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ORIGINAL RESEARCH

Optimal Approach and Strategies to Strengthen Pharmacovigilance in Sub-Saharan Africa: A Cohort Study of Patients Treated with First-Line Artemisinin-Based Combination Therapies in the Nanoro Health and Demographic Surveillance System, Burkina Faso

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Background and purpose: Resource-limited countries face challenges in setting up effective pharmacovigilance systems. This study aimed to monitor the occurrence of adverse events (AEs) after the use of artemisinin-based combination therapies (ACTs), identify potential drivers of reporting suspected adverse drug reactions (ADRs) and monitor AEs among women who were inadvertently exposed to ACTs in the first trimester of pregnancy.

Patients and methods: We conducted a prospective observational study from May 2010 to July 2012 in Nanoro Health and Demographic Surveillance System (HDSS), Burkina Faso. The HDSS area was divided into active and passive surveillance areas to monitor AEs among patients (regardless of age or sex) who received a first-line ACT (artemether–lumefantrine or artesunate–amodiaquine). In the active surveillance area, patients were followed up for 28 days, while in the passive surveillance area, patients were encouraged to return voluntarily to the health facility to report any occurrence of AEs until day 28 after drug intake. We assessed the crude incidence rates of AEs in both cohorts and performed Cox regression with mixed random effects to identify potential drivers of ADR occurrence.

Results: In total, 3170 participants were included in the study. Of these, 40.3% had reported at least one AE, with 39.6% and 44.4% from active and passive surveillance groups, respectively. The types of ADRs were similar in both groups. The most frequent reported ADRs were anorexia, weakness, cough, dizziness and pruritus. One case of abortion and eight cases of death were reported, but none of them was related to the ACT. The variance in random factors showed a high variability of ADR occurrence between patients in both groups, whereas variability between health facilities was low in the active surveillance group and high in passive surveillance group. Taking more than two concomitant medications was associated with high hazard in ADR occurrence, whereas the rainy season was associated with low hazard.

Conclusion: This study showed that both passive and active surveillance approaches were useful tools. The HDSS allowed us to capture a few cases of exposure during the first trimester of pregnancy. The passive surveillance approach, which is more likely to be implemented by malaria control programs, seems to be more relevant in the Sub-Saharan African context.

Keywords: HDSS, artemisinin-based combination therapies, safety, pregnancy, malaria, rural, Burkina Faso

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Introduction

Prior to the registration and marketing of a new drug, available data on safety and efficacy are limited to observations from pre-clinical animal studies and pre-registration clinical trials (i.e. Phase I–III). Since the thalidomide case in 1961,[1] it has been recognized unanimously that post-licensure safety data on newly registered active substances are crucial for evaluating their risk/benefit profile over time. Pharmacovigilance (PV), which is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem",[2] remains the cornerstone to fully and adequately assess the safety of the drugs when they are used in "real-life" conditions among a large number of people. However, setting up a PV system is difficult, even in developed countries which are usually characterized by effective healthcare systems.[3,4] It is unclear how such a system can be efficiently set up and managed in Sub-Saharan African (SSA) countries characterized by poorly performing healthcare systems and limited resources.[5–8]

Nevertheless, we should recognize that the medical product regulatory framework and the PV landscape in Africa are currently improving.[9] In Burkina Faso, a National Pharmacovigilance Monitoring Committee was created in 2011 within the drug regulatory authority, named "Direction Générale de la Pharmacie du Médicament et des Laboratoires (DGPML)", under the Ministry of Health, although the organization of PV activities was established in 2008 with the traditional spontaneous reporting system. In 2010, the country became officially a full member of the World Health Organization (WHO) Program for International Drug Monitoring. However, as in most SSA countries, the PV system based on spontaneous reporting by health professionals in Burkinabe healthcare settings has not yet reached an appropriate performance level, as the reporting rates are still very low.[10,11] In 2015, only 72 reports were referenced in VigiBase™ (the WHO global individual case safety reports database).[12] In SSA countries in general and Burkina Faso in particular, the factors that could explain such low spontaneous reporting are numerous and complex. Some authors have mentioned important health system obstacles to PV growth in Africa, including weak overall national health infrastructure and systems, poor understanding of PV, lack of PV in the formal curriculum of health professionals' training and low interest by healthcare professionals.[10,13-16]

Over the past decade, Burkina Faso has experienced a large-scale deployment of new essential drugs, especially artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria.[17] Although ACTs have been used successfully in Southeast Asia[18] and other SSA countries,[19–23] where they appear to be safe and well-tolerated, there is relatively limited experience with these medicines in Burkina Faso, where malaria transmission intensity is substantially higher. In addition, the pattern of antimalarial medicine use in real-life is quite different.[24–26] Despite this large-scale deployment of ACTs, the National Malaria Control Program (NMCP) had established neither a PV unit nor any staff specifically dedicated to PV of antimalarial drugs.[16] Meanwhile, the current malaria treatment guidelines and the training modules on malaria do not take PV into account; therefore, no information on adverse drug reactions (ADRs) was collected by the NMCP. In addition, the safety of ACTs when used in standard conditions in vulnerable populations, including pregnant women during the first trimester of pregnancy and patients with a concomitant chronic illness, is of concern. A study conducted in Burkina Faso revealed that about half of drugs used (including ACTs) with regard to trimester of pregnancy could be considered as potentially risky based on the United States Food and Drug Administration (FDA) or Australian Therapeutic Goods Administration (TGA) drug risk classification.[27] These situations are necessarily accompanied by a crucial need to promote and ensure the safety and efficacy of these drugs. In this study, we propose a practical approach for PV through a Health and Demographic Surveillance System (HDSS) to monitor actively and passively the safety of the two first-line antimalarial treatments (artemether–lumefantrine [AL] and artesunate–amodiaquine [ASAQ])[28] in real-life conditions. Since developing countries are facing several difficulties in setting up functional PV systems, this platform provided the opportunity to easily monitor and assess public health issues such as PV while significantly reducing the costs of implementation.[29,30] The aim of this study was to monitor passively versus actively adverse events (AEs) among the population living in Nanoro HDSS of Burkina Faso, who attended public health facilities and received an ACT (ASAQ or AL), and to assess the factors associated with the time of reporting a suspected ADR occurrence. In addition, through HDSS, the study aimed to monitor AEs

in pregnant women who were inadvertently exposed to ACTs in the first trimester of pregnancy.

