Article

# Prescription pattern of unlicensed and off-label medicines for children aged 0 - 5 years in a tertiary hospital and a primary health care centre in Nigeria

**Raymond Chukwuma Okechukwu,** BPharm, Pharm D, FPCPharm

*Centre for Community Medicine and Primary Healthcare, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria*

**Ochuwak E Aghomo,** BPharm, MPharm, PhD

*Clinical Pharmacy Department, University of Benin, Benin City, Nigeria*

**Background**. Many medicines prescribed for children are unlicensed for their age category or used outside the specifications in the medicine licences (off-label use), and few medicines have been properly tested for use in children in clinical trials prior to licensing. These problems raise ethical and safety concerns about use of medicines in children. The pattern and extent of unlicensed and off-label use of medicines in the Nigerian health care system has been poorly documented.

**Objectives**. This research was carried out to study the pattern and extent of unlicensed and off-label use of medicines in children aged 0 - 5 years in a tertiary hospital and a primary health care centre in Nigeria.

**Method**. A retrospective study of prescriptions received by children during admission or as outpatients during the 12-month period April 2003 - March 2004 was done.

**Results**. The 531 children included in the study received 2 190 prescriptions during the study period. Of these 446 (20.4%) were for unlicensed use and 470 (21.5%) for off-label use. The most common form of unlicensed medicine use was modification of licensed dosage forms (e.g. crushing of tablets to make suspensions), while the most frequent pattern of off-label use was using doses other than those recommended for the paediatric age categories.

**Conclusion**. Unlicensed and off-label medicines are widely used for children in the centres studied. Further research on this subject is recommended in other parts of Nigeria and Africa.

The prescription and use of unlicensed and off-label medicines for children present deep ethical and moral challenges. Children often receive several prescription, non-prescription (over-the-counter) and/or herbal medicines when they become ill. Most of these medicines have not been properly tested in controlled clinical trials for their age group.[1] Younger children have been shown to receive more medicines than older children and adolescents.[2,3] Following the sulphanilamide and thalidomide tragedies of the 1930s and 1960s, respectively, there has been growing global concern about the safety of medicines administered to children.[4,5] Parents, caregivers and policy makers have a legal and moral responsibility to protect children from problems caused by medicines, particularly adverse reactions.[6]

Children are not just small adults. They are the most precious resource of any nation, and their health is vital for the future success of any society. Their vital organs, especially the liver, kidney and brain, are not fully developed. Their metabolism and excretion of medicines may differ from those in adults, predisposing them to harmful effects. For example, it has been demonstrated that for some medicines hepatic glucoronidation is lower in children aged 13 - 24 months than in adults.[7] Some researchers have shown that children, especially younger ones, are particularly vulnerable to adverse effects of medicines.[8,9] Furthermore, young children are unable to describe what they experience. Crying may be the only sign of distress they may show when affected by adverse medication events. There is therefore considerable cause for concern about use of medicines in children.

It is common practice to estimate paediatric doses of medicines from approved adult doses. Doses in the British National Formulary or manufacturer's data sheets are partially based on an adult with an average body weight of 60 kg. Calculating paediatric doses from this base without acknowledging children's physiological and metabolic differences may result in therapeutic failure (too little drug) or toxicity (too much).[10] Many medicines given to children have no suitable paediatric dosage forms because children are rarely included in clinical trials before medicines are licensed. Adult medicines are therefore frequently reformulated for children, e.g. crushing tablets or capsules to obtain liquid preparations. This situation has left children as 'therapeutic orphans'.[11] Prescribing of medicines for them is largely empirical rather than evidence-based[5] and clinicians commonly make educated guesses about doses and efficacy rather than rely on data from paediatric clinical trials. Conducting clinical trials in children in fact presents moral, ethical and legal problems, and this issue has generated much interest and debate among health care scientists, parents and policy makers.[12] In summary, most medicines used in children are either unlicensed for them or used off-label. Unlicensed use of a medicine refers to its use without a product license or marketing authorisation, while off-label use is use of a medicine outside the terms of its product licence.[13]

The problem of unlicensed and off-label use of medicines in children has engaged the interest of many health care professionals and researchers.[1] This practice is not illegal in many countries, but it is not free of risk. It poses a challenge of maintaining the delicate balance between risks and benefits of medicine therapy in children that has generated much interest and debate. This health care problem and strategies to remedy it have been extensively researched and documented in many industrialised countries, notably the USA,[1,6] the UK,[14] Europe[6,15] and parts of Asia. On the African continent there has been little or no documented research on this subject. A report from Kenya on patterns of self-medication among schoolchildren[16] did not look at unlicensed or off-label use of the medicines. There is no reason to suppose that this problem does not exist in Africa. In fact it would be expected to be extensive in view of inadequate health facilities, illiteracy, poverty and poor reporting of adverse effects. Research on this subject has therefore become imperative in our environment.

