded for children in the country for reasons of unavailability, the medicines were actually available elsewhere in suitable dosage forms.

While efforts were made to ensure a fairly-wide national coverage in the choice of study locations, the possibility of selection bias in this approach is acknowledged. However, this potential bias was minimized by selecting some of the major hospitals in the three selected geo-political zones; thus the study tried to achieve at least a 50% national coverage.

CONCLUSIONS

Policies aimed at improving access to medicines in Nigeria have not included compounding as a source of medicines for children. In keeping with several other countries, compounding of age-appropriate medicines for children occurs in local/national hospitals because suitable, licensed products are not manufactured or made available in Nigeria. Compounding does not include the same quality assurance measures as licensed manufacturing so there are risks that children get a poor quality medicine with possible consequences on safety and efficacy.

When compounding is necessary, a formulary of evaluated monographs should be available to guide pharmacists on methods of preparation, simple quality assurance measures, storage and shelf life of the product. The use of commercial suspending agents may be costly so there should be research to determine an appropriate suspending vehicle that could be manufactured and licensed locally.

Policy expansion to provide guidance on compounding as a source of medicines for children is necessary to safeguard paediatric public health. Nigeria should have a policy on compounding of medicines alongside information on the availability of suitable, licensed products for importation and should determine those medicines that could best be manufactured and licensed locally.

Regular review of medicines compounded in Nigerian hospitals would provide information that could be used to determine medicines supply policy for Nigerian children.

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Table 1 Summary of the questionnaire used

| Question | Options/Specific items | Response Type |
|------------------------------------|---|----------------------|
| Name of product | | a |
| Dosage form | E.g., syrup, suspension, solution, other (specify) | b |
| Strength of product (mg/ml) | | a |
| Starting material | Raw materials, adult formulation | b |
| Quantity dispensed | | a |
| Method of compounding | | a |
| Source of formula | Local formulary, journal, textbook, pharmacopoeia, other (specify) | b |
| Container | Plastic, glass, other | b |
| Dosage instructions | | a |
| Dosing device recommended | Spoon, (oral) syringe, other (specify) | b |
| Expiry date | E.g., 5, 7, 14, or 28 days | a |
| Source of expiry date | Local formulary, journal, textbook, pharmacopoeia, , other (specify) | b |
| Why was product compounded | No available age-appropriate formulation, liquid product out-of-stock, high cost of commercial product, other (specify) | b |

Notes: a = open-ended; b = closed with options for comments

Table 2 Range of active pharmaceutical ingredients (APIs) and the three most frequently compounded in seven hospitals in Nigeria (2011) grouped according to level of hospital

| Level of hospital | Name of hospital | No. of APIs compounded | Three most frequently compounded APIs |
|-------------------|---|------------------------|---|
| Tertiary | University of Benin Teaching Hospital (UBTH) ¹ | 32 | Hydrochlorothiazide 16 % (139/896), Spironolactone 14 % (127/896), Vitamin D 11 % (97/896). |
| | Lagos University Teaching Hospital (LUTH) | 30 | Furosemide 38 % (420/1115), Zinc 24 % (264/1115), Digoxin 16 % (182/1115). |
| | Niger Delta University Teaching Hospital (NDUTH) | 15 | Chlorpromazine 33 % (33/99), Pyridoxine 15 % (15/99), Ciprofloxacin 12 % (12/99). |
| Secondary | Massey Street Children Hospital (MSCH) | 7 | Isoniazid 43 % (120/278), Rifampicin 40 % (112/278), Pyrazinamide 11 % (31/278). |
| | General Hospital Isolo (GHI) | 4 | Spironolactone 53 % (10/19), Hydrochlorothiazide 32 % (6/19), Furosemide 11 % (2/19). |
| | Asokoro District Hospital (ADH) | 20 | Zinc 35 % (93/266), Nevirapine 14 % (36/266). |

| | | |
|------------------------------------|---|---|
| | | Calcium 12 % (32/266). |
| Maitama District Hospital (MDH) | 2 | Quinine 97 % (63/65), Zinc 3 % (2/65). |

Notes: 1. UBTH also provides secondary, and some primary, level health care service (UBTH, 2015).

