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RECONSTITUTION OF ORAL ANTIMALARIAL SUSPENSIONS: AN UNRECOGNIZED FACTOR IN ANTIMALARIAL DRUG RESISTANCE

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ABSTRACT: Malaria is a foremost universal public health problem, especially in the African region and development of resistance to the older and new generation malaria therapy, has become a persistent health threat requiring urgent solutions. This study intended to assess the ability of human subjects to accurately reconstitute antimalarial dry suspensions according to the manufacturer's instructions. Two hundred (200) dry powders for suspension were procured and distributed to 200 human subjects, and the volumes reconstituted were noted. Results showed that only 24 subjects (12%) were able to reconstitute the suspensions as required by the manufacturer, while ninety-seven subjects (48.5%) made reconstitutions above the required volume and 79 subjects (39.5%) reconstituted below the required volume. Error in reconstitution was as high as 76%. This study emphasizes the need for health caregivers; especially nurses and pharmacists to make the required reconstitutions before dispensing the medication and also give adequate counsel to patients on the appropriate way to make reconstitutions to avoid untoward effects due to over or underdosing.

INTRODUCTION: Malaria is a serious and sometimes fatal disease caused by a parasite that is spread to humans through the bite of infected Anopheles mosquitoes, and the main strains that cause ill health and death are *Plasmodium falciparum* and *Plasmodium vivax*. In certain parts of Africa, *P. falciparum* is the prevalent strain while in other areas it is *P. vivax*. Although, malaria is a global health problem and contributes significantly to mortality, underdevelopment, and poverty in the endemic regions of the developing world, this problem is greatest in Africa, with reports of over 80 percent of malaria cases and consequent death [1].

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Malaria affects all ages and economic groups with a devastating impact on pregnant women and under-five children [2]. The total cost of malaria treatment in sub-Sahara Africa has been estimated to be the US $12 billion per year, with 40 percent of public health expenditures in high-burden countries going to malaria control and management. In 2015 alone, about 214 million cases were reported, although it was also postulated that there was a decrease in the reported clinical cases of malaria (37%) and mortality rate (60%) globally from 2000-2015. [3] It is no longer news that one of the biggest challenges in controlling malaria today is, how to combat drug resistance; however, the handicap is in the development of effective strategies in preventing and controlling such resistance. The most popular reason put forward for drug resistance is large circulation and continued use of fake and counterfeit drugs, unfortunately, even though appreciable efforts have been made in dealing with these, resistance to drugs has not declined.

We opine that there is the need to change strategy by expanding the net of root causes of drug resistance. Although there are various projections for the future to tackle the burden of malaria one of which is the Global Technical Strategy for Malaria 2016-2030, [3] it is only at best a "control" strategy. Furthermore, the World Health Organization (WHO) approved for implementation, the use of Artemisin in combination drugs as first-line treatment in malaria along with diagnostic tests as supportive tools. Pharmacological treatment of malaria with drugs such as Atovaquone-proguanil, Artemether-lumefantrine (ACTs), quinine, doxycycline, tetracycline, clindamycin, mefloquine, and artesunate, has been suggested to be combined with non-pharmacological measures for effective protection [4].

Plasmodium falciparium, responsible for malaria infection in Sub Sahara has reported resistance to such antimalarials like chloroquine, mefloquine, sulfadoxine-pyrimethamine, halofantrine and quinine [5]. More recently, the subject of partial resistance or delayed response (*P. falciparum*) to Artemisinin Combination Therapies has also been described. This poses a great concern, therefore WHO recommends routine monitoring of the effectiveness of these antimalarials especially in the endemic regions. Investigations of antimalarial therapy in regions like Cambodia, Viet Nam and Thailand recorded treatment failure with ACTs and evidence of various mutations of *P. falciparum* [3].

In a study of the quality assessment of various antimalarials conducted in Gabon, one sample of the artemether-lumefantrine tablet was reported to have failed the TLC and HPLC content evaluation test, and the same artemether-lumefantrine antimalarial tablet did not meet the criteria set for disintegration test [6]. Another study in Ghana examined the feature of various artemether-lumefantrine dosage forms (tablet, suspension, and injections) circulating the market and reported that all the formulations but one suspension met the required standards [7].