Most research on unlicensed and off-label use of medicines has been on the general paediatric population. So far there has been scanty research on the younger and more vulnerable patients, especially those aged 0 - 5 years. There is a paucity of information on the use of medicines in this way, as well as on their safety and efficacy in paediatric patients.[17]

- What is the extent of this pattern of use of medicines in children in Nigeria and other parts of Africa?
- What are the statistics in the most vulnerable paediatric age category (0 - 5 years) in our practice environment?
- What is the extent of health care professionals' awareness of this problem?
- Are there effective and systematic strategies to address this problem?

These and other questions need to be addressed in order to promote better use of medicines in children in our practice environment.

## Objectives

This study was undertaken to determine the extent and pattern of use of unlicensed and off-label medicines in children 0 - 5 years of age in Nigeria and to compare the findings in a tertiary hospital and a primary health care (PHC) centre.

The research was carried out at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi (the tertiary hospital) and the community medicine and primary health care centre in Neni (the PHC centre), both in Anambra state, Nigeria. The city of Nnewi is one of the industrial and commercial nerve centres of Anambra state and has a fair infrastructure. Neni, on the other hand, is a typical rural settlement with few social amenities. The community medicine and primary health care centre of the teaching hospital located there has clinical and service units providing health care to patients from the surrounding communities. Complex cases are usually referred to NAUTH.

## Materials and methods

Prescriptions received by the children in the study population during the 12-month period April 2003 - March 2004 were obtained from the medical records units at the two centres and analysed to determine unlicensed or off-label use, according to the method described by other researchers.[13] Prescribed medicines were categorised as unlicensed if they are not licensed/recommended for use in children, or if their licensed dosage form had been modified. They were characterised as off-label if their use in the children was outside conditions specified in their information leaflets with respect to dosage, age of patient, indications, route of administration and/or contraindications. Information on the medicines analysed was obtained from the *British National Formulary* (2002),[18] the *Pocket Pediatrician*,[19] *Brands of Choice* quick reference,[20] and the *Canadian Compendium of Pharmaceuticals and Specialties*[21] as well as patient information leaflets. All children aged 0 - 5 years who were admitted to either centre or attended as an outpatient during the study period and had received at least one medicine prescription were included in the research population. Children whose apparent diagnosis was not indicated in their medical record or for whom no medical records were available were not included.

Patient data were collected using the patient medical/medication charts (folder) obtained from the medical record units of both centres. The following information was recorded for each patient: age, gender, diagnosis, medicine(s) prescribed, dosage and duration of use of the prescribed medicines, route of administration, patient's hospital number and date of attendance.

## Results

Five hundred and thirty-one paediatric patients were included in the study, of whom 301 (56.7%) were treated at the tertiary hospital and 230 (43.3%) at the PHC centre; 295 of the children (55.6%) were males and 236 (44.4%) females.

During the study period 41 different diseases were diagnosed and treated in the patients at the tertiary centre and 26 at the PHC centre. The diseases were categorised into five groups and a miscellaneous category (Table I). Ninety medicines were prescribed in the tertiary centre and 62 in the PHC centre. The medicines were categorised according to the Canadian version of the World Health Organization (WHO) Anatomical Therapeutic Chemical Classification index. The categories and frequency of prescription for each medicine are presented in Table II. Paracetamol (12.1%), vitamin C (7.6%), quinine (7.0%), chloroquine (6.6%) and multivitamins (6.2%) were the five most frequently prescribed medicines.

The 531 children in the study received a total of 2 190 medicine prescriptions from both centres. Those at the tertiary centre received 1 147 (52.4%) of the prescriptions and those at the PHC centre 1 043 (47.6%). The prescription rates for the two centres were therefore 3.8 and 4.5 per child, respectively. The overall prescription rate for both centres was 4.1 prescriptions per child.