Ethics

Ethical approval for the study was granted by Centre Muraz Institutional Ethical Committee (ref. no. 03-2010C/E-CM), Burkina Faso National Ethics Committee for Research in Health (no. 2010–27) and WHO research Ethic Review Committee (WHO/TDR-A70283). The study was registered in the ClinicalTrials.gov registry (identifier: NCT01232530). Written informed consent was obtained from all participants prior to their enrolment. Participants who fulfilled the inclusion criteria and agreed to be enrolled in the study were asked to provide written inform consent. For illiterate participants, an independent witness was asked to attend the consent procedures and then attest and sign the consent. A parent or legal guardian provided written informed consent on behalf of any patient under 18 years of age. All procedures followed were carried out in accordance with the Helsinki Declaration as revised in 2013.

Materials and Methods

Study Site

The study was carried out in the Nanoro HDSS catchment area, which is located in a rural setting, in the centre-west region of Burkina Faso, approximately 85 km from Ouagadougou, the capital city. The HDSS area (594.3 km^2) lies between longitudes 1°892537 and 2° 83146 west and latitudes 12°857955 and 12°872863 north, and includes a total of 24 villages and six peripheral health facilities (Figure 1). Details of the study area and population have been described elsewhere.[31,32] The area has hot weather throughout the year (mean temperature >30°C) and two seasons. The rainy season occurs from June to November (average rainfall: 700 mm/year) while the dry season lasts from December to May. In the baseline of the initial census carried out in 2009, 54,781 individuals were recorded (52,502 residents and 2,279 visitors), of whom 56.1% were female. Vital events such as pregnancies, births, migrations and deaths are monitored on a weekly basis. Data on individuals and household characteristics are updated during regular 4-monthly household visits. Malaria incidence is seasonal (three periods of incidence)[33] and remains the main disease in this area, accounting for about 45.0% of all consultations and 52.1% of hospitalizations. In this area, the level of adherence to first-line antimalarial drugs seems to be good (86.0%).[34]

Study Design, Study Population and Sample Size Justification

This was a prospective observational study conducted between May 2010 and July 2012 among the population living in the Nanoro HDSS catchment area, Burkina Faso. The study population consisted of inhabitants living in the health facilities catchment area of Godo, Nanoro, Nazoanga, Seguedin, Soum and Soaw, regardless of age and gender. For routine PV, there is no sample size calculation because when a new drug policy is implemented, the whole population is followed up. Nevertheless, it was essential to provide a clue about the expected number of ACT treatments. In Nanoro health district, according to the health information system, the rate of health facility attendance was about 40%. Considering that about 60% of patients were treated for malaria, we assumed there were about 12,600 treatments per year overall. From previous experience, we expected that approximately 80% of them would agree to participate in the study. Therefore, we had to observe approximately 10,080 treatments per year or 20,160 treatments for 2 years, which was adequate to detect "rare" adverse events (incidence occurring at a frequency of 1 out of 1000 patients or more) with a 95% probability.

Study Participants' Enrolment, Follow-Up and Data Collection

Enrolment and follow-up of participants were defined according to two approaches of surveillance : active surveillance and passive surveillance. To do this, the HDSS area was subdivided into two parts (ratio 1:1) by taking into account the size of the population and the number of health facilities (Table 1). In both areas, we also implemented surveillance of women who were inadvertently exposed to ACTs in the first trimester of pregnancy. Alongside these surveillances, a nested study which had assessed the efficacy of AL versus ASAQ in real-life conditions of use for treatment of uncomplicated malaria among patients of all age groups was set up. The results relating to this study have been reported elsewhere.[35] Patients' enrolment and follow-up, data collection, as well as the assessment of the relationship between ACT and AE occurrence, were performed by trained healthcare workers (study staff: physicians, nurses, lab technicians and village reporters).

In the Passive Surveillance Area

This surveillance included the resident population of the health facilities' catchment areas of Godo, Seguedin and Soaw. Patients attending the health facilities in these areas,