Table 3 The 10 most frequently compounded active pharmaceutical ingredients (APIs) with therapeutic indication (clinical use) in a sample of seven hospitals in Nigeria in 2011

| No. (Rank) | API | Therapeutic indication/ Clinical use | No. of items compounded (n) | % of all compounded items (n/2845¹) |
|-----------------------|---------------------|---|--|---|
| 1 (1) | Zinc | Diarrhoea | 433 | 15.2 |
| 2 (1) | Furosemide | Heart failure | 433 | 15.2 |
| 3 (2) | Rifampicin | Tuberculosis | 263 | 9.2 |
| 4 (3) | Isoniazid | Tuberculosis | 242 | 8.5 |
| 5 (4) | Digoxin | Heart failure | 208 | 7.3 |
| 6 (5) | Hydrochlorothiazide | Diuretic | 149 | 5.2 |
| 7 (6) | Spirolactone | Diuretic | 138 | 4.9 |
| 8 (7) | Vitamin D | Rickets | 97 | 3.4 |

| | | | | |
|---------------|-----------------------------|-----------------------|----|------|
| 9 (8) | Propranolol | Migraine ² | 95 | 3.3 |
| 10 (9) | Pyrazinamide | Tuberculosis | 93 | 3.3 |
| | Total of all compounding | | | 75.5 |

Notes: 1. Total items compounded. 2. Propranolol is classified as an anti-migraine medicine in the EMLc but was used in combination with hydrochlorothiazide and spironolactone for cardiovascular indications in the survey.

Table 4 Commercial availability of the 10 most commonly compounded medicines as age-appropriate dosage¹ forms in UK, US, India, and Nigeria (2011)

| API in compounded medicine | Age-appropriate dosage form(s) and strengths available in: | | | |
|-------------------------------|--|---|----------------------------------|----------------------------|
| | UK | US | India | Nigeria |
| Zinc | Not available | Not available | Dispersible tablets ² | Not available ³ |
| Furosemide | Oral liquid 20,40, or 50mg/5ml | Oral liquid 10, and 40mg/5ml | Oral liquid 10mg/ml | Not available |
| Rifampicin | Syrup 100mg/5ml | Syrup 100mg/5ml | Syrup 100mg/5ml | Not available ⁴ |
| Isoniazid | Combination products; none of which is age-appropriate | 50mg/5ml solution | Not available | Not available |
| Digoxin | Elixir 50 microgram/ml | Oral solution 50 microgram/ml | Elixir 50 microgram/ml | Not available ⁵ |
| Hydrochlorothiazide | Not available | 50mg/5ml solution | Not available | Not available |
| Spirolactone | Not available ⁶ | Not available | Not available | Not available |
| Vitamin D | Available as a combination A,D, and C drops | Ergocalciferol Oral Liquid 8,000units/ml | Not available | Not available |

| | | | | |
|---------------------|----------------------------------|----------------------------------|---------------------------|---------------|
| Propranolol | Oral solution 20mg, and 40mg/5ml | Oral solution 10mg, and 40mg/5ml | Not available | Not available |
| Pyrazinamide | Not available (tablet only) | Not available (tablet only) | Oral suspension 250mg/5ml | Not available |

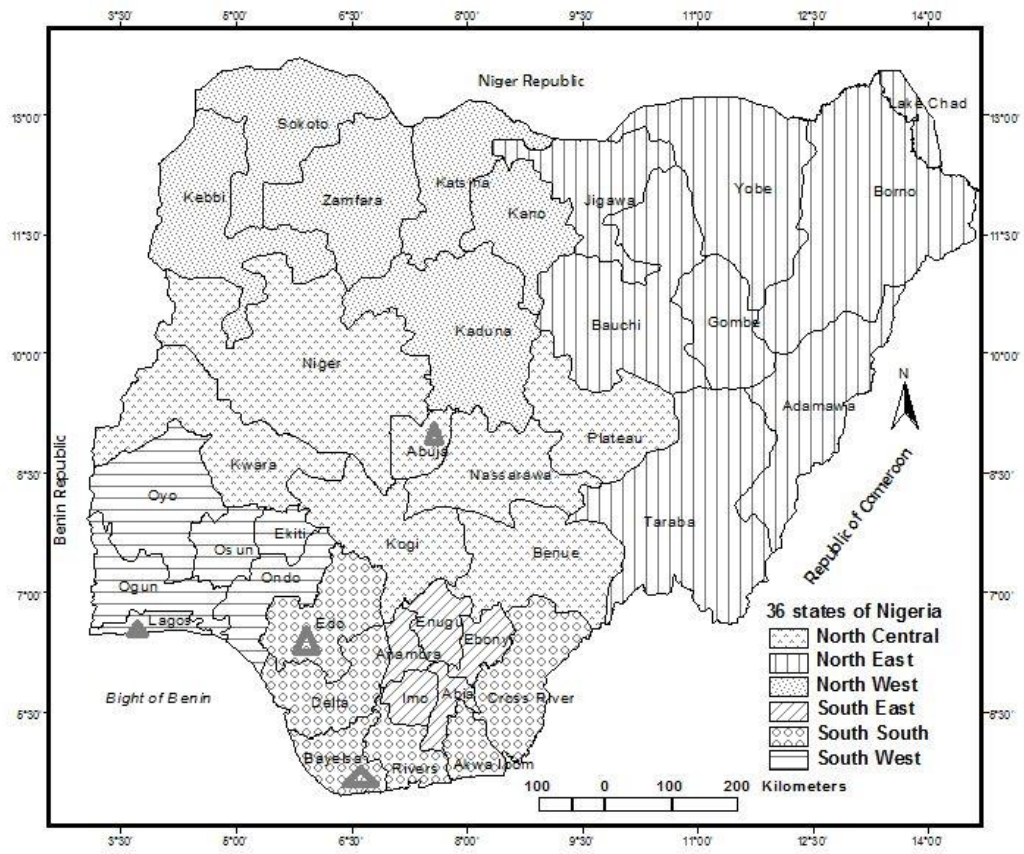
Notes: 1. Age-appropriate dosage forms here include dispersible, soluble, or chewable tablets and oral liquids. Crushable tablets are not included unless specifically formulated as such and not used for manipulation purposes. 2. Not listed in the compendia used; but known to be commercially available in India. 3. Dispersible tablets currently manufactured locally. 4. Currently available locally as a 100mg/5ml oral syrup. 5. The elixir is now available in Nigeria. 6. Liquid product available only as 'specials' or from importing companies.