Of all the medicines prescribed, 446 (20.4%) were unlicensed and 470 (21.5%) were off-label. The proportions of unlicensed prescriptions for the patients at the tertiary centre and the PHC centre were 13.9% and 27.5%, respectively, and for off-label prescriptions 24.0% and 18.7%, respectively. The proportions of unlicensed and off-label medicines prescribed for the children at the two centres are presented in Fig. 1. Examples of unlicensed and off-label uses of medicines at the two centres are shown in Tables III and IV.

**Table I. Categories of diseases treated in the study patients**

| Disease category | Tertiary centre (*N* (%)) | PHC centre (*N* (%)) |
|---|---|---|
| Malaria | 196 (39.3) | 133 (43.3) |
| Respiratory tract infections | 76 (15.23) | 105 (34.2) |
| Gastro-enteritis | 26 (5.2) | 18 (5.9) |
| Sepsis | 41 (8.2) | 12 (3.9) |
| HIV/AIDS | 23 (4.6) | 1 (0.3) |
| Miscellaneous* | 137 (27.4) | 38 (12.4) |
| Total | 499 (100) | 307 (100) |

*Including helminthiasis, boils, epilepsy, prematurity, colitis, allergy, tuberculosis, measles, meningitis, injection abscess, otitis media, mycosis, poisoning, etc.

**Table II. Categories of medicines prescribed to the study patients**

| Category of medicine | Tertiary centre (*N* (%)) | PHC centre (*N* (%)) |
|---|---|---|
| Allergy therapy agents | 66 (5.7) | 123 (11.8) |
| Antiprotozoal agents | 282 (24.6) | 287 (27.5) |
| Analgesic agents | 144 (12.5) | 196 (18.8) |
| Anthelmintics | 6 (0.5) | 35 (3.4) |
| Antibacterial agents | 161 (14.3) | 120 (11.5) |
| Peptic ulcer therapy | 8 (0.7) | 1 (0.1) |
| Antituberculosis agents | 18 (1.6) | 0 (0.00) |
| Antifungal agents | 12 (1.5) | 4 (0.4) |
| Antiviral agents | 20 (1.7) | 0 (0.0) |
| Adrenal therapy | 15 (1.3) | 2 (0.2) |
| Anti-epileptic agents | 34 (3.0) | 6 (0.6) |
| Haematopoietic/ anaemia therapy | 98 (8.5) | 56 (5.4) |
| Vitamins | 150 (13.1) | 190 (18.2) |
| Electrolytes | 103 (9.0) | 10 (1.0) |
| Miscellaneous | 30 (2.6) | 13 (1.2) |
| Total | 1 147 (100.3) | 1 043 (100.0) |

## Discussion

The most prevalent diseases treated in the children were malaria, respiratory tract infections, sepsis and gastro-enteritis. There were more malaria cases at the tertiary centre (29.3%) than at the PHC centre (16.5%), probably owing to differences in environmental sanitation. There were more cases of complex conditions such as retroviral disease (HIV/AIDS), meningitis, glomerulonephritis, prematurity and thrombophlebitis at the tertiary centre than at the PHC centre, probably because of the referral status of the tertiary centre.

Each child received an average of 4 prescriptions. This figure is lower than the 5.5 reported by O'Donnell *et al*. in Australia.[22] There were more medicine prescriptions per child at the PHC centre than at the tertiary centre, which could be because the prescribers at the latter are mainly consultant physicians while those at the PHC centre are medial officers, residents and senior registrars who may not be as prudent as the consultants in the use of medicines.

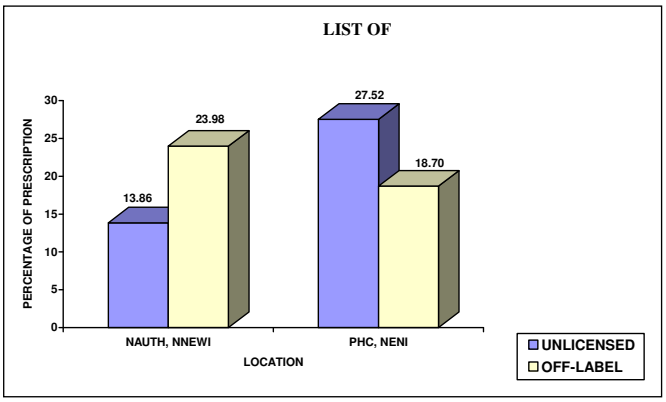


*Fig. 1. Proportions of unlicensed and off-label prescriptions at the two study centres.*