The quality of chloroquine tablets found in Senegal, Burkina Faso and Mali were found to be substandard when tablet dissolution and content uniformity were assessed [8]. Pregnant women are more prone to malaria which most often leads to various complications, and this has led to the endorsement of the practice of Intermittent Preventive Therapy (sulfadoxine-pyrimethamine) in pregnant women by the World Health Organization. Research piloted in Tanzania reported after quality control testing that one of the failed samples was an antimalarial quinine sulfate 300 mg tablets which was confirmed to be falsified [9].

A similar study on the quality of sulfadoxine-pyrimethamine used in the routine care of pregnant women was also conducted in Ghana, and it was observed that the tablets did not meet the criteria set for *in-vitro* dissolution thus implying that the drug release and consequently bioavailability is compromised [10]. A study conducted in Enugu, Nigeria showed that purchase of artemisinin combination therapy samples using convenience approach revealed the high prevalence of low-quality ACTs. In total, about 9.3 % of the samples were either substandard, degraded or falsified [11].

The high costs of ACTs affect their accessibility; therefore various programmes have been initiated to subsidize their costs for private retailers. Consequently, it was observed that these programmes improved the use and availability of ACTs for children under five years of age [12]. In a similar but different study, done in Ethiopia, it was discovered that that the low affordability of artemether-lumefantrine influenced its availability and accessibility [13]. Affordability of common antimalarials is a major issue as a study conducted in Malawi showed that cost for one course of treatment was greater than the daily income of a low paid government official [14].

Another study reported that antimalarials such as quinine, artemether, and sulfadoxine-pyrimethamine were available in the three health care facilities examined although in varying amounts [2]. Their finding is similar to that of [15] which showed that quinine and sulfadoxine-pyrimethamine were more frequently available in retail outlets compared to the new generation antimalarials (ACTs).

Artemisinin and Artemisinin combination drugs are formulated as a dry powder for reconstitution due to its poor solubility in water and instability. These

formulations are marketed mostly for pediatrics and are essential because these groups of people have low immunity, therefore are vulnerable. Various studies have shown the therapeutic effectiveness of these ACTs in this special population [16, 17, 18].

It is pertinent to ensure that these dry powders are reconstituted properly to minimize errors leading to over dosing or under dosing and consequent toxicity and treatment failure respectively.

The study to evaluate the effectiveness of preservatives in seven (7) samples of artemisinin combination therapy dry powder suspensions reported that only two (2) of the samples met the criteria as specified by the European Pharmacopoeia. In Africa, a study to assess the quality of various dosage forms of artemisinin derivatives showed that 71% of the reconstituted dry powders were of minimal quality. They also observed non-homogenous mixtures and powder aggregation after reconstitution which could result in inaccurate dosing [19].

Another investigation steered in Palestine on the reconstitution, administration, and storage of antibiotic suspensions showed that 86.8% of mothers included in the study were guided by the information leaflet for the reconstitution of antibiotic suspensions [1]. In France, a study focused on the errors made by caregivers in the reconstitution of Amoxicillin and Josamycin. The results postulated that about 46% and 56% of caregivers were not proficient in the reconstitution of amoxicillin and Josamycin respectively which led to a gross underdosing and overdosing respectively [20].

Errors by parents or healthcare givers in administering liquid medications to pediatric patients are very common and are more significant in dosage forms that require reconstitution like antibiotics and antimalarials [21]. Such errors could arise from the quantity of water used for reconstitution, but the training of these caregivers and enlightenment on the appropriate ways to carry these reconstitutions would go a long way in preventing errors.

The study by (Hu *et al*., [22] examined the consequence of various methods or forms of learning programs on caregiver's knowledge of reconstitution and use of antibiotic. The patients were grouped to read the medicine information leaflet, receive step by step illustration or receive step by step illustration including face to face counseling from the pharmacist. They found out that the group that read the drug information leaflet alone had less knowledge of medication reconstitution and usage while those that received illustrations and pharmacist intervention had more knowledge. In developed countries such as USA and UK, pharmacists sometimes help patients with the reconstitution of medications thereby avoiding potential errors emanating from caregivers.

However, in developing or underdeveloped countries, this is not so due to the deficiency of human resources and the enormous number of patients to be attended to.