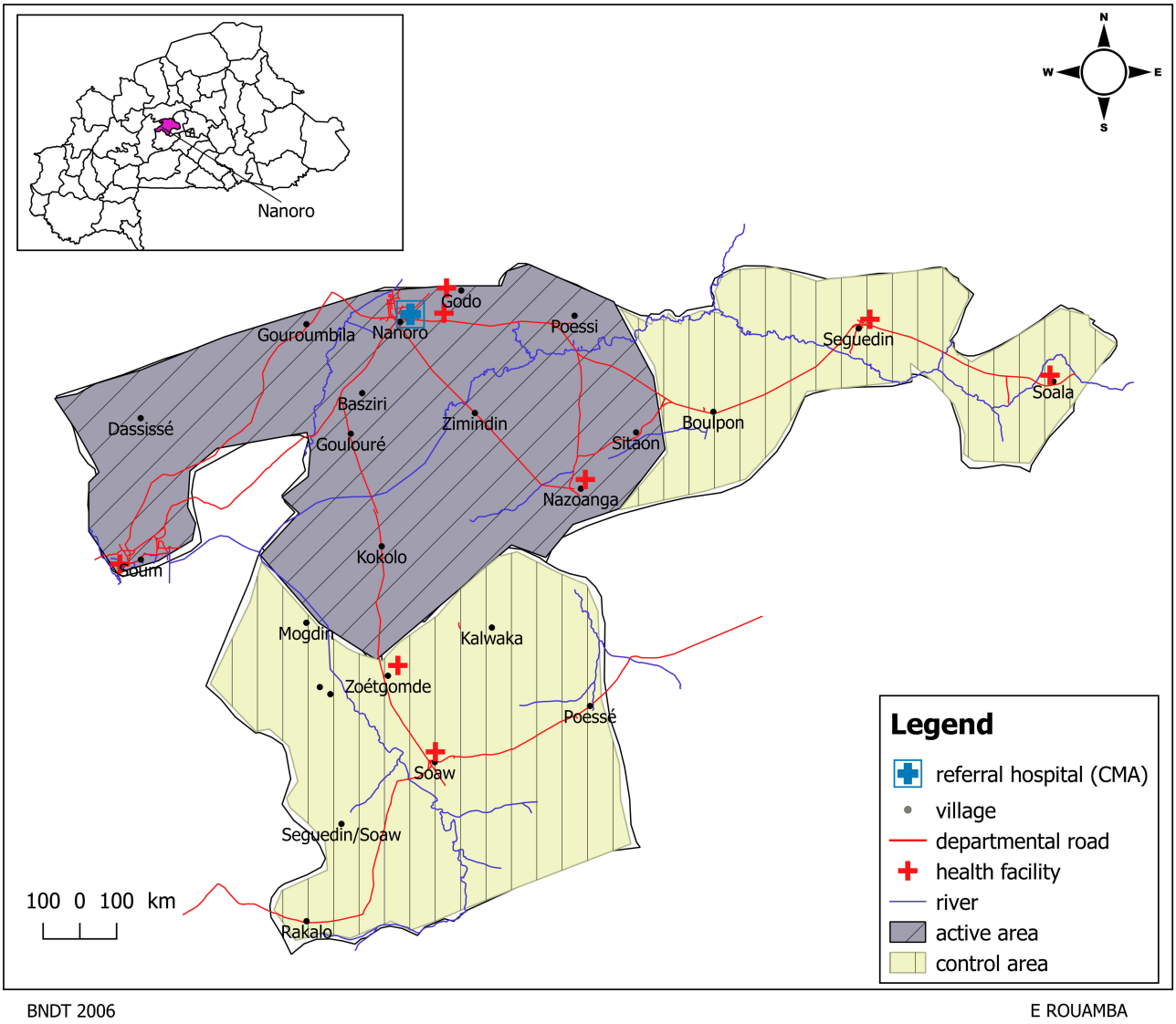

Figure 1 Location of the study area showing active area (active surveillance) and control area (passive surveillance).

diagnosed with malaria (presumptively or rapid diagnostic test [RDT]/microscopically confirmed) and treated with an ACT were identified. The treatment administered was recorded in a drug exposure log book and the patients were encouraged to report passively any AEs/ADRs occurring within 28 days after drug intake. When a patient voluntarily returned to report the occurrence of events, his or her informed consent was required prior to the collection of clinical symptoms and concomitant medications.

In the Active Surveillance Area

This surveillance included the resident population of the health facilities' catchment areas of Nanoro, Nazoanga and Soum. All patients with a diagnosis of malaria (presumptive or RDT/microscopically confirmed) and treated with an ACT were included and actively followed up (after obtaining their informed consent) at days 7, 14 and 28. At each visit, data on medical history, clinical condition and concomitant treatments were collected. In addition, patients were encouraged to return to the health facility at any time outside the scheduled visits if they experienced any health problem.

Surveillance of Pregnant Women Inadvertently Exposed to ACTs in the First Trimester of Pregnancy

Pregnant women were identified during the regular 4-monthly household visits and during a continuous weekly vital event monitoring by HDSS village reporters. The list of pregnant women was matched with the drug exposure log book in order to detect possible exposure to ACTs during the first trimester. All suspected cases of exposure to an ACT

Table 1 Resident Population Size by Village, According to the Two Approaches of Surveillance

Active Surveillance			Passive Surveillance		
HF Area	**Village**	**Population**	**HF Area**	**Village**	**Population**
Nanoro	Nanoro[a,b]	5127	Seguedin	Seguedin[a]	3488
	Poéssi	2146		Soala	2258
	Gouroubila	603		Boulpon	3570
	Basziri	1655	Godo	Godo[a]	1268
	Goulouré	2331	Soaw	Rakalo	1982
Soum	Soum[a]	4167		Seguedin Soaw	984
	Dassisse	1471		Kolokom	431
Nazoanga	Nazoanga[a,b]	4292		Bokin	229
	Sitaon	1041		Mogdin	888
	Zimidin	1507		Mogdin	888
	Kokolo	1164		Zoetgomde	763
				Poesse	3457
				Kalwaka	1770
				Soaw[a]	5910
	Total	25,504		Total	26,998

Notes: [a]Village where the health facility is located. [b]Health facility where the efficacy of artemether–lumefantrine versus artesunate–amodiaquine in real conditions of use for treatment of uncomplicated malaria was assessed.
Abbreviation: HF, health facility.

during the first trimester were included (if informed consent was obtained) in the pregnancy cohort after exposure confirmation and followed up until delivery to record all medical events and pregnancy outcomes.[36]

For this study, no study drug was administered directly to the patients by the study staff. Patients had obtained their prescriptions from the health facility staff as routinely done, and then obtained their drugs from the public health facility drug store. At enrolment, sociodemographic data, such as the age, gender and educational level, as well as the weight of each patient, were collected; information regarding ACTs administered, such as brand and generic name, whether the medicine was prescribed or over the counter (OTC), manufacturing and expiry dates, batch number, daily dose (see Table S1 in supplementary material), concomitant medication including traditional or herbal medicine and concomitant illness was also collected (if available). During the surveillance (active or passive group and pregnant women), at each contact, data on clinical condition and concomitant treatments were collected by the study staff.

