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PERCEPTION OF THE EFFICACY OF ARTEMISININ-BASED COMBINATION THERAPY (ACT) AND CHLOROQUINE PRESCRIPTION PATTERN AND AMONG NURSES IN SOUTH-WEST NIGERIA

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ABSTRACT

Background-Malaria remains a threat to millions of children despite the recent advances recorded in the fight against the disease which remain the 3rd largest killer of children below the age of 5 years in endemic regions. Drug resistant plasmodium species continues to limit the fight against malaria, while the spread of fake and substandard antimalarial drugs has been recognized as a major problem across Africa because of its association with drug resistant parasite. We aim to find out the prescription pattern of chloroquine among nurses in South-West Nigeria and perception of artemisinin-based combination therapy (ACT).

Design and methods-About 180 pre-tested questionnaires were administered to randomly selected nurses out of which 155 were sufficiently completed and suitable for analysis. **Results**-Majority (56.1%) still have confidence in the efficacy of CQ which was still being prescribed by 45.2% of the respondents. CQ was mostly prescribed by those who had previous ACT treatment failure experience (54.3%) with their patients, P=0.03; as well as those who believe that ACT resistance malaria is now in circulation (44.3%). Fifty (32.3%) of our respondents claimed that they had come across fake and substandard ACT, from which 40.0% now prescribe CQ.

Discussion-The high rate of CQ prescription in this study showed that many of the health workers were still resistant to the change in antimalarial treatment policy, which is related to unsatisfactory experience with ACT. Additional measures are urgently required to verify this experience so as to win the confidence of healthcare workers away from chloroquine.

Key words- Artemisinin-based combination therapy (ACT), chloroquine, substandard antimalarial

LA PERCEPTION DE L'EFFICACITE DE LA THERAPIE COMBINEE A BASE D'ARTEMISININE. (ACT) ET LA MODELE DE PRESCRIPTION DE CHLOROQUINE CHEZ LES INFIRMIERS AU SUD - OUEST DU NIGERIA.

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RESUME :

Contexte : Le paludisme reste une menace aux millions d'enfants en dépit des progrès récents enregistrés dans la lutte contre la maladie et ce qui reste la troisième cause de décès des enfants de moins de 5 ans dans les régions endémiques. Les espèces de plasmodium résistantes aux médicaments continuent à limiter la lutte contre le paludisme, alors que la dispersion des drogues anti paludismes contrefaits et non conformes a été reconnue comme un problème majeur à travers l'Afrique en raison son association avec parasite résistant aux médicaments. Nous nous efforçons de trouver le modèle de prescription de chloroquine parmi les infirmiers au Sud - Ouest du Nigeria et la perception de thérapie combinée à base d'artémisinine (ACT).

Conception and Méthodes : Environ de 180 questionnaires pré – testés ont été administrés aux infirmiers choisis au hasard dont 155 ont été suffisamment complétés et appropriés pour analyser.

Résultats : La majorité (56,1%) ont encore confiance dans l'efficacité de CQ qui était encore prescrit par 45,2% des répondants. CQ était surtout prescrit par ceux qui ont eu une expérience précédente de l'échec du traitement de ACT (54,3%) avec leurs patients=0,03, et également ceux qui croient que la résistance du paludisme au ACT est maintenant en circulation (44,3%). Cinquante (32,3%) de nos répondants ont maintenu qu'ils avaient rencontré par hasard un ACT contrefait et non confirmé, desquels 40,0% prescrivent maintenant CQ.

Discussion : Le taux élevé de prescription de CQ dans cette étude a montré que beaucoup de travailleurs de santé étaient encore résistants au changement de politique de traitement antipaludique, qui est lié à l'expérience insatisfaisante avec ACT. Méthodes supplémentaires sont nécessaires de toute urgence pour vérifier cette expérience pour gagner la confiance des travailleurs de la santé de la chloroquine.

Mots - clés : La thérapie à base d'artémisinine ; (ACT), Chloroquine antipaludique non conformé.