This study, therefore, was conducted to assess the inconsistency or otherwise of different subjects in reconstituting Artemether-lumefantrine oral powder for suspension.

MATERIALS AND METHODS: Artemether-lumefantrine 180 mg / 1080 mg powder for suspension, (Ultimar plus®), water, measuring cylinders (100 mL),

Product Details: Manufacturing date: 05/14, Expiry Date: 05/17, Batch No: 140512, NAFDAC No: A4-6956, Manufactured by Shanxi Federal Pharmaceuticals Co, Ltd.

The pictorial in **Fig. 1** shows a representation of the antimalarial product used for the study. Two hundred (200) units of artemether-lumefantrine antimalarial oral powder for suspension were procured from a wholesale pharmacy and coded (A1 - A200) for identification purposes. The coded samples were then distributed within AMAC, Abuja, Nigeria to various subjects who were instructed to reconstitute the suspensions with water according to the manufacturer's (leaflet) instructions.

After reconstitution, the samples were retrieved and taken to the laboratory for analysis. In the laboratory, the suspensions were shaken to achieve a homogenous mix, and each sample suspension was poured into a measuring cylinder to measure its actual volume (mL).

FIG. 1: PICTORIAL REPRESENTATION OF ANTI-MALARIAL ORAL POWDER FOR SUSPENSION IN PRODUCT PACKAGE

RESULTS AND DISCUSSION: Drugs in liquid dosage forms are more readily available for pediatrics, geriatrics and those with such conditions that limit swallowing of solid dosage forms and same prescribed due to the convenience of administration. Also, dosing of these liquid formulations can be tailored to individual needs. Consequently, more of these liquid dosage forms; especially antibiotics and antimalarials, are being manufactured as a powder for reconstitution due to stability concerns [22, 23]. Incidences of error in medication with these dry powders have been reported to be as high as 63% with those due to reconstitution having a significant percentage.

Also, other issues relating to storage and dosing which could lead to treatment failure and possible development of resistance have been implicated in medication errors [9]. In HIV infections, for example, no suitable liquid combination or individual formulations for children exists more so, they cannot be administered the solid combination formulations given to adults. Therefore there is a need for pediatric formulations of ART for easy administration to these special group [24]. Where these liquid formulations are available, as in the treatment of malaria in children, and adults who enjoy the benefits of taking these liquid malaria formulations are reported [25], it is very important that its reconstitution is done properly.

Malaria burden is greatest in African regions with about 90% deaths being recorded from the 80% reported cases. Deaths due to malaria infection is estimated to be about 445,000 and those attributed to children being about 285,000 alone in the year 2016 [26]. Those children less than five (5) years are the major focus of antimalarial therapy in those endemic areas because they are more at risk. The strategies to control this disease include the use of insecticide-treated nets (ITN), insecticide sprays and chemotherapeutic agents. The antimalarial therapy recommended for use by the WHO is the Artemisinin-based combination therapies (ACTs) in uncomplicated malaria infection, but the tablets are not recommended for children who weigh less than 5 kg, this makes it imperative that the quality of ACTs formulated as liquid products be assured. Artemether-lumefantrine suspensions are administered only once daily for 3 days instead of twice daily for 3 days recommended when taking the tablets; this improves patient compliance. However, the comparative study of artemether-lumefantrine suspensions and tablets by [27] showed that both formulations were well tolerated and effective in the treatment of malaria infection due to *P. falciparum*. There has been a case report on dosing error with antimalarials which led to detrimental effect [28, 29]. It becomes very important then to ensure that methods/processes that would guarantee quality and efficiency be adhered to; as in the appropriate reconstitution of the powders for suspensions and dosing of the required volume.

Fig. 2 below is a pictorial showing the singular analysis (volume estimation) carried out on the received samples while **Table 1** shows the volumes of individual reconstituted suspensions which were used in further analysis of the results.

FIG. 2: PICTORIAL REPRESENTATION OF ALREADY RECONSTITUTED SUSPENSIONS ANALYZED IN THE LABORATORY

The distribution of subjects and the corresponding volumes of reconstituted suspensions are presented in **Fig. 3**. It was observed that a large number of subjects (97) representing 48.5% of the total subjects reconstituted the suspensions to volumes above the required 60 mL.

