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Pharmacovigilance reporting during seasonal malaria chemoprevention campaign: Findings from northern Nigeria

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ABSTRACT

Background: Seasonal malaria chemoprevention (SMC) campaign is known to reduce malaria-related morbidity and mortality among children aged 3 -59 months in the Sahel regions of Africa. However, the success of the intervention may be adversely affected by the absence of a robust pharmacovigilance system to monitor safety. This paper aims to describe our pharmacovigilance reporting experience during the campaigns conducted across seven states in Nigeria in 2020.

Methods: The SMC campaigns were held over four cycles from July to November 2020, with nearly 12 million eligible children reached by trained community drug distributors. Suspected adverse drug reactions were reported routinely through the national pharmacovigilance (PV) system. Completed PV forms submitted to the National Agency for Food, Drugs Administration and Control were retrieved and analyzed.

Results: The adverse drug reaction (ADR) reporting across the seven states was low, with no ADR reports from five states. The ADRs reported included abdominal pain, weakness, diarrhea, fever, rash, and vomiting. Vomiting was the most reported ADR, accounting for almost half (28/57) of all reported cases. Children aged 12–59 months accounted for most (~86%, 49/57) of the ADR reports, with over 70% (40/57) of these reports completed by community health extension workers. The system organ classification of ADRs showed that the gastrointestinal system was mainly affected (65%, 37/57).

Conclusion: Our experience suggests gaps with the pharmacovigilance surveillance system, highlighting the need to consider an active surveillance system, address behavioural factors, and explore the use of a digital reporting system.

Abbreviations: ADR, Adverse Drug Reaction; CDD, Community Drug Distributor; CHEWs, Community Health Extension Workers; CHO, Community Health Officer; HF, Health Facility; ICSR, Individual Case Safety Report; NAFDAC, National Agency for Food, Drug Administration and Control; NMEP, National Malaria Elimination Programme; NPC, National Pharmacovigilance Centre; PV, Pharmacovigilance; SMC, Seasonal Malaria Chemoprevention; SP, Sulphadoxine Pyrimethamine; SPAQ, Sulphadoxine Pyrimethamine + Amodiaquine; SOC, System Organ Classification; WHO, World Health Organization.

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Background

Malaria is one of the leading causes of morbidity and mortality globally [1]. In 2020, there were an estimated 241 million malaria cases in 85 malaria endemic countries including the territory of French Guiana increasing from 227 million in 2019 [1]. Countries in the WHO African Region accounted for most of this increase. Specifically, Nigeria and Congo jointly accounted for 39% of the global malaria cases and deaths, with children under five years being the most affected group [1,2].

Seasonal malaria chemoprevention (SMC) targeted at children under five years is one of the interventions aimed at preventing malaria [3]. It involves administering a combination of sulphadoxine, pyrimethamine and amodiaquine (SPAQ) to healthy, eligible children between the ages of 3 and 59 months during the peak of the rainy season in the Sahel region of Africa [4,5]. Once administered, the therapeutic level attained can protect children against malaria throughout the peak of the rainy season [6]. Provided the drugs are administered according to the recommended guideline, this intervention can reduce malaria cases by 75%, and by extension, malaria mortality [4,5].

The success of the intervention depends on the efficacy and safety of the SPAQ. While satisfactory efficacy and safety are preconditions for marketing authorization, post-marketing surveillance is highly encouraged to identify safety issues that may arise during large-scale use. To effectively identify and respond to safety issues post authorization, a reliable pharmacovigilance system capable of detecting, monitoring and reporting adverse drug events associated with the drugs used for the SMC campaign must be in place. Countries and health programmes adopt an active or passive pharmacovigilance strategy and, in some instances, a combination of both. With the active pharmacovigilance system, cases of adverse drug reactions are actively sought. On the other hand, the passive approach relies on the end-users to report suspected adverse drug reaction cases.

In Nigeria, ADRs are reported passively using ADR forms that are obtainable from the 36 state offices of the National Agency for Food and Drug Administration and Control (NAFDAC), the National Pharmacovigilance Centre (NPC) NAFDAC Headquarters, or any of the other pharmacovigilance centres across the country [7,8]. The completed ADR forms are expected to be returned to the form collection centers [7]. In line with the national strategy, all suspected cases of ADR are expected to be reported using the ADR form and transmitted to the designated centres (see appendix A for a more detailed description of Nigeria's pharmacovigilance system).