Identification, Reporting of Adverse Events (Individual Case Safety Reports) and Explanatory Variables

An AE was defined as any untoward medical occurrence, irrespective of its suspected relationship to the study medications, as per International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP).[37] The primary endpoint of interest for this study was clinical safety in standard conditions of use, assessed through the incidence rate of AEs occurring in both cohorts within 28 days after the first dose of ACT was taken.

The patients were assessed by the study staff according to a standardized checklist and the information was recorded on an individual case report form. AEs were documented as described by the participant or caregiver, reviewed and coded using the Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC). A severity grading scale, based on the toxicity grading scales developed by the WHO (Toxicity Grading Scale for Determining the Severity of Adverse Events) and the National Institutes of Health, Division of Microbiology and Infectious Diseases,[38] was used to grade the severity of all symptoms.

The relationship between ACT and AEs, regardless of their severity, was assessed by the local investigator (study physicians) on the basis of clinical judgment, possible alternative causes (e.g. concomitant therapy, concomitant disease), time of occurrence relative to the treatment and available information on the antimalarial drug. Therefore, AEs were classified into two categories: unsuspected (when the event relationship met the classification of "definitely unrelated" or "unlikely") or suspected (when the event

relationship met the classification of "possible", "probable" or "certain").

Notification of the occurrence of serious adverse events (SAEs), regardless of their relationship to the ACT, was transmitted to the national ethics committee, the DGPML (according to their standard AE forms for PV) and the study sponsor within 24 hours.

Data Management and Statistical Analysis

Data were captured using individual paper case report forms and then double-entered and verified using a database designed under MySQL 5. Statistical analyses were performed using R® software (R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses were implemented as required in each cohort. Numerical variables were summarized into median and interquartile range (IQR). Categorical variables were summarized using cross-tabulation. The Wilcoxon test or chi-squared test was used the compare the populations' characteristics at baseline. The estimates of the incidence of each AE in both cohorts were performed based on crude rates. A reported AE with a relationship classified as "possible", "probable" or "certain" was classified as a suspected ADR and considered as a dependent variable. The independent variables or covariates included sex, age, symptoms reported at day 0, concomitant drug prescribed at day 0, history of drug use and malaria transmission season. To account for patient-specific random effects and within-health-facility a possible homogeneity in ADR occurrence and reporting, a Cox regression model with mixed random effects (frailty model) was used to assess the effect (association) separately in both cohorts. We stated that the data have two levels, and the binary response variable (ADR occurrence) for the patient is nested within the health facility. Therefore, the hazard function of ADR occurrence for patient i in health facility j at time t is specified as follows:

$$\lambda(t; \chi_{ij}, \omega_{ij}) = \lambda_0(t)exp(\chi_{ij}\beta, + u_j + \omega_{ij})$$

where χ_{ij} are the observed values for the covariates, whereas β is the model fixed effect coefficient associated with the covariates. In this formula, u_j represents the health facility-specific random effect and measures the difference between the average hazard at health facility j and the average hazard in the entire Nanoro HDSS area. The term ω_{ij} is the patient-specific random effect, i.e. the deviation of the i^{th} patient from the average for the j^{th} health facility.

We performed a frailty model to determine the strength of association between the occurrence of suspected ADR and each independent variable listed above. All independent variables which exhibited a p-value <0.2 in the univariate regression were included in a Cox multivariable analysis.

The analysis was performed by excluding the patients (included in the study) with missing data on the outcome variable. Then, sensitivity analysis including patients by assuming that they experienced an ADR at the average time (estimated through Kaplan–Meier analysis) for a patient to report an AE after drug administration was performed. Likewise, sensitivity analysis including patients with missing data regarding the outcome by assuming that they did not experience any ADR during the 28 days of follow-up was performed. The estimates were presented using the mean of hazard ratios (HRs) and their 95% CI (confidence interval).

Results

Trial Profile and Baseline Characteristics of the Study Participants

During the period of the study, ASAQ Winthrop® was the only available ACT in the public health facilities, despite the adoption of two first-line treatments. Figure 2 describes the trial profile. A total of 18,826 participants with uncomplicated malaria received a first-line antimalarial drug in the health facilities within the HDSS catchment area. Of these, 76.9% (14,485/18,826) who were permanent residents in the study area were screened to participate in the study. Among them, 7906 and 6579 were residents in the active and passive surveillance areas, respectively. A total of 2679 patients was enrolled inthe active surveillance cohort (because 680 were enrolled in another study and 4547 met other reasons for exclusion [refusal to consent, lack of witnesses to attend the consent process, etc.]); among these, 2613 (97.5%) completed the follow-up of 28 days. However, in the passive surveillance area, only 7.5% (491/6579) returned spontaneously to the health facility to report the treatment outcome. Therefore, in both cohorts, a total of 3170 patients was included in the analysis.

The distribution of baseline characteristics of the participants at enrolment was similar in the two surveillance groups, except for the history of fever and axillary temperature (Table 2).