TABLE 1: LABELLED ANTIMALARIAL SUSPENSIONS AND THEIR RESPECTIVE RECONSTITUTED VOLUMES (mL)

SC	V RS	SC	V RS	SC	V RS	SC	V RS	SC	V RS
A1	58	A41	69	A81	41	A121	57	A161	60
A2	60	A42	55	A82	55	A122	59	A162	78
A3	60	A43	70	A83	61	A123	69	A163	61
A4	94	A44	61	A84	63	A124	60	A164	50
A5	98	A45	64	A85	72	A125	62	A165	60
A6	71	A46	50	A86	60	A126	59	A166	51
A7	96	A47	92	A87	72	A127	61	A167	50
A8	57	A48	56	A88	83	A128	72	A168	61
A9	63	A49	72	A89	60	A129	63	A169	57
A10	73	A50	53	A90	90	A130	75	A170	62
A11	78	A51	60	A91	61	A131	63	A171	60
A12	63	A52	59	A92	65	A132	54	A172	54
A13	61	A53	55	A93	67	A133	68	A173	65
A14	64	A54	93	A94	59	A134	50	A174	60
A15	65	A55	83	A95	55	A135	69	A175	63
A16	62	A56	62	A96	82	A136	58	A176	63
A17	60	A57	58	A97	70	A137	85	A177	57
A18	57	A58	51	A98	71	A138	56	A178	59
A19	60	A59	64	A99	91	A139	41	A179	46
A20	58	A60	70	A100	60	A140	61	A180	51
A21	40	A61	71	A101	64	A141	38	A181	58
A22	55	A62	99	A102	97	A142	98	A182	52
A23	74	A63	53	A103	63	A143	60	A183	60
A24	59	A64	59	A104	60	A144	62	A184	55
A25	60	A65	64	A105	60	A145	77	A185	60
A26	99	A66	51	A106	72	A146	59	A186	55
A27	89	A67	57	A107	25	A147	63	A187	50
A28	61	A68	90	A108	52	A148	94	A188	53
A29	74	A69	62	A109	50	A149	44	A189	64
A30	60	A70	73	A110	90	A150	74	A190	55
A31	72	A71	88	A111	69	A151	57	A191	55
A32	58	A72	72	A112	52	A152	63	A192	49
A33	60	A73	47	A113	52	A153	56	A193	47
A34	56	A74	62	A114	58	A154	67	A194	60
A35	55	A75	47	A115	60	A155	61	A195	50
A36	91	A76	62	A116	90	A156	81	A196	50
A37	48	A77	57	A117	62	A157	43	A197	70
A38	70	A78	70	A118	57	A158	53	A198	58
A39	54	A79	58	A119	74	A159	110	A199	60
A40	92	A80	55	A120	55	A160	70	A200	49

Key: SC - Sample code, V RS - Volume of reconstituted samples

Also, a high proportion of subjects (39.5%) were observed to have reconstituted the volumes to less than the required volume while only 24 subjects (12%) reconstituted accurately according to the manufacturer's stated volume (60 mL).