The National Malaria Elimination Program (NMEP) in collaboration with international non-governmental organizations and the state ministries of health across six northern Nigeria states —Bauchi, Jigawa, Kano, Katsina, Kebbi, Sokoto and Yobe States—implemented SMC campaigns in 2020 following WHO guidelines and Nigeria's national pharmacovigilance reporting system.

There is paucity of safety data across several West African countries when SPAQ is massively distributed during the implementation of the SMC campaign, a gap that was further pointed out by implementers and other stakeholders [9]. Published safety studies on SPAQ for SMC intervention have been under randomized control trial conditions [10]. We, therefore, set out to bridge this evidence gap by conducting this study. More specifically, this paper examines ADR reporting rate, type of suspected ADR, including affected organ system, and the designation of the ADR reporters from the SMC campaigns conducted across seven northern states in Nigeria while highlighting potential strategies for strengthening the pharmacovigilance system.

Ethics approval

Approval for the SMC implementation was granted by the various state ministry of health in the implementing states in Nigeria. This approval includes pharmacovigilance study during the campaign.

Methods

Design

We cross-sectionally analyzed pharmacovigilance data from the SMC campaigns implemented by the NMEP from July 2020 to November 2020 across seven states in Nigeria. The SMC campaigns were implemented in all the wards and local government areas of Bauchi, Jigawa, Kano, Katsina, Kebbi, Sokoto and Yobe States. Before the campaigns, health facility workers recruited for the campaigns were trained on identifying and reporting adverse drug reactions using the national pharmacovigilance forms and in line with the national pharmacovigilance system. They were also provided with the pharmacovigilance form (NAFDAC Yellow Form). During each SMC cycle, trained community drug distributors (CDDs) visited households to administer SPAQ (see Table 1 for brands and dosage used for the campaign) to eligible children within the target communities. The CDDs explained the reason for the visit to caregivers and encouraged them to visit health facilities with their children in case of any suspected adverse reaction. This includes but is not limited to vomiting, weakness, and convulsion.

Data collection

At the end of the SMC round, the completed PV forms from the health facilities were picked up by the programme field officers. The program team analyzed these completed reports at the state level to identify trends in ADR reporting and then

Table 1
Details of the drugs used during the campaigns.

Brand Name	Manufacturer	Packaging	Generic Name	Age	Dosage	
					Day	Dose
SPAQ-CO	[+]Guillin Pharmaceuticals, China	Co-blister 50 × 3 + 1 Tabs (Orange-coloured blister)	Amodiaquine 76.5 mg + Sulphadoxine/Pyrimethamine 250/12.5 mg dispersible tablets (SPAQ1)	Children 3 month to less than 12 months	1	Amodiaquine 76.5 mg plus 1 tablet of Sulphadoxine/Pyrimethamine 250/12.5 mg
					2	Amodiaquine 76.5mg
					3	Amodiaquine 76.5mg
SPAQ-CO	[+]Guillin Pharmaceuticals, China	Co-blister 50 × 3 + 1 Tabs (Red-coloured blister)	Amodiaquine 153 mg + Sulphadoxine/Pyrimethamine 500/25 mg dispersible tablets (SPAQ2)	Children 12 months to 59 months	1	Amodiaquine 153 mg plus 1 tablet of Sulphadoxine/Pyrimethamine 500/25 mg
					2	Amodiaquine 153mg
					3	Amodiaquine 153mg

[+] Dispersible tablet of SPAQ 1 and SPAQ 2 were sourced from Guillin Pharmaceuticals in China, the only source of WHO prequalified SPAQ dispersible tablet at the time of program implementation.

transmitted them to the National Pharmacovigilance Centre through the National Agency for Food and Drug Administration and Control (NAFDAC) offices in the respective states. For this study, the copies of the forms sent to NADFAC were analyzed. All the ADR forms analyzed were collated in December 2020.

