

Risk management of adverse effects of antimalarial drugs: Knowledge of Physicians and Pharmacists in KAYES, MALI.

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Abstract-In order to improve therapeutic compliance and prevent antimalarial drug resistance, we conducted this study to evaluate the knowledge of physicians and pharmacists in Kayes on the management of adverse effects of antimalarial drugs. **Methods:** A cross-sectional study was conducted from July to November 2017 among physicians and pharmacists selected by simple random sampling and practicing in the Kayes region for more than one year. The survey was based on a questionnaire proposed by the national pharmacovigilance center. In addition to a descriptive analysis of the results, a logistic regression analysis was performed to assess potential factors that could be associated with knowledge. **Results:** Among 151 physicians and pharmacists participated in the study, less than 40% had better knowledge about the management of antimalarial drug adverse events. Physicians and pharmacists working in government facilities were more likely to have better knowledge compared with those working in other facilities (OR=8.38; 95% CI: 2.48-28.30). In addition, pharmacists were more likely to have better knowledge than physicians (OR=3.48; 95% CI: 1.21-12.19). **Conclusions:** The frequency of good knowledge of the management of adverse drug reactions to antimalarials is insufficient, although membership in government structures and profession seem likely to improve it.

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1. Introduction

Despite the intensification of malaria control activities through the Roll Back Malaria initiative [1], progress in malaria incidence and deaths in Africa has slowed, mainly due to stagnation in several countries with moderate or high transmission [2].

Early diagnosis and prompt treatment with an effective antimalarial drug remain the priority strategy recommended by the World Health Organization (WHO). It is based on the use of artemisinin-based combination therapy (ACT) including artesunate-amodiaquine (AS-AQ) and artemether-lumefantrine (AL) for the treatment of uncomplicated malaria [3]; and the use of artesunate or quinine dihydrochloride for severe malaria [4].

Although these antimalarials are much safer [5], data on the safety profile of their long-term use in the general population of sub-Saharan Africa remain scarce outside of clinical trials. Indeed, several studies have reported safe use of ACTs, particularly the AS-AQ combination [6-10].

In Mali, with financial support from the President's Malaria Initiative (PMI) and the Global Fund the AS-AQ combination was scaled up in 2010 [11]. Patients living in endemic areas are likely to receive repeated antimalarial treatments over the course of a year. Thus, the collection and analysis of post-approval safety data becomes important [12]. Indeed, post-marketing safety is likely to improve adherence to treatment and prevent antimalarial drug resistance [5,13,14].

However, most sub-Saharan African countries lack expertise, resources [12], and medical personnel seem to have little knowledge of the adverse effects of these new therapeutic strategies [15].

To improve therapeutic compliance and prevent antimalarial drug resistance, we conducted this study to assess the knowledge of physicians and pharmacists in Kayes on the antimalarial adverse effect management and determine the associated factors.

2. Method:

2.1. Participants

This was a cross-sectional study of medical health professionals (Physicians and Pharmacist) in the public and private sector in Kayes conducted between July and November 2017.

In 2016, in terms of health, Kayes region included: ten (10) health districts, one (1) Public Hospital Establishment of 2nd reference; six (6) private clinics; two hundred and thirty-three (233) functional Community Health Centers (Csom); one (1) polyclinic; two (2) military garrison infirmaries; thirty-five (35) medical offices and forty-three (43) private pharmaceutical dispensaries; with nine

hundred and five (905) health workers, including one hundred and seventy-five (175) doctors and fifty (50) general pharmacists [16].

The number of general practitioners and pharmacists participating in the study was calculated by estimating the expected frequency of best knowledge at 50% with a precision of 5%, and applying a confidence level of 95% and 80% of the study power. The sample size of general practitioners calculated was 120 physicians and 44 general practitioners.

A simple random sampling technique was used to select physicians and pharmacists from the public and private sectors to be included in the study. Health professionals selected by random draw who had been practicing for more than one year and who were willing to give their consent to participate in the study were invited to join our study. General practitioners and pharmacists who did not give their consent, as well as those practicing for less than one year, specialist physicians and pharmacists; and general practitioners and pharmacists not involved in malaria management (diagnosis, treatment and follow-up, dispensing of drugs) were excluded from our study.

2.2. Questionnaire and administration:

An anonymous self-administered questionnaire was used for data collection.

The questionnaire included open-ended and closed-ended questions related to the characteristics of physicians and pharmacists (age, gender, seniority, training received on malaria and pharmacovigilance), practices regarding diagnosis, identification and management of adverse events, and reporting of adverse events.

Responses to practices regarding diagnosis, identification and management of adverse events, and reporting of adverse events were rated as correct and incorrect according to the Malaria Management Guide [5,14] to determine the level of knowledge of adverse events of antimalarials. A threshold of an average of 75% correct was defined as good knowledge.

2.3. Validity of the questionnaire:

The selection of the questionnaire items was made according to the literature and the opinions of the national pharmacovigilance center and the national malaria control program. The questionnaire was pre-tested on a sample of 20 doctors and 12 pharmacists in Bamako. This activity will make it possible to approve the collection tools developed, to correct any errors, to reformulate certain questions with regard to the context, and to adopt appropriate strategies for use in the field.