INTRODUCTION

Malaria is among the top 3 killers of children all over the world where it is estimated that more than 3 billion people are at risk of infection. About 198 million malaria cases with associated 584,000 deaths were estimated to have occurred all over the world in 2013 (1). Malaria burden is heaviest in Africa where about 90% of all the death occurs, with 78% of such deaths in children below the age of 5 years. Malaria is also the 3rd on the list of top ten causes of death in Nigeria, and the country is said to incur malaria death than any other country in the world (2). The current malaria control strategy include the use of long lasting insecticide treated nets (LLITN), use of indoor residual insecticide spray (IRS), prompt diagnoses and treatment of cases with artemisinin bases combination therapy (ACT). Malaria control has been hampered by the development of resistance by mosquitoes to commonly used insecticides as well as development of resistance by plasmodium species to every antimalarial drug that has ever been deployed in malaria chemotherapy.

Chloroquine (CQ) has been in the frontline of malaria treatment and control since it was first discovered in 1934. It is also said to be the most successful antimalarial drug of all time (3,4). Resistance against CQ was believed to have emerged from South America (5) and South East Asia (6) from where it spread to West Africa and other countries of the world (7,8). The reduced efficacy of CQ prompted the WHO to come up with the policy change in antimalarial chemotherapy whereby it was agreed that CQ should be substituted as the first line drug in countries where resistance is more than 25% threshold (9).

Nigeria formally adopted policy change from CQ to ACT in 2004, and since then, there were many challenges from health care workers as well as patients in terms of compliance to the new treatment guidelines (1).

The most recent WMR which showed that prevalence of malaria infection in Sub-Sahara Africa among the children aged 2-10 years fell from 26% in 2000 to 14% in 2013. And in Nigeria which has the largest number of global malaria death, under 5 mortality rate also reduced from 213 per 1,000 live birth in 1990 to 117 per 1,000 live birth in 2013 (10). Against the background of this positive development, only about 9-26% of children with malaria as at 2013 were treated with ACTs. Some of the reasons behind this was said to be due to the fact that many of the children did not seek treatment, while many of those who sort treatment were not given any antimalarial drug (1).

A study conducted in 2013 on the use of ACT in Nigeria showed that CQ was still being used by about 39% of the respondents while ACT was used by only about 13.6%. The same study also revealed that nurses were the second most important group of health care workers that prescribe antimalarial drugs following doctors (11). A similar study conducted in Kenya showed that insufficient supply of ACT, cost and availability of inappropriate antimalarial such as amodiaquine were some of the reasons why healthcare workers still don't comply with ACT treatment policy (12). Another possible reason why health care workers may still be having problem with the compliance to ACT treatment policy despite the fact that it has been in place for the past 10 years might be because many still have confidence in the older drugs. Presence of fake and substandard ACT in circulation may be associated with treatment failure which might cause health care workers to have diminished confidence and be tempted to fall back on the older drugs. A recent survey of fake antimalarial drugs in Nigeria showed that 6.8% of the ACT in circulation was substandard, while another 1.3% was already degraded. About 1.2% of the circulating ACT was also found to be falsified (13). Fake and substandard antimalarial drugs, especially ACT, mostly find their way to Africa from Asian countries. In a study by Newton *et al* that investigated the rate of counterfeit antimalarial drugs en route to Africa from

Asia, fake drugs were found in 8 of the 11 countries sampled. Some of the unwholesome antimalarial drugs sampled included counterfeit artesunate that contains chloroquine, counterfeit dihydroartemisinin containing just acetaminophen, and counterfeit artemether-lumefantrine containing pyrimethamine (14).

Several studies have shown that nurses are important part of the health care team involved in management of malaria in the community and are often involved in prescription of antimalarial drugs. They sometimes constitute the first point of contacts in malaria treatment at primary health care level (15,16,17). Despite the change in treatment policy, Onyeaso and Oluwole found out that Chloroquine was the most frequently prescribed antimalarial drug for malaria prophylaxis by primary healthcare providers in a study in Nigeria. The reason for this was said to include ease of availability, affordability and insufficient knowledge of healthcare providers regarding efficacy and resistance of antimalarial drugs (17). Study in Tanzania also showed that SP was not well received by the healthcare workers several years after it was substituted for CQ (18). Similar studies in Kenya and Ghana also showed that Health care workers were resistant to malaria treatment policy change in a similar way malaria seems to be resistant to the changed medication (19, 20). The study in Kenya even showed that qualified healthcare workers (Doctors and Trained Nurses) were more likely to be less compliant with the new treatment policy. Longitudinal study in Tanzanian where malaria treatment policy had been changed 2ce in a decade found out that healthcare workers compliance to the new antimalarial drugs worsens over time (21). It was suggested that this may be based on their routine experiences in the clinical management of patients whereby the healthcare workers may be the first to notice inadequate clinical response to treatment before the attention of other stakeholders is eventually drawn to it.