Reporting of Adverse Events Through Active and Passive Surveillance

By the end of the follow-up, at least one AE was reported in 40.3% (n/N = 1278/3170 [95% CI 38.6–42.0]) of the

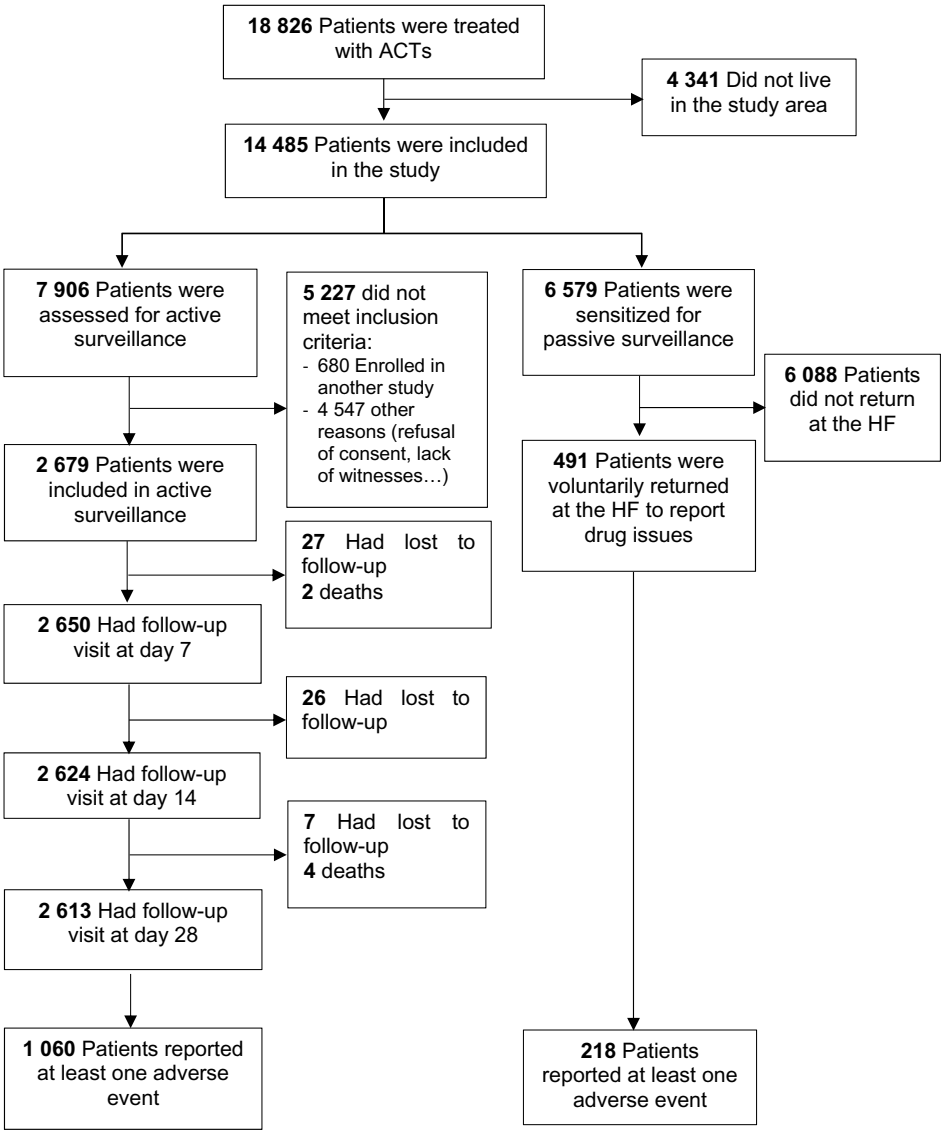

Figure 2 Trial profile.

whole study patients, 39.6% (n/N = 1060/2679 [95% CI 37.7–41.4]) and 44.4% (n/N = 218/491 [95% CI 40.0–48.8]) in the active and passive surveillance groups, respectively. Out of the 2758 AEs (2129 and 629 in active and passive groups, respectively) reported, 76 (52 and 24 in active and passive groups, respectively) were classified as SAEs. The most frequently reported events, classified by SOC, were general disorders (22.2%), gastrointestinal disorders (17.5%), and respiratory, thoracic and mediastinal disorders (11.0%). The incidence rates of AEs reported by SOC are summarized in Table 3.

During the follow-up through the study period in both groups, 60.2% of AEs reported were classified as mild in term of intensity (severity grading) of AE. The different SAEs were mainly represented by hospitalization (1.9%), death (0.2%) and life-threatening events (0.1%). However, all of the deaths were considered as unrelated to ASAQ. The safety outcomes reported in both cohorts are summarized in Table 4.

Reporting of Adverse Events Among Women Who Had Been Inadvertently Exposed to ACT During the First Trimester

In the surveillance of pregnant women, only 13 pregnant women were identified as having been inadvertently exposed to ACT during the first trimester of pregnancy. Of the 13 pregnant women, 10 were exposed in their third month of pregnancy, two were exposed in

Table 2 Demographic and Clinical Characteristics of Study Participants at the Time of Enrolment

Parameters	Total (N=3170)	Cohort		
		Active (n=2679)	Passive (n=491)	*p* value
Age (years)				
Median (25;75% IQR)	3.5 (1.4–9.9)	3.3 (1.4–8.1)	3.7 (1.4–11.6)	0.19
Age class (years), n (%)				
0–5	2017 (63.6)	1727 (64.5)	290 (59.1)	0.007
6–13	575 (18.1)	491 (18.3)	84 (17.1)	
14–17	127 (4.1)	102 (3.8)	25 (5.1)	
≥18	451 (14.2)	359 (13.4)	92 (18.7)	
Gender, n (%)				0.15
Female	1543 (48.7)	1289 (48.1)	254 (51.7)	
Male	1627 (51.3)	1390 (51.9)	237 (48.3)	
Symptoms, n (%)				
Fever in previous 24 hours	2634 (83.1)	2554 (95.3)	80 (16.3)	<0.001
Temperature ≥37.5°C	2208 (69.6)	2107 (78.6)	101 (20.6)	<0.001
Headache		627 (23.4)	–	
Asthenia		49 (1.8)	–	
Muscle joint pain		211 (7.9)	–	
Anorexia		134 (5.0)	–	
Vomiting		440 (16.4)	–	
Nausea		24 (0.9)	–	
Dizziness		43 (1.6)	–	
≥3 symptoms		825 (30.8)	–	
Quantity of concomitant medication[a]	2 (1–3)	2 (1–3)	2 (1–2)	0.21
Prior history of medicine use, n (%)	796 (25.2)	671 (25.0)	125 (25.5)	0.89
Season, n (%)				0.23
Low	1260 (45.7)	960 (45.1)	300 (47.9)	
High	1495 (54.3)	1169 (54.9)	326 (52.1)	
Level of education[b]				0.79
No formal education	453 (60.2)	386 (60.5)	67 (58.3)	
Primary	262 (34.8)	219 (34.3)	43 (37.4)	
Secondary	38 (5.0)	33 (5.2)	5 (4.3)	