Antibacterial agents, antiprotozoal agents, analgesics, vitamins and haematopoietic/anaemia medications were the most frequently prescribed categories of medicines in both centres. This finding is in agreement with the high incidence of malaria and other infectious diseases that present with symptoms of pyrexia and anaemia. The prescription rate for paracetamol (12.1%) was comparable to the 15% reported in Rotterdam by Choonara and Conroy.[23]

The frequent use of injections in children of this age group is at variance with the WHO recommendation that injections be used in children only when absolutely necessary. Injections, particularly intramuscular ones, are usually painful and should be avoided in children.[24] Of all prescriptions received by the children in this study 20.4% were unlicensed and 21.5% were off-label. There was more off-label than unlicensed medicine use. However, this rate was higher than rates reported in similar studies by other researchers: 11% in Australia,[22] 10% in France[25] and 10% in the UK.[23] The combined figure for unlicensed and off-label use in this research, 41.9%, is similar to rates reported in the UK (55%),[14] Europe (42%)[16] and Australia (58%).[22]

The most common pattern of unlicensed use of medicines observed in this study was reformulating adult dosage forms for paediatric use. Tablets were frequently prescribed, to be crushed and made into a suspension with water or another suitable liquid. This finding is similar to that reported in The Netherlands, where extemporaneous modification of adult dosage forms for children was reported to be very common.[26]

The most common form of off-label use of medicines in this study was prescribing doses in excess of recommended paediatric doses. Total daily doses of 15 ml of multivitamin preparations were commonly prescribed. This is in excess of the recommended daily doses of 0.3 ml for 0 - 6-month-old children, 0.6 ml once daily for 6-month-old children, and 5 ml for 2 - 6-year-old children.

### Limitations of this research

The greatest limitations to a study of this type are insufficient patient medical, demographic and medication data. The information used was obtained from the medical record units of the research

**Table III. Examples of unlicensed use of medicines**

| Name of medicine | Unlicensed use |
|---|---|
| Triprolidine | Not licensed for children below 2 years, prescribed for child <3 months |
| Piroxicam | Not licensed for children <6 years, prescribed for children <5 months<br>Licensed for use only in children with chronic juvenile arthritis, used as antipyretic in children |
| Paracetamol (as tablet) | Not licensed for children <6 years, prescribed for children <3 years |
| Salbutamol | Unlicensed for children <2 years, prescribed for infants of 8 months |
| Co-trimoxazole (as tablet) | Not licensed for children <12 years, prescribed for children <4 years |
| Ciprofloxacin | Not licensed for children <5 years, prescribed for child 2.5 years |
| Iron dextran | Not licensed for children <14 years, prescribed for 7-month-old infant |
| Promethazine | Not licensed for children <2 years, prescribed for children <1 year |

**Table IV. Examples of off-label use of medicines**

| Name of medicine | Off-label use |
|---|---|
| Multivitamin | 0.3 ml recommended for neonates (0 - 6 months), 5 ml prescribed<br>5 ml/d recommended for children, 15 ml/d prescribed |
| Folic acid | 2 - 5 mg per day recommended for children 1 - 5 years, 15 mg/d prescribed |
| Pyrantel pamoate | 2 tablets or 5 ml suspension recommended for children 2 - 6 years, 10 ml single dose prescribed for 2-year-old child |
| Vitamin C | 100 - 200 mg/24 h recommended, 300 mg/24 h frequently prescribed |
| Promethazine | 5 - 15 mg recommended for children 2 - 5 years, 37.5 mg prescribed for children <2 years |
| Diphenhydramine | 0.5 - 5 ml recommended every 3 - 4 hours for children 1 - 6 years, 5 ml prescribed for 2-month-old babies |
| Gentamicin | 2 mg/kg recommended for children 2 weeks - 12 years old, 5 - 10 mg/kg prescribed for this age group |

centres, namely patients' prescriptions, treatment charts and notes on medical diagnoses. Difficulties included incomplete medication histories, medical histories and medical records.

## Conclusion

Just under half (41.9%) of the medicines prescribed for the children in this study were for unlicensed and off-label uses. More extensive research is recommended in Nigeria and the rest of Africa to document the extent of this problem and formulate appropriate solutions. Further research is required on the safety of use of medicines in this way. Our children require safe and effective therapy with good-quality medicines. Children are precious gifts of God to us. Their protection and safety from medicine-induced harm should be the concern of all of us. Their welfare is the guarantee of the welfare and the future of our continent.

We were encouraged and motivated by Dr C C Ibeh and Fr. Barth. Amobi, and express our gratitude to them. We also thank Miss Ukwueze Modesta, who typed the manuscript. To you all we say thank you and God bless.