Ability of malaria to develop resistance to ACT has never been in doubt; there are reports of resistance to ACT in South -East Asia, the same area where resistance to CQ was believed to have originated (21, 22, 23). A recent publication from eastern part of Nigeria reported 3 cases of *Plasmodium falciparum* malaria that showed early treatment failure (ETF) to artemisinin-based combination therapy. All the 3 cases showed adequate clinical response when treated with quinine. The publishers suggested that

the failure might as well be due to questionable quality of the ACT, but then other patients that were treated with the same batch of drug were said to have responded adequately (24). This study aimed at investigating the level of chloroquine prescription among nurses in South West in Nigeria as well the possible role their experience with the use of ACT might play.

MATERIALS AND METHODS

About 180 pre-tested questionnaires were administered to randomly selected nurses in Sagamu, South-West Nigeria between the month of March and May 2015 to access the level of confidence they still had in CQ. Nurses in both private and public health care facilities were targeted for this purpose. Informed consent were obtained from the participants who were also made to realize that the questions were meant for research purpose only, and that answers provided will be made confidential. One hundred and sixty nine of the questionnaires (94%) were retrieved out of which 155 were sufficiently completed and suitable for analysis. The questionnaires were entered into Excel spread sheet and later exported to PSPP GNU statistical software version 0.8.5 for analysis. Results were cross tabulated and chi square was used to test for degree of association between the variables. Associations were said to be significant when P value was found to be less than 0.05.

RESULTS

Most of our respondents (58%) practice in public hospitals while 25% practice in private hospitals, and the rest work at both settings (Figure 1). Seventy six (49%) of the respondents are younger than 30 years old while 67 (43%) have less than 5 year post basic qualification experience (Table 1). Majority (56.1%) still have confidence in the efficacy of CQ while another 18.1% were not sure whether the drug is no longer efficacious, $P=0.01$. Many of the nurses above 40 years of age (69.1%) and majority of those who have between 11 to 20 years of post-qualification experience (71.4%) still have confidence in CQ efficacy $P=0.001$. Sixty three (40.7%) of the respondents have experienced ACT treatment failures with their patients during the course of their practice which were eventually treated with another antimalarial. Majority of those who still have confidence in the efficacy of CQ were those that have experienced treatment failure with ACT (68.3%), Table 1.

TABLE 1: ASSOCIATION BETWEEN CONFIDENCE IN EFFICACY OF CQ AND AGE, YEARS OF EXPERIENCE AND ACT TREATMENT FAILURE EXPERIENCE.

	Confidence in the efficacy of CQ			
	Yes (%)	No(%)	Not sure(%)	Total(%)
Age				
<30	33(43.4)	29(38.2)	14(18.4)	76(100)
30-40	25(67.6)	7(18.9)	5(13.5)	37(100)
>40	29(69.1)	4(9.5)	9(21.4)	42(100)
Total	87(56.1)	40(47.1)	28(18.1)	155(100)
P=0.01				
Years of experience				
<5	27(40.3)	27(40.3)	13(19.4)	67(100)
5-10	22(66.7)	8(24.2)	3(9.1)	33(100)
11-20	20(71.4)	1(3.6)	7(25.0)	28(100)
>20	18(66.7)	4(14.8)	5(18.8)	27(100)
P=0.001				
ACT treatment failure experience				
Yes	43(68.3)	12(19.0)	8(12.7)	63(100)
No	36(49.3)	22(30.1)	15(20.6)	73(100)
Not sure	8(42.1)	6(31.6)	5(26.3)	19(100)
P=0.15				

The younger nurses (30.1%) and those with less than 5 years of experience (28.45%) had fewer experience with ACT treatment failure compared to the older and more experienced nurses. But the older and more experienced nurses were more sure of their perception of ACT treatment failure with only 2 (4.8%) of those above 40 and only 1 (3.8%) of those with 11 to 20 years of experience in the not sure category.