Notes: [a]Excluding antimalarial drugs (artesunate–amodiaquine) taken at day 0. (See Table S2 in supplementary material for more details.) [b]The denominator included only subjects above 7 years old.
Abbreviation: IQR, interquartile range.

their second month of pregnancy and only one in her first month of pregnancy. During the follow-up of these pregnant women, 12 women had experienced deliveries of live newborns (including one with twins, raising the total to 13). No congenital malformations were observed during surface examination of these 13 live newborns. One woman in the active group had experienced a spontaneous abortion with a birth defect (a type of cervical agenesis and defect of the dome of the skull). After investigation, this abortion (with birth defect) was judged not to be related to ASAQ, because the event occurred just 4 days after a malaria treatment episode. Therefore, this abortion was probably caused by placental malaria or fetal loss due to the major birth defect.

Serious Adverse Events and Suspected Adverse Drug Reactions

Of the AEs reported, none was evaluated as definitively drug related. Reported AEs that were "possibly" or "probably" related to ASAQ, as established by the local investigators, occurred mostly within 3 days after treatment and were significantly more frequent in the passive group. A total of 584 ADRs was documented during the entire course of the study period. The most commonly reported

Table 3 Incidence Rate of Events Reported by System Organ Class (Grouped by MedDRA Coding) in the Two Cohorts

MedDRA System Organ Class	Total (N=3170)		Active Cohort (n=2679)		Passive Cohort (n=491)	
	n[a]	IR[b]	n[a]	IR[b]	n[a]	IR[b]
General disorders	703	221.8	568	212.0	135	274.9
Gastrointestinal disorders	551	173.8	415	154.9	136	277.0
Respiratory, thoracic and mediastinal disorders	348	109.8	290	108.2	58	118.1
Ear and labyrinth disorders	252	79.5	208	77.6	44	89.6
Psychiatric disorders	207	65.3	134	50.0	73	148.7
Skin and subcutaneous tissue disorders	66	20.8	59	22.0	7	14.3
Musculoskeletal and connective tissue disorders	61	19.2	49	18.3	12	24.4
Blood and lymphatic system disorders	32	10.1	26	9.7	6	12.2
Nervous system disorders	30	9.5	19	7.1	11	22.4
Eye disorders	21	6.6	15	5.6	6	6.1
Renal and urinary disorders	9	2.8	8	3.0	1	2.0
Pregnancy, puerperium and perineal conditions	2	0.6	2	0.7	0	0

Notes: [a]Indicates the number of events; a patient could have one or more events at a time. [b]Indicates the incidence rate per 1000 (n/N).

ADRs among patients in both groups were anorexia, general weakness, vomiting, dizziness, nausea and cough.

A total of 62 patients (42 and 20 in the active and passive groups, respectively) experienced 76 SAEs during the 28 days of follow-up (see Table S3 in supplementary material). Of the 76 SAEs reported, four (5.3%) were considered by the local investigators as being probably related to the study medication. The different types of SAE reported during the active and passive surveillance are summarized in Table 5.

Factors Associated with the Time to Report Suspected ADR Occurrence

As presented in Table 6, concomitant medications used by patients at day 0 (most frequently metronidazole, cotrimoxazole, quinine, chlorpheniramine, amoxicillin, etc.) had a significant effect on ADR occurrence in both cohorts. This result was a 2.18- and 4.70-fold increase in risk (adjusted) of ADR occurrence in the active and passive surveillance cohorts, respectively. In the active surveillance group, the season of malaria transmission was significantly associated with a decreased risk of ADR reporting (adj. HR: 0.45, 95% CI: 0.20–0.92). This significant association also existed in the passive surveillance group (adj. HR: 0.45, 95% CI: 0.38–0.53). In the active surveillance group, the data indicate that when the patient's age is relatively low, the risk of reporting an ADR decreased. However, this finding regarding the significant association with the age group was not observable in the passive surveillance group.

The variance in random factors showed a high variability of ADR occurrence between patients in both groups (standard deviation [SD] equal to 0.385 and 1.892 for active and passive surveillance, respectively), whereas variability between health facilities was low in active surveillance (SD 0.006) and high in passive surveillance (SD 1.378).

The sensitivity analysis performed did not produce differences in the results from the main analysis.

Discussion

The results of our study show that a PV system based on an HDSS platform could be a useful tool for effective assessment and monitoring of the safety of newly registered drugs in resource-limited settings, especially in rural areas. Currently, over 4121 drugs have been registered by the drug regulatory authority in Burkina Faso.[39] A robust PV is needed to monitor the possible AEs in the population. However, despite the government's effort to build a sustainable and functional PV system, the reporting of ADRs remains scarce and several obstacles to such poor reporting have been identified previously.[15,16] In order to improve and increase the reporting rate of ADRs of medicinal products by patients and healthcare professionals, the WHO launched a new web application (VigiAccess™) in April 2015.[40] In addition, in June 2017 the Ministry of Health of Burkina Faso formally launched a web-RADR application (Recognizing Adverse Drug Reactions), which can be used on tablets and smartphones. Nevertheless, such applications are difficult to implement in rural areas owing to the lack of internet and poor telephone telecommunication services, combined with an absence or low level of education of the population. Our study was carried out with the objectives to support and strengthen the national PV activities for effective identification of potential ADRs, and to enhance patient care and patient safety in relation to the use of medicines. Therefore, the study focused on the feasibility of a PV system using the HDSS