2.4. Data analysis and processing:

To describe the characteristics of the participants we used standard descriptive statistics (frequency for categorical variables, means and standard deviation for quantitative variables) and a logistic regression analysis was performed to assess potential factors that could be associated with knowledge of adverse effects of antimalarials considering a $p < 0.05$ as the level of significance. The fit of the multivariate model was checked by the Hosmer-Lemeshow test and all analyses were performed using R (version 3.5.3)

2.5. Ethical consideration

All the methods and techniques used in this study were carried out in accordance with international standards of research ethics and data protection. Participation in the study was voluntary and anonymous.

Administrative authorization to conduct the study was sought and obtained from Regional Health Delegation, and participant consent was sought and obtained.

3. Results:

3.1. Socio-professional characteristics of participants

Out of a total of one hundred and sixty-four (164) physicians and general pharmacists selected, one hundred and fifty-one (151) agreed to answer our questions; among them 110 physicians and 41 general pharmacists. The respondents were mainly male (90.7%) and the average age was 39.55 ± 4.44 years SD with an average professional seniority of 6.68 ± 3.69 years SD.

Table 1 elucidates the socio-professional characteristics of participants.

3.2. Attitudes to managing adverse drug reactions to antimalarials

Among Of the 151 general practitioners and pharmacists involved in the management of malaria, 52 (39.1%) decided to prescribe symptomatic

treatment to manage adverse events. In contrast, slightly more than 40% ($n=62$) of general practitioners and pharmacists reported doing nothing; and almost 90% ($n=135$) reported not reporting adverse events (Table 2).

3.3. Factors associated with good risk management knowledge of antimalarial drug adverse events

Except for age and the nature of the work structure, none of the socio-professional characteristics were significantly associated with improvement in the proper management of adverse drug reactions among physicians and pharmacists in the univariate analysis.

Physicians and pharmacists over 40 years of age were more than twice as likely to have better knowledge of adverse events than others ($OR=2.17$ and $p \text{ value}=0.026$); and those in government practice were more than three times as likely to have better knowledge of adverse events than those in private practice ($OR=3.15$ 95% CI: 1.43-6.93) (table 3)

Adjusted for potential confounders, type of profession, and nature of practice structure significantly increased knowledge of antimalarial drug adverse events. Participation in pharmacovigilance and/or malaria training in the past 12 years increased knowledge of antimalarial drug adverse events (adjusted $OR=1.49$). However, this increase was not statistically significant ($p=0.457$). In addition, general pharmacists were statistically three times more likely than general practitioners ($OR=3.48$, 95% CI: 1.21-12.19) to have increased knowledge of antimalarial drug side effects. Medical professionals (physicians and pharmacists) working in government facilities were also statistically more likely than those working in private facilities ($OR=8.38$ 95% CI: 2.48-28.30) to have greater knowledge of antimalarial drug side effects (table 3).

Table 1: Socio-professional characteristics of general practitioners and pharmacists involved in malaria management in Kayes, July November 2017.

Socio-professional characteristics	Numbers (N=151)	Percentage (%)
Gender		
Male	137	90,7
Female	14	9,3
Ages		
≤ 40 years	93	61,6
> 40 years	58	38,4
Profession		
Physician	110	72,8
Pharmacist	41	27,2
Professional seniority		
≤ 5 years	59	39,1
> 5 years	92	60,9

Practice environment		
Urban	112	74,2
Rural	39	25,8
Nature of the work structure		
Governmental	43	28,5
Community	36	23,8
Private	72	47,7
Less than one year of training in pharmacovigilance and/or malaria		
No	119	78,8
Yes	32	21,2

Table 2: Attitudes toward managing adverse effects of antimalarial drugs of general practitioners and pharmacists involved in the management of malaria in Kayes, July-November 2017.

	Numbers (N=151)	Percentage (%)
Management ADR		
Do nothing	62	41,1
Symptomatic treatment	59	39,1
Stop the treatment and change the molecule	24	15,9
Decrease the dose by extending the duration of the treatment	3	2,0
Seek input from colleagues	3	2,0
Reporting ADR		
No	135	89,4
Yes	16	10,6

Table 3 : Factors associated with good risk management knowledge of antimalarial drug adverse events of general practitioners and pharmacists involved in malaria management in Kayes, July-November 2017.