Analysis of adverse drug reaction reports

The information listed below was extracted from the submitted ADR forms.
1. Adverse drug reactions reported
2. Age of the child
3. Profession of reporter
4. System Organ Class

We used descriptive statistics for all the analyses. Specifically, we estimated the number of ADR reports per 1,000,000 children for each of the seven states, the reporters' profession (frequency and percentage), the number of reported adverse drug reactions segregated by age (3 - <12 months and 12–59 months) and the WHO-ART system organ class (SOC) classification of the ADRs segregated by age.

Results

SPAQ was administered to approximately 12,000,000 children aged 3–59 months across the targeted communities in seven northern Nigeria states. High coverage of four courses of treatment was achieved across the communities where the intervention was implemented from July –November 2020.

Reporting Rates for Suspected Adverse Drug Reaction

Only two of the seven states (Bauchi and Jigawa) reported adverse drug reaction using the national pharmacovigilance reporting system. Bauchi and Jigawa States had a total of 42 and 15 pharmacovigilance reports, respectively. This translates to 0.15 reports per 1,000,000 children and 0.03 reports per 1,000,000 children in Bauchi and Jigawa States, respectively (Table 2)

Profession of Reporters

Most (70%, 40/57) of the reporters from the two states that had ADR reports were community health extension workers, while one of the reporters was a housewife. Seven of the reports (12.2%) did not include information on the job title of the reporter (Table 3).

Table 2
Reporting rates for adverse drug reactions per 1000,000 children across implementing states.

State	Number of Treatments (Cycle 1 - 4)	Number of PV Reports	Number of reports /1000,000 children
Bauchi	2876,436	42	0.15
Jigawa	5650,589	15	0.03
Kano	12,347,805	0	-
Katsina	7359,312	0	-
Kebbi	4541,495	0	-
Sokoto	4725,111	0	-
Yobe	3127,059	0	-

Table 3
Profession of pharmacovigilance reporter.

Profession of PV Reporter	Number (%)
Community Health Extension Worker	40 (70.2)
Community Health Officer	9 (15.8)
Housewife	1 (1.8)
Not stated	7 (12.2)

Table 4
Number and the type of suspected adverse drug reaction reported segregated by age group.

Age Group	Presentation and number of reported ADR						
	Abdominal Pain	Weakness	Diarrhea	Fever	Rash	Vomiting	Total
3 - <12 months	0	3	1	0	0	4	8
12 – 59 months	4	10	4	1	6	24	49
Total	**4**	**13**	**5**	**1**	**6**	**28**	**57**

Table 5
System Organ Class of Suspected Adverse Drug Reaction segregated by age group.

System Organ Class (SOC)	Age Group		
	3 - <12 months	12 - 59 months	Total
Gastrointestinal System Disorders	5	32	37
Skin and Appendages Disorders	0	6	6
Body as a whole General Disorders	3	11	14
Total	**8**	**49**	**57**

Type of suspected adverse drug reaction reported

In 2020, six types of adverse drug reactions to SPAQ were reported during the seasonal malaria chemoprevention campaign (Table 4). Vomiting (persistent for more than 2 hours) was the most reported adverse drug reaction during the campaign, accounting for almost half (28/57) of all reported cases.

From the 57 suspected adverse drug reaction reports submitted by Bauchi and Jigawa States, most (86%, 49/57) of the reactions were observed among children aged 12 – 59 months as shown in Table 4. Gastrointestinal system disorders accounted for 65% (37/57) of the reports with 86.5% (32/37) of cases found in children aged 12 – 59 months (Table 5). Skin rashes associated with SPAQ was reported only in children aged 12 – 59 months and accounted for 10.5% (6/57) of the reports submitted.

Discussion

In 2020, more than 12 million children below the age of five were exposed to SPAQ across seven northern Nigeria states to protect them from malaria. Only two of the seven states implementing the SMC campaigns had ADR reports. These two states, Bauchi and Jigawa, had reporting rates of 0.15/1000,000 and 0.03/1000,000 children, respectively. Community health extension workers completed more than 85% of the 57 ADR reports. Of the six types of suspected ADRs, vomiting represents the most reported adverse drug reaction accounting for nearly half of the total reports.