Table 4 Safety Outcomes

Event		Total (N=3170)		Active Cohort (n=2679)		Passive Cohort (n=491)	
		n[a]	IR[b]	n[a]	IR[b]	n[a]	IR[b]
Reason to consider event as serious	Death	8	2.5	6	2.2	2	4.1
	Life-threatening	6	1.9	6	2.2	0	0.0
	Hospitalization	61	19.2	39	14.6	22	44.8
	Disability/incapacity[c]	1	0.3	1	0.4	0	0.0
Any SAE during 28 days of follow-up		76	24.0	52	19.4	24	48.9
SAE intensity	Moderate	12	3.8	9	3.4	3	6.1
	Severe	52	16.4	31	11.6	21	42.8
	Life-threatening	12	3.8	12	4.5	0	0
Number of persons who had SAE		62	19.6	42	15.7	20	40.7
Specific SAE during 28 days of follow-up	Severe anemia	1	0.3	1	0.4	0	0
	Lethargy	1	0.3	0	0	1	2.0
	Severe convulsions	1	0.3	1	0.4	0	0
	Severe somnolence	1	0.3	1	0.4	0	0
	Severe dizziness	2	0.6	0	0	2	4.1
	Spontaneous abortion	1	0.3	1	0.4	0	0
Time of event occurrence[d]	During first 3 days	903	284.9	564	210.5	339	690.4
	Between 4 and 7 days	447	141.0	377	140.7	70	142.6
	After 7 days	1345	424.3	1188	443.4	157	319.8

Notes: [a]Indicates the number of events; a patient could have one or more events at a time. [b]Indicates the incidence rate per 1000 (n/N). [c]One case of rheumatoid arthritis. [d]Numbers may not add up to total number due to missing values.

Abbreviation: SAE, serious adverse event.

platform, as suggested elsewhere.[29] The encouraging results reported here could be used as the basis to improve the national PV system in Burkina Faso by setting up similar approaches in the other four HDSS sites in the country.[31,41-43] This approach can be also replicated in any other limited resource setting where an HDSS platform is available.

Both systems of surveillance (active and passive) appeared to be useful tools for monitoring the safety of widely available and utilized medicines. Indeed, about 39.6% and 44.4% of study participants reported at least one AE during the 28 days of follow-up, respectively, in the active and passive surveillance systems. These rates were higher than those reported in another study carried out in Ghana, a neighboring country of Burkina Faso, where only 29.4% of patients reported at least one event.[44] Similarly to what has been reported previously with ASAQ, we found that general disorders (anorexia and asthenia), gastrointestinal disorders (vomiting, diarrhea, abdominal pain) and skin disorders (pruritus) comprised the majority of reported ADRs.[35,45-48] Our study did not report any new ADRs and the types of events reported reflected the types of events expected in patients treated with ASAQ, as nearly all events reported are listed in the WHO Summary of Product Characteristics.[49]

In the passive surveillance system, we noted a relative underreporting of AEs when we compared the number of people sensitized to take part in this group (N=6579) and the absolute number of patients who actually reported events. In contrast to this relative underreporting, a remarkable finding in this study is the fact that spontaneous ADR reports in the passive surveillance group were more relevant in terms of crude incidence rate and severity than in active surveillance. This finding shows that a PV system based on spontaneous reporting is feasible and could be effective in Burkina Faso's rural resource-limited settings. However, with the low rate (7.5%) of patients who voluntarily returned to report AEs (probably due to the lack of interest of the population in the study area), such a notification system may be accompanied by regular community sensitization, training of health workers and implementation of PV focal points with personnel to promote

Table 5 Suspected Adverse Drug Reactions During the Study Period

Adverse Drug Reaction	Total (N=3170)		Active Cohort (n=2679)		Passive Cohort (n=491)	
	n[a]	IR[b]	n[a]	IR[b]	n[a]	IR[b]
Total	548	173.0	384	143.0	164	334.0
No serious (top 20)	544	172.0	383	143.0	161	328.0
Anorexia	109	34.4	76	28.4	33	67.2
General weakness	87	27.4	58	21.6	29	59.1
Cough	76	24.0	50	18.7	26	53.0
Vomiting	47	14.8	24	9.0	6	12.2
Dizziness	37	11.7	26	9.7	11	22.4
Diarrhea	36	11.4	30	11.2	23	46.8
Abdominal pain	36	11.4	22	8.2	14	28.5
Pruritus	14	4.4	12	4.5	2	4.1
Nausea	14	4.4	7	2.6	2	4.1
Fever	13	4.1	11	4.1	0	0.0
Rhinitis	9	2.8	9	3.4	0	0.0
Somnolence	9	2.8	5	1.9	7	14.3
Insomnia	7	2.2	7	2.6	0	0.0
Muscle/joint pain	6	1.9	6	2.2	4	8.1
Headache	6	1.9	4	1.5	0	0.0
Tinnitus	5	1.6	3	1.1	0	0.0
Anemia	4	1.3	4	1.5	2	4.1
Epigastric pain	4	1.3	4	1.5	0	0.0
Dermatosis	3	0.9	3	1.1	2	4.1
Chest pain	2	0.6	2	0.7	0	0.0
Serious	4	1.3	1	0.4	3	6.11
Gastroenteritis	1	0.3	0	0	1	2.0
Convulsion	1	0.3	1	0.4	0	0
Dizziness	1	0.3	0	0	1	2.0
General weakness	1	0.3	0	0	1	2.0

Notes: [a]Indicates the number of events; a patient could have one or more events at a time. [b]Indicates the incidence rate per 1000 (n/N).