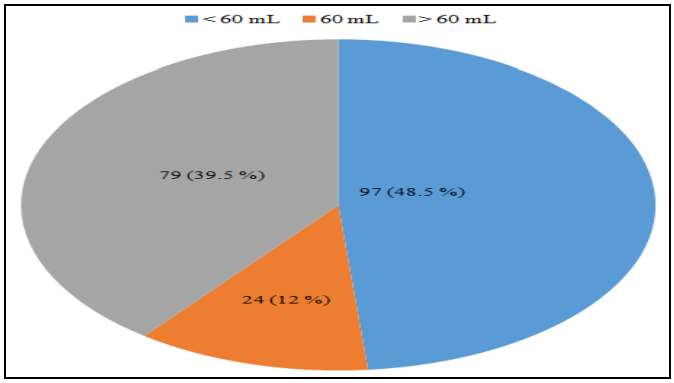

FIG. 3: PIE CHART SHOWING DISTRIBUTION OF SUBJECTS AND VOLUMES OF RECONSTITUTED SUSPENSIONS

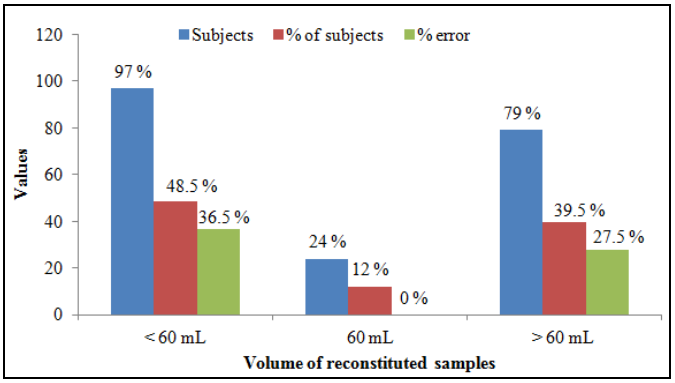

FIG. 4: CHART SHOWING ERROR (%) IN RECONSTITUTED VOLUMES

Fig. 4 shows that 97 subjects reconstituted to volumes less than 60 mL accounting for 36.5% error in reconstitution while 79 subjects reconstituted to volumes greater than 60 mL accounting for 27.5% error and only 12% of the subjects reconstituted to exact volume. This translates to 176 subjects (88%) making mistakes which amount to about 76% error. This is a high percentage of error with devastating consequences in possible under and overdosing of this antimalarial formulation.

Inappropriate reconstitution signifies that the right dose would not be administered; optimum dosing restricts the spread of antimalarial resistance and alterations in drug pharmacokinetics [16]. Dosing children with tablets and fractions of it rather than the appropriate liquid formulations makes them susceptible to suboptimal plasma concentrations and reduced metabolism of drug [30]. Dosing inadequacies could be as a result of the method/process of reconstitution of dry powder formulations; incorporation of excess water, for example, dilutes the product and reduces the potency of the active ingredient which could result in under dosing and reduced efficacy [31, 32]. On the other hand, the addition of too little water makes the active ingredient concentrated which can lead to overdosing and untoward effects. Accurate dosing is essential in the administration of all formulations; however, caution is required in pediatric formulations due to the vulnerability of these age groups. To prevent the development and extent of resistance to ACTs as being experienced globally, it is necessary to ensure that patients receive the correct dose of the antimalarial. Furthermore, optimum dosing of antimalarial results in completely eradicates the *P. falciparum* parasite and consequent recurrent infection [33, 34].

A different but related study by Ryu and Lee [12] focused on the accuracy of the actual dose of liquid medication administered using a variety of measuring devices. Their results which showed that only about 10% of subjects administered a dose above 10% of the required dose (5 mL) is in contrast with ours where 48.5% of subjects reconstituted to volumes above the required. This tells us that if these large numbers of subjects are actual caregivers, they will endanger the lives of their patients.

In our study, the product bottle had been calibrated and fitted with a dosing cup which could be used to measure the water to reconstitution. The varied discrepancies observed could be attributed to inappropriate method or process of reconstitution by the patients, it also suggests that the patients did not use the tools (leaflet, dosing cups) provided by the manufacturer for this product. Similar findings have also been reported [20] where it was revealed that reconstitution errors occurred in 46% and 56% of two antibiotics studied due to the reluctance of patients to read the medicine leaflet instructions, for such reasons as was not comprehensible. This present study also shows that some subjects were reluctant to read the leaflets, while others failed to read the leaflet claiming to have administered the drug before and relied on such knowledge/experience. This could be the reason why only a minority of subjects was able to reconstitute appropriately to the required volume.

Correct practices in dispensing medications are essential to reduce the risk of medication errors and treatment failure; such as giving correct counsel, providing the appropriate tools like syringes and water for dilution. The study by Al-Ramahi *et al*., [1] showed that about 86% of the caregivers understood and followed the manufacturer's instructions while 44% sought pharmacist's intervention the interpretation of such instructions.

Another report [35] showed how a caregiver erroneously administered 9 mL of amoxicillin powder to a boy instead of 9 mL of the required suspension. The report also revealed another scenario where a mother noticed her son's medication looked more viscous than usual and was only half full, suggesting that the suspension was not reconstituted with the appropriate amount of diluent. These show the extreme importance of appropriate dispensing by trained personnel and discourage dispensing of un-reconstituted medications in order to avoid fatal consequences.