The ADR reporting rates for the SMC campaigns were abysmally low, falling short of the WHO's recommended standard of more than 200 ADR cases per 1,000,000 population [12]. This low ADR reporting is common in Nigeria and has been reported in several studies [13–18]. Although the training of health workers on pharmacovigilance reporting has been shown to improve ADR reporting for public health programmes [14], the results from this study indicate that this may not be sufficient. The low reporting rate despite pre-implementation training of participating health workers could be due to the poor attitude of the health workers towards ADR reporting. Also, the trainings may have failed to boost healthcare workers' knowledge and attitude towards pharmacovigilance reporting. Another plausible reason for the low level of ADR reporting is the passive nature of ADR surveillance system. During the SMC campaigns, caregivers were instructed by community drug distributors to report to the health facilities if the children who used the prophylactic SPAQ showed signs of adverse drug reactions such as vomiting, rashes, and convulsion. This passive surveillance approach largely relies on caregivers reporting ADRs to the health facilities. Also, suppose a caregiver sought care outside the target health facility that provided the medication. In that case, the suspected ADR may not be reported due to a lack of awareness of the reporting protocol. These concerns are vital given the poor health-seeking behaviour in the region where the campaigns were held [19]. The passive ADR surveillance system may therefore be insufficient or not fit for purpose in the region as its success is partly dependent on the health-seeking behaviour of the caregivers within the community. Implementing an active surveillance system where caregivers are directly contacted and asked about any suspected ADRs in children who received SPAQ may help address the challenges of a passive reporting system. Studies have shown that ADR reporting rates are typically higher with an active ADR surveillance system [20].

Most of ADR reports were completed by either a community health extension worker (70.2%, 40/57) or a community health officer (15.8%, 9/57) (Table 3). This is because primary health centres in Nigeria are staffed mainly by this cadre of health workers [21]. Our results suggest that these health workers can provide pharmacovigilance services during the SMC campaign with the requisite training. Pre-implementation training is crucial as studies have shown that health workers in Nigeria's primary health centres have a poor understanding of pharmacovigilance [22]. Despite the pre-implementation training on pharmacovigilance for the SMC campaigns, capacity gaps persist, as evidenced by low reporting rates and the absence of reporters' name on 12.2% (7/57) of the submitted pharmacovigilance forms (Table 3). Also, caregiver's reporting of ADR as observed in this study is also desirable as it could include perspective about ADRs that may be missing from reports completed by health care workers [23]. A similar finding has been reported in a study conducted in Lagos, Nigeria [23,24]. Overall, this is in line with NAFDAC's recommendation of direct reporting of suspected ADR to the National Pharmacovigilance Centres (NPC) by patients [25]. However, the low literacy rate in some parts of Nigeria may reduce the chances of direct ADR reporting by patients and caregivers [26].

Vomiting represents the most reported adverse drug reaction accounting for almost half of the total reports. This finding aligns with a previous study on SMC in Senegal, where vomiting was also the most reported (53.0%, 490/924) ADR [11]. As expected, the system organ classes classification revealed that most of the suspected adverse drug reactions were gastrointestinal system- and skin-related. A similar finding has also been reported in several studies on adverse drug reaction reporting in pediatrics [27–29]. With gastrointestinal and dermatological reactions as the most commonly self-reported adverse reactions to sulphonamide-based drugs [30,31], SP may be the major culprit for most of the reported adverse drug reactions [30]. The other reported ADRs—weakness, diarrhea, fever and abdominal pain—have not been widely reported or linked to the use of SPAQ used during SMC campaigns in Africa among children under the age of five years.

Overall, this study provides real-world safety data associated with the mass administration of SPAQ in the northern region of Nigeria. We believe that the insights offered by this study can be leveraged to strengthen post-marketing surveillance in Nigeria and other low- and middle- income countries. Strengthening pharmacovigilance is particularly critical to ensuring access to safe and effective health interventions as outlined in the health-related United Nations' Sustainable Development Goals and African Union's Agenda 2063. For example, suppose ADRs are not actively tracked during SMC campaigns and other similar community-based programmes. In that case, programme implementers may not be aware of the full range of ADRs that intervention recipients should be counselled on. By not providing this needed information, rumours may begin to spread about the "harmful" nature of the intervention leading to loss of trust and rejection of the effective intervention, thereby impeding the achievement of health-related development goals.