Socio-professional characteristic	Better knowledge of risk management of antimalarials		Analyse univariée		Analyse multivariée	
	Yes (n=56) Numbers (%)	No (n=95) Numbers (%)	OR [CI 95%]	p value	OR [CI 95%]	p value
Gender						
Male	52(92,9)	85(89,5)	1,53[0,45-5,13]	0,491	1,42[0,38-5,34]	0,596
Female	4(7,1)	10(10,5)	1		1	
Ages						
≤ 40 years	28(50,0)	65(68,4)	1	0,026	1	0,116
> 40 years	28(50,0)	30(31,6)	2,17[1,09-4,27]	0,291	1,85[0,85-4,01]	0,022
Profession						
Physician	38(67,9)	72(75,8)	1		1	
Pharmacist	18(32,1)	23(24,2)	1,48[0,71-3,08]	0,321	3,48[1,21-12,19]	0,207
Professional seniority						
≤ 5 years	19(33,9)	40(42,1)	1		1	
> 5 years	37(60,1)	55(57,9)	1,41[0,71-2,81]	0,334	1,74[0,73-4,12]	0,638
Practice environment						
Urban	44(78,6)	68(71,6)	1,45[0,67-3,17]	0,004	0,77[0,26-2,25]	0,001
Rural	12(21,4)	27(28,4)	1		1	
Nature of the work structure						
Governmental	25(44,6)	18(18,9)	3,15[1,43-6,93]		8,38[2,48-28,30]	
Community	9(16,1)	27(28,4)	0,75[0,30-1,87]		1,22[0,27-5,45]	
Private	22(39,3)	50(52,6)	1		1	
Less than one year of training in pharmacovigilance and/or malaria						
No	42(75,0)	77(81,1)	1	0,381	1	0,457
Yes	14(25,0)	18(18,9)	1,42[0,64-3,15]		1,49[0,51-4,34]	

4. Discussion

4.1. Main results

Our study shows that most physicians and pharmacists are not aware of the risks of adverse effects of antimalarial drugs. Indeed, less than 40% (n=56) of participants had a better knowledge of the risks of adverse effects. However, pharmacists were much more likely to have better knowledge than general practitioners (OR=3.48, p value=0.026). This could be attributed to pharmacists' much more pharmacology-focused academic training, pharmacists' much higher prior exposure to adverse event management, and their proximity to patients. Several studies have confirmed good control of adverse events by pharmacists compared with physicians [17-20].

The lack of knowledge of the risks of adverse reactions by health professionals (physicians and pharmacists) can have most serious of which would be the absence of identification of an ADR related to antimalarial drugs, with a risk of repercussion on therapeutic compliance, which can lead in the long term to antimalarial drug resistance. Indeed, physicians with a better understanding of the risks generally adopt a better attitude towards the offending drug. The positive attitudes adopted by general practitioners and pharmacists (permanent cessation, symptomatic treatment) to deal with the risks of antimalarial drugs in our study confirm these assertions.

Although the training received on pharmacovigilance and/or malaria in the last 12 months was not statically associated with an increase in knowledge of the risks of adverse effects (adjusted OR=1.49, p=0.457); we can think that the information-training approach on the risks of adverse effects of antimalarial drugs could have an impact on the proper use of these drugs than those who did not receive the training. In addition, health professionals (physicians and general pharmacists) working in government facilities were more likely to have better knowledge of antimalarial drug side effects (OR=8.38 95% CI: 2.48-28.30) than those working in private facilities. This may be due to capacity building of staff in government facilities through multiple training and supervision.

Mali like other countries, has an established pharmacovigilance system. This system aims to collect data on adverse drug reactions that have occurred in the country. The system relies on voluntary reporting of ADRs by health professionals in hospitals and community settings. Under-reporting remains the main problem of pharmacovigilance in Mali as in many countries [21,22]. In fact, less than 11% (n=16) of health professionals (physicians and general pharmacists) stated that they did not report adverse drug

reactions to the national malaria control program or to the national pharmacovigilance center.

4.2. Strengths and limitations

The role of general practitioners and pharmacists in the management of malaria and the management of adverse effects of antimalarial drugs is crucial to improve compliance and prevent resistance to antimalarial drugs because it allows the monitoring of patients' treatment under real conditions. To our knowledge, this is the first study conducted in Mali to evaluate the knowledge of physicians and pharmacists on the management of adverse effects of antimalarial drugs.

Adverse reactions to antimalarial drugs are considered one of the major contributors to morbidity and mortality, placing a heavy burden on health systems [13]. Pharmacovigilance is one of the most effective methods of generating signals about post-marketing adverse drug reactions.

Even if the sample size was not reached, our study is fairly representative of general practitioners and pharmacists in Kayes.

A declarative bias, specific to any descriptive epidemiological study by self-questionnaire, remains possible. However, it is unlikely that the physicians would have conducted even a brief review of the literature before answering the questionnaire, given the time constraints of their medical practice.

Although this study is geographically limited in scope, it provides baseline data on the knowledge of Malian physicians and pharmacists about the adverse effects of antimalarials.

Replication of the study with a much larger sample size would be useful to draw a more accurate conclusion.

5. Conclusions

Knowledge of adverse events remains very low. However, capacity building of medical staff through multiple training and supervision involving non-governmental structures could improve it.

Conflict of interest: None

Authors' contributions

TRAORE Boubacar: Protocol development, data analysis and writing of the article.

TSOUMBOU-BAKANA Gladys: correction of the protocol and the article.

OUMAR Aboubacar Alassane: correction and validation of the protocol and the article

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