Table 5 Dosage forms of the 10 commonly-compounded medicines as listed in the EMLc and NEML, with proportions considered age-appropriate for use in young children.

| | API | Dosage form(s) listed in | |
|-----------|---|--|----------------------|
| | | EMLc, 3rd list, 2011 | NEML, 2010 |
| 1 | Zinc | Solid oral dosage form* | Tablet, Oral liquid |
| 2 | Furosemide | Tablet, Oral liquid | Tablet |
| 3 | Rifampicin | Solid oral dosage form*, Oral liquid | Capsule, Tablet |
| 4 | Isoniazid | Tablet, Oral liquid | Tablet |
| 5 | Digoxin | Tablet, Oral liquid | Tablet, Oral liquid |
| 6 | Hydrochlorothiazide | Tablet (scored) | Tablet |
| 7 | Spirolactone | Tablet, Oral liquid | Tablet |
| 8 | Vitamin D (as ergocalciferol or cholecalciferol) | Solid oral dosage form*, Oral liquid | Capsule, Oral liquid |
| 9 | Propranolol | Tablet | Tablet |
| 10 | Pyrazinamide | Tablet, Oral liquid, Dispersible tablet | Tablet |
| | Age-appropriate (%) | 7 (70 %) | 3 (30 %) |

* Tablet or capsule

Figure 1 Map of Nigeria showing the locations of study sites indicated by the triangles in the six geopolitical zones.



Source: www.intechopen.com

Figure 2 Therapeutic categories of the 10 most frequently compounded active pharmaceutical ingredients making up 75.6 % (2151/2845) of compounding in a sample of seven hospitals in Nigeria in 2011.

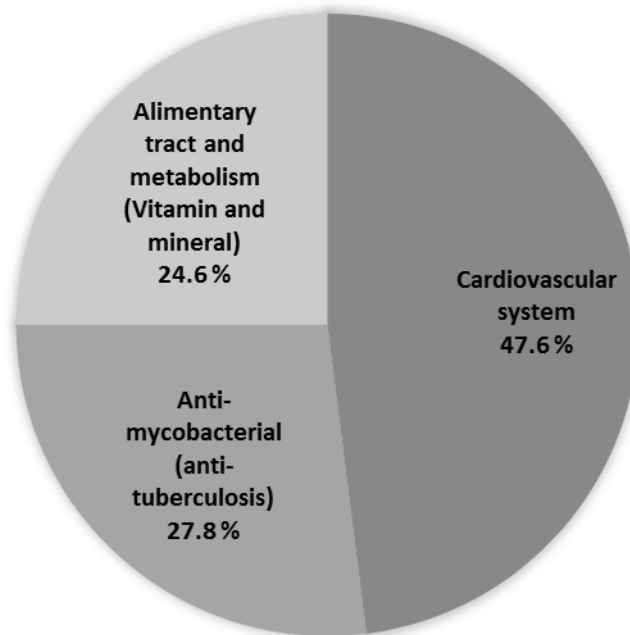


Figure 3 Reasons for compounding (n = 2399)