Our study showed that 70 (45.2%) of our respondents still prescribe CQ (P=0.02). It was also discovered that CQ was mostly prescribed by those who had previous ACT treatment failure experience (54.3%) with their patients, P=0.03; as well as those who believe that ACT resistance malaria is now in circulation (44.3%). Fifty (32.3%) of the nurses admitted that they had come across self-recognized fake ACT before (Figure 2), out of which 40% now prescribe CQ, (Table 3).

TABLE 2: RELATIONSHIP BETWEEN ACT TREATMENT FAILURE EXPERIENCE AND AGE AS WELL AS YEARS OF EXPERIENCE OF RESPONDENTS

	ACT treatment failure experience			
	Yes (%)	No (%)	Not sure (%)	Total (%)
Age				
<30	23(30.1)	40(52.6)	13(17.1)	76(100)
30-40	20(54.1)	13(35.1)	4(10.8)	37(100)
>40	20(47.6)	20(47.6)	2(4.8)	42(100)
P=0.06				
Years of experience				
<5	19(28.4)	35(52.2)	13(19.4)	67(100)
5-10	17(51.5)	13(39.4)	3(9.1)	33(100)
11-20	14(50.0)	13(46.4)	1(3.8)	28(100)
>20	13(48.2)	12(44.4)	2(7.4)	27(100)
P=0.10				

TABLE 3: PATTERN OF CHLOROQUINE PRESCRIPTION AMONG RESPONDENTS.

	Still prescribe CQ to patients		
	Yes (%)	No (%)	Total (%)
Age			
<30	30(39.5)	46(60.5)	76(49.0)
30-40	24(64.9)	13(35.1)	37(23.9)
>40	16(38.1)	26(61.9)	42(27.1)
Total	70(45.2)	85(54.8)	155(100)
P=0.02			
Years of experience			
<5	26(38.8)	41(61.2)	67(43.2)
5-10	17(51.5)	16(48.5)	33(21.3)
11-20	14(50.0)	14(50.0)	28(18.1)
>20	13(48.2)	14(51.9)	27(17.4)
Total	70(45.2)	85(54.8)	155(100)
P=0.57			
ACT treatment failure experience			
Yes	38(54.3)	25(29.4)	63(40.7)
No	24(34.3)	49(57.7)	73(47.1)
Not sure	8(11.4)	11(12.9)	19(12.3)
P=0.01			
Encounter fake ACT			
Yes	28(40.0)	22(25.9)	50(32.3)
No	24(34.3)	47(55.3)	71(45.8)
Not sure	18(25.7)	16(18.8)	34(21.9)
P=0.03			
ACT resistance is in circulation			
Yes	31(44.3)	13(15.3)	44(28.4)
No	16(22.9)	39(45.9)	55(35.5)
Not sure	23(32.9)	33(38.8)	56(36.1)
P=0.00			

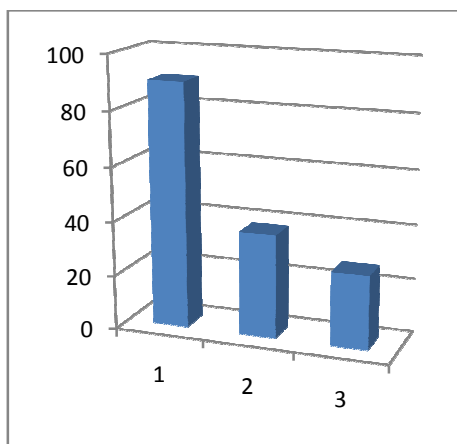


FIGURE 1. PLACE OF PRACTICE. (1) PUBLIC HOSPITAL = 90 (58%), (2) PRIVATE HOSPITAL= 38 (25%), (3) BOTH PUBLIC AND PRIVATE= 27 (17%).