CONCLUSION: It is recommended that pharmacists ensure that these oral dry powders are reconstituted before handing them over to patients. In the event that this is not possible, pharmacists should ensure that adequate information and proper counselling is given to caregivers/patients on the appropriate manner of reconstitution. This study

lends credence to the database of information which could be used in constituting appropriate platforms for establishing enlightenment in both hospital and community practices.

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REFERENCES:

1. Al-Ramahi RJ, Zaid A and Anabousi H: Problems associated with reconstitution, administration, and storage of antibiotic suspensions for pediatrics: a cross-sectional study in Nablus city, Palestine. BioMedical Central Research Notes 2015; 8(8): 760.
2. World Health Organisation (WHO), 2018. Malaria. Available from: http://www.who.int/news-room/fact-sheets/detail/malaria.
3. World Health Organization (WHO), Key points: World malaria report. Available from: http://www.who.int malaria/media/world-malaria-report-2017/en/
4. Center for Disease Control (CDC). Available from: https://www.cdc.gov/malaria/travelers/drugs.html
5. Center for Disease Control (CDC). Available from: https://www.cdc.gov/malaria/malaria_worldwide/reduction /drug_resistance.html
6. Visser BJ, Meerveld-Gerrits J, Kroon D, Mougoula J, Vingerling R and Bache E: Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab®: a field study. Malaria Journal 2015; 14: 273.
7. Prah J, Ameyaw EO, Afoakwah R, Fiawoyife P and Oppong E: Quality assessment of Artemether-Lumefantrine Samples and Artemether Injections sold in Cape Coast Metropolis. Journal of Tropical Medicine 2016: 1-6.
8. Sawadogo CW, Al-Kamarany M, Al-Mekhlafi HM, Elkarbane M, Al-Adhroey AH, Cherrah Y and Bouklouze A: Quality of chloroquine tablets available in Africa. Annals of Tropical Medicine and Parasitology 2011; 105(6): 447-53.
9. Mziray S, Mwamwitwa, K, Kisoma S, Augustine S, Fimbo A, Hipolite D, Sillo H and Kaale E: Post Marketing Surveillance of Anti-malarial Medicines in Tanzania. Pharmaceutical Regulatory Affairs 2017; 6(1): 1-5.
10. Yeboah DF, Afoakwah R, Nwaefuna EK, Verner O and Boampong JN: Quality of Sulfadoxine-Pyrimethamine given as antimalarial prophylaxis in pregnant women in selected health facilities in the central region of Ghana. Journal of Parasitology Research 2016; 9231946.
11. Kaur H, Allan EL, Mamadu I, Hall Z, Ibe O and El Sherbiny M: Quality of Artemisinin-Based Combination Formulations for Malaria Treatment: Prevalence and Risk Factors for Poor Quality Medicines in Public Facilities and Private Sector Drug Outlets in Enugu, Nigeria. PLoS ONE 2015; 10(5): e0125577.
12. Opiyo N, Yamey G and Garner P: Subsidising artemisinin-based combination therapy in the private retail sector. Cochrane Database of Systematic Reviews 2016; 3.
13. Orioma R: Availability, Price and Affordability of Artemisinin-based Combination Therapies and Other Antimalarial drugs in the Oromia Regional State of Ethiopia: Implication on Universal Access to Malarial Treatments. Available from: http://apps.who.int/medicine docs/documents.
14. Khuluza F and Heide L: Availability and affordability of antimalarial and antibiotic medicines in Malawi. PLoS One 2017; 12(4): e0175399.
15. Palafox B, Patouillard E, Tougher S, Goodman C, Hanson K and Kleinschmidt I: Prices and mark-ups on antimalarials: evidence from nationally representative studies in six malaria-endemic countries. Health Policy and Planning 2015; 1-13.
16. Sowunmi A, Akano K, Ayede AI, Ntadom G, Adewoye EO, Fatunmbi B and Aderoyeje T: Therapeutic efficacy and effects of artesunate-amodiaquine and artemether-lumefantrine on malaria-associated anaemia in Nigerian children aged two years and under. Infectious Diseases of Poverty 2016; 5: 70.
17. Abuaku BK, Mensah BA, Ofori MF, Myers-Hansen J, Derkyi-Kwarteng AN, Essilfie F, Dokurugu M, Amoakoh E, Koram KA and Ghansah A: Efficacy of artesunate/amodiaquine in the treatment of uncomplicated malaria among children in Ghana. American Journal of Tropical Medicine and Hygiene 2017; 97(3): 690-95.
18. The West African Network for Clinical Trials of Antimalarial Drugs (WANECAM): Pyronaridine-artesunate or dihydroartemisinin-piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomized, multicenter, open-label, longitudinal, controlled, phase 3b/4 trial. The Lancet 2018; 391(10128): 1378-90.
19. Atemnkeng MA, De Cock K and Plaizier-Vercammen J: Post-marketing assessment of content and efficacy of preservatives in Artemisinin-derived antimalarial dry suspensions for pediatric use. Malaria Journal 2007; 6: 12.
20. Berthe-Aucejo A, Girard D, Lorrot M, Bellettre X, Faye A, Mercier JC, Brion F, Bourdon O and Port-Labarthe S: Evaluation of frequency of Paediatric oral liquid medication dosing errors by caregivers: Amoxicillin and Josamycin. Archive of Disease in Childhood 2016; 101: 359-64.
21. MEDSAFE: Preventing pediatric medication errors. Prescriber Update 2015; 36(1): 14.
22. Hu H, Wu F, Hu F, Yang H, Lin S and Shen L: Effectiveness of education programs about oral antibiotic suspensions in pediatric outpatient services. Pediatrics and Neonatology 2013; 54(1): 34-42.
23. Stanley CN and Igala SE: Effect of different storage conditions on the stability and efficacy of some reconstituted oral antibiotic suspensions sold in Portharcourt, Nigeria. Journal of Pharmaceutical Research International 2017; 20(3): 1-10.
24. Schlatter AF, Deathe AR and Vreeman RC: The need for pediatric formulations to treat children with HIV. AIDS Research and Treatment 2016; 1-8.
25. Taillandier J, Esnault Y and Alemanni M: Multicentre study group. A comparison of fluconazole oral suspension and amphotericin B oral suspension in older patients with oropharyngeal candidiasis. Age and Ageing 2000; 29: 117-123.