**Conflicting interest:** None.

**References**

1. Nahata MC. Licensing of medicines for children in USA. *Paediatric and Perinatal Drug Therapy* 1997; 1: 50-51.
2. Schirm E, van-den-Berg F, Gebben H, Sauer P, De-Jong-van-den-Berg L. Drug use of children in the community assessed through pharmacy dispensing data. *Br J Clin Pharmacol* 2000; 50(5): 473-478.
3. Bücheler R, Schwab M, Mûürike K, *et al*. Off-label prescribing to children in primary care in Germany: retrospective cohort study. *BMJ* 2002; 324: 1311-1312.
4. Steinbrook R. Testing medicines in children. *N Engl J Med* 2002; 347(18): 1462-1470.
5. Hutchinson F, Hall C. Unlicensed medicines in neonatal care; criteria for use. *Journal of Neonatal Nursing* 2003; 9(5): 150-152.
6. Crawley FP. Why do research in children? *Applied Clinical Trials* 2002; July: 14-16.
7. Strassburg CP, Strassburg A, Kneip S, *et al*. Developmental aspects of human hepatic drug glucoronidation in young children and neonates. *Gut* 2002; 50(2): 259-265.
8. Gazarian M. Why are children still therapeutic orphans? *Australian Prescriber* 2003; 26(6).
9. Conroy S. Children's portions: Sharon Conroy analyses the lack of suitably licensed medicines for children and describes how to make the best of what's available. *Chemist & Druggist* 2004; 262(6466): 25-27.
10. Cheung C-L, Sung S-T, Persaud J. Putting children first – why paediatric clinical trials must be conducted. *Pharmaceutical Journal* 2002; 269: 843.

11. Cole CJ, Kauffman RE, Trocradle GJ, Lambert GH. Is the 'therapeutic orphan' about to be adopted? *Pediatrics* 1996; 98: 118-123.
12. Giaquinto C. Clinical trials in children: A challenging need. 2003. http://www.samedanltd.com/members/archives/EPC/Spring2003/CarloGiaquinto.htm (accessed 22 August 2003).
13. Turner S, Nunn AJ, Choonara I. Unlicensed drug use in children in the UK. *Paediatr Perinat Ther* 1997; 1: 52-55.
14. Nunn AJ. Using unlicensed and off-label medicines. 2002. http://www.dial.org.uk/docs/topics-unlicensedmedicines.pdf (accessed 22 September 2003).
15. Nunn T. Medicines: Tried and tested or an unknown risk. Medicines for Health. 2003. http://www.abpi.org.uk/publications_details/mttur_children.asp (accessed July 2005).
16. Geissler PW, Nokes K, Prince RT, Oochiambo RA, Aagaard HJ, Ouma JH. Children and medicines: Self-treatment of common illnesses in Amond Luo school children in western Kenya. *Soc Sci Med* 2000; 50(12): 1771-1783.
17. Stephenson T. Medicines for children – the last century and the next. *Arch Dis Child* 2001; 85: 177-179.
18. *British National Formulary*. London: BMJ Group and Royal Pharmaceutical Society of Great Britain, 2002.
19. Esau R. Pharmacology and drug dosage guidelines. In: Seear M, ed. *The Pocket Paediatrician*. Cambridge: Cambridge University Press, 1998.
20. Obi CC. *Brands of Choice: An A-Z index of NAFDAC-Approved Brands of Pharmaceutical Products in Nigeria.* Ontario, Canada: Lindoz Books, 2002.
21. *Canadian Compendium of Pharmaceuticals and Specialties*. Canada: Canadian Pharmaceutical Association, 2002.
22. O'Donnell CPF, Stone RJ, Morley CJ, Unlicensed and off-label drug use in an Australian neonatal intensive care unit. *Pediatrics* 2002; 110(5): e-52.
23. Choonara I, Conroy S. Unlicensed and off-label use of drugs in children: implication for safety. *Drug Saf* 2002; 25(1): 1-5.
24. Avenel S, Bomkratz A, Dassien G, Janand JC, Danan C. The incidence of prescription without marketing product license in a neonatal intensive care unit. *Arch Pediatr* 2000; 7: 143-147.
25. Chalumeau M, Tréluyer JM, Salanave B, *et al*. Off label and unlicensed drug use among French office based paediatricians. *Arch Dis Child* 2000; 83: 502-505.
26. 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. *Pediatrics* 2001; 108: 1089-1093.