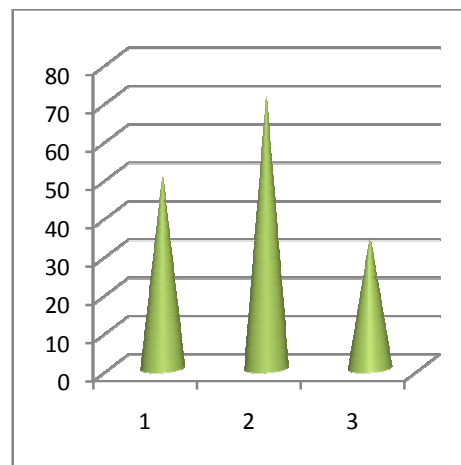


FIGURE 2: HAD COME ACROSS RECOGNIZED FAKE ACT BEFORE? (1) YES =50 (32.3%), (2) NO= 71 (45.8%), (3) NOT SURE =34 (21.9%)

DISCUSSION

The WHO recommends regular antimalarial treatment efficacy trials so as to keep an eye on impending Plasmodium resistance. Clinical efficacy trials with standardized protocol are the best way of doing this. In this study, we sampled the opinion of important stakeholders in the field of malaria

treatment and control, nurses, to find out their perception of ACT efficacy as well as the level of confidence they still have in chloroquine.

The number of nurses who still prescribe CQ in this study is still high, 70(45.2%). This is similar to studies in Kenya and Tanzania which also found poor compliance with the new antimalarial treatment policy. The relationship between the confidence in the efficacy of CQ and its prescription rate with age and years of experience of our respondents may actually be related to the long years of experience they had with it, before it became a failed drug. Adherence to CQ by healthcare workers in similar Nigerian study was attributed to its cheaper price and ease of availability (17).

The numbers of respondents who still have confidence in CQ suggest that the drug is not a 100% failed drug. But then, is important to effectively educate healthcare workers about the rationale behind the policy change in the first place. It is important to let all stakeholders appreciate the fact that only 25% failure rate was what informed the change, and that some degree of treatment success is still expected, which does not warrant early return to its use.

Perception of nurse's ACT treatment failure as recorded in this study will need further investigation, especially when it is associated with CQ prescription. The recent claim of 3 cases of ACT treatment failure by Ajayi and Ukwaja (24) also supported this nurse's suspicion. High prevalence of this perception among the more experienced healthcare workers calls for concern because the impression can readily be transmitted to the younger ones who they are expected to instruct and mentor. A similar study in Tanzania also found out that personal experience among healthcare worker including doctors, was responsible for poor adherence to new antimalarial treatment policy. The same study also showed that healthcare workers easily bring their experience to bear when prescribing drugs for their patients (21).

Experience of our respondent's with fake and substandard antimalarial drugs further suggests that the menace of unwholesome ACT is still a reasonable treat in Africa and this should be further investigated in a more formalized study. The issue of fake and substandard ACT calls for urgent remedial attention since it is found in this study to be associated with increased CQ prescription by health care workers.

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We will like to recommend that standard methods should be developed to evaluate and document the personal experience of healthcare workers regarding antimalarial treatment failure. Records from such data can serve as an adjunct to the standard clinical efficacy trial. When healthcare workers realize that their experience contributed to decision that lead to a change in treatment policy, they are more like to adhere to such a joint decision compare to when they perceive the policy emanated from a group of sponsored researchers alone.

One limitation of our study is that there was no documented laboratory evidence of malaria in patients that were said to have experienced treatment failure with ACT by our respondents. But then this is also not sufficient to dismiss the claims of these respondents because most malaria cases in Africa are still being treated without laboratory evidence.

Conflict of interest declaration-

I, Dr Efunshile AM hereby declare on behalf of my co-authors that none of us has any potential conflict of interest whatsoever.

Author's contribution-

Deign the study-AME, OO, DI, CNI, AA

Administer the questioner-OO

Analyse the results- AME, AA

Writing of the manuscript- AME, OO, DI, CNI, AA

Read and approve the final manuscript- AME, OO, DI, CNI, AA

Significance for public health

Despite the change in the malaria treatment policy in Nigeria over the last 10 years, our study showed that a large proportion of the healthcare workers still prescribe chloroquine. This practice was significantly associated with the believe that ACT resistance malaria is now in circulation as well as the experience of the workers with ACT treatment failure. Urgent measures have to be taken to investigate the believe of this group of healthcare workers so as to reinforce confidence in ACT in order to sustain the progress made so far in the fight against malaria.

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