Limitation of the study

First, the low ADR reporting rates in the two states with report do not necessarily translate to a good safety profile for SPAQ. Some suspected ADRs may not have been reported to the health facility by the caregivers. Similarly, the healthcare workers may not have submitted some ADR reports to the designated centres in accordance with the national pharmacovigilance guidelines. Second, the fact that there were no suspected ADR reports from five states (Kano, Katsina, Kebbi, Sokoto, and Yobe States), does not necessarily mean there were no ADRs following drug administration. This limitation highlights the need to strengthen ADR reporting in all health facilities and states implementing SMC to ensure no case is missed. Third, this study did not attempt to identify determinants of poor ADR reporting. Lastly, this study is descriptive and did not attempt to establish causality.

Conclusions

The abysmally low ADR reporting from the 2020 SMC campaigns suggests gaps in the pharmacovigilance surveillance system. From our experience, the training of health workers and supply of pharmacovigilance forms appear to be insufficient to address these gaps. Further research is therefore needed to identify behavioural and other factors that could be responsible for poor reporting to inform strategies that can help improve the pharmacovigilance system. SMC implementers and other relevant stakeholders could also explore options such as active surveillance for ADRs, deployment of self-reporting electronic applications and other technologies that have been proven to improve timeliness and accuracy of ADR reporting during the SMC campaigns. Overall, this study has shown an urgent need to strengthen the pharmacovigilance system during SMC implementation to ensure adequate ADR reporting.

Ethics approval and consent to participate

Approval for the SMC implementation was granted by the various state ministry of health in the implementing states in Nigeria.

Consent for publication

Consent for participation and publication was received from all participants whose data appear in this study, through the Publication Ethics Committee of the State Ministries of Health of the respective states.

Availability of data and material

Copies of the pharmacovigilance forms generated from the campaign, collated and shared with the National Agency for Food, Drug Administration and Control are available from the corresponding author on reasonable request.

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Authors' contribution

K.R conceptualized the study protocol, K.R and A.J.I wrote the first draft of the manuscript, J.A, C.D, K.M., D.O. and O.O provided feedback during manuscript development. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A: Nigeria National Pharmacovigilance Reporting System for Adverse Drug Reaction

The Nigeria National Pharmacovigilance system is coordinated by the National Pharmacovigilance Center situated within the National Agency for Food and Drug Administration and Control (NAFDAC) — Nigeria's drug regulatory agency [11]. The agency expects all suspected or actual adverse reactions to drugs and other related substances to be reported using the pharmacovigilance reporting form, also known as yellow form or individual case safety report (ICSR) form [8]. A typical adverse drug reaction form provides information on:

- Patient demographics: name, age, sex, and weight
- Adverse drug reaction: description, date reaction started and stopped, and outcome — recovered fully, congenital abnormality, recovered with abnormality, life-threatening and death
- Suspected drug: brand and generic names, batch number, NAFDAC number, expiry date
- Concomitant medicines: all medicines taken in the last three months
- Source of report

This form can be obtained from

Any NAFDAC state office in the 36 states in the country.

The National Pharmacovigilance Center (NPC) NAFDAC Headquarters, Wuse Zone 7, Abuja.

Any of the Zonal Pharmacovigilance Centres (Ahmadu Bello University Teaching Hospital, Shika, Federal Medical Centre, Owerri, Lagos University Teaching Hospital, Lagos, University of Benin Teaching Hospital, Benin, University of Ilorin Teaching Hospital, Ilorin and University of Maiduguri Teaching Hospital, Maiduguri)

Reports of adverse drug reaction are transmitted to the nearest pharmacovigilance centre. Recently, an online ADR reporting form can be used to report adverse drug reactions electronically [7].

In addition to healthcare providers (pharmacists, doctors, and nurses), organizations or individuals holding a marketing authorization for medicinal products are expected to report any suspected ADR to their products. Reporting is usually not mandatory; rather it is voluntary [10]. Overall, Nigeria's pharmacovigilance system is a passive surveillance system that involves the reporting of adverse drug reactions when a patient presents with such reactions.

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