26. World Health Organization, (WHO). Available from: http://apps.who.int/iris/bitstream/10665/250294/1/WHO-HTM-GMP.
27. Juma EA, Obonyo CO, Akhwale WS and Ogutu BR: A randomized, open-label, comparative efficacy trial of artemether-lumefantrine suspension versus artemether-lumefantrine tablets for the treatment of uncomplicated Plasmodium falciparum malaria in children in western Kenya. Malaria Journal 2008; 7: 262.
28. Akoria OA and Anamefuna FC: Medication error with artesunate-amodiaquine: Case report and root cause analysis. African Journal of Medical and Health Sciences 2014; 13(1): 62-65.
29. Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C and Falade CO: Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: A report from three study sites in sub-Saharan Africa. Malaria Journal 2008; 7: 190.
30. Worldwide Antimalarial Resistance Network (WWARN) DP Study Group: The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin-piperaquine: A pooled analysis of individual patient data. Public Library of Science Medicine 2013; 10: 1001564.
31. Batchelor HK and Marriott JF: Formulations for children: problems and solutions. British Journal of Clinical Pharmacology 2015; 79(3): 405-18.
32. Ivanoska V, Rademaker CMA, van Dijik L and Mantel-Teeuwisse AK: Pediatric drug formulations: A review of challenges and progress. Pediatrics 2014; 134(2): 361-372.
33. Beeson JG, Boeuf P and Fowkes FJI: Maximizing antimalarial efficacy and the importance of dosing strategies. BMC Medicine 2015; 13: 110.
34. Worldwide Antimalarial Resistance Network (WWARN) Lumefantrine PK/PD Study Group: Artemether-lumefantrine treatment of uncomplicated *Plasmodium falciparum* malaria: a systematic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data. BMC Medicine 2015; 13: 227.
35. Gaunt MJ: Avoid Dispensing Unmixed Powder for Oral Suspension. Pharmacy Times Publication 2016.

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