ADR reporting.[10,13,50] Moreover, to build a functional and sustainable PV system based on routine spontaneous reporting, the National Pharmacovigilance Monitoring Committee needs to liaise with the nursing/medical schools to introduce training on PV, especially spontaneous reporting, for students prior to graduation.[10,50]

The active surveillance seems to be relevant in term of numbers of AEs reported, but it requires resources that are difficult to mobilize and sustain in resource-limited settings. In such contexts, the use of the HDSS platform combined with existing resources (such as personnel and an established database which is constantly updated) could be an alternative to reduce the cost of this surveillance. In addition, the introduction of newer technologies such as cell phones to report and investigate AEs to any medical products or certain specific therapeutic classes could provide added value.[44,51-53] The latter could facilitate rapid identification of drug safety signals, provided that connectivity conditions are good.

The approach used to monitor pregnancy exposure to ASAQ in this study allowed us to identify 13 women who had been inadvertently exposed to ASAQ during the first trimester of pregnancy. To improve the information on the safety of drugs used during pregnancy, the WHO recommends the implementation of a pregnancy registry with the objective to obtain reliable information on obstetric, medical and drug history during pregnancy, and to diagnose, assess, monitor and manage pregnancy and the outcomes of pregnancy, including congenital malformations, stillbirths and prematurity.[54] The HDSS platform will make the pregnancy exposure registry more effective in providing reliable PV data during pregnancy.[29]

In both surveillance systems, during the malaria transmission season (which coincides with the rainy season), we noticed that the number of ADRs reported decreased significantly. In addition, with the increase in the number of concomitant medication prescriptions, the risk of occurrence of ADRs increased. This could be explained partly by the fact that during the period of high malaria transmission, the diagnosis of malaria episodes (with malaria RDTs) is more accurate[55] and therefore would improve the accuracy in the drug prescription for illness management (less prescription of concomitant therapy). At the same time, the rainy season coincides with the beginning of farming activities, and families usually move from their usual homeland to hamlets with limited geographical accessibility. Therefore, it is possible that patients (especially caregivers) did not report ADRs of mild to moderate intensity.

Although the study has achieved its aims, we faced several constraints during the conduct of the project. Firstly, information about AEs was mostly self-reported and, thus, dependent on the patients' reporting and recall. To partly solve this psychological constraint, to enhance the recall of AEs, data collection tools have been itemized by including a list of symptoms, especially those documented as ADRs related to ASAQ. Data collection tools also included symptoms of acute diseases commonly encountered in the study area, as well as drug-related AEs for drugs commonly used to treat these diseases. However, AEs recorded in this study following the prescription of ASAQ were similar to malaria symptoms.

Table 6 Determinants of Adverse Drug Reaction Occurrence After Taking Amodiaquine–Artesunate During 28 Days of Follow-Up in Both Active and Passive Surveillance

		Active Surveillance				Passive Surveillance			
		Univariate		Multivariable		Univariate		Multivariable	
		HR (95% CI)	*p*value	Adj. HR (95% CI)	*p* value	HR (95% CI)	*p* value	Adj. HR (95% CI)	*p* value
Fixed Effect									
Sex	Male Female	1 0.76 (0.68; 0.86)	<0.001	1 0.95 (0.80; 1.12)	0.38	1 1.07 (0.6; 1.89)	0.18	1.41 (0.63; 3.15)	0.25
Age (years)	≥18 14–17 6–13 0–5	1 0.56 (0.36; 0.88) 0.44 (0.35; 0.55) 0.15 (0.12; 0.17)	 0.001 <0.001 <0.001	1 0.53 (0.29; 0.95) 0.44 (0.24; 0.82) 0.18 (0.08; 0.39)	 <0.001 <0.001 <0.001	1 1.03 (0.19; 5.53) 0.49 (0.14; 1.65) 0.35 (0.14; 0.88)	 0.97 0.16 0.007	 1.12 (0.19; 6.75) 0.33 (0.02; 5.03) 0.30 (0.01; 8; 04)	 0.86 0.27 0.32
Weight		1.04 (1.03; 1.04)	<0.001	1.00 (0.99; 1.02)	0.82	1.02 (1.01; 1.04)	0.006	0.99 (0.92; 1.07)	0.82
Symptoms at day 0	≤2 >2	1 1.47 (1.26; 1.71)	<0.001	1 0.93 (0.78; 1.12)	0.31	– –		– –	
Concomitant medication	<2 ≥2	1 1.27 (0.98; 1.63)	0.07	1 2.18 (1.54; 3.09)	<0.001	1 5.10 (2.91; 8.93)	<0.001	1 4.70 (2.11; 10.46)	<0.001
Temperature at day 0	<37.5 ≥37.5	1 0.61 (0.53; 0.69)	<0.001	 0.92 (0.76; 1.12)	 0.24	1 1.52 (0.76; 3.05)	 0.20	1 1.05 (0.40; 2.77)	 0.90
Drug use before day 0	No Yes	1 1.49 (1.31; 1.69)	<0.001	1 1.60 (1.34; 1.91)	<0.001	1 1.53 (0.75; 3.13)	0.14	1 1.54 (0.65; 3.63)	0.17
Transmission season	Low High	1 0.37 (0.33; 0.41)	<0.001	1 0.45 (0.38; 0.53)	<0.001	1 0.49 (0.27; 0.88)	0.017	1 0.45 (0.20; 0.92)	0.005
Random effect				SD				SD	
Patient specific HF specific				0.385 0.006				1.892 1.378	

Abbreviations: HF, health facility; HR, hazard ratio; adj. HR, adjusted hazard ratio; SD, standard deviation.

This could lead to a bias in the evaluation of causal links with the study drug.

Secondly, the frequent stockouts of ACT drugs observed during the study period did not optimize recruitment to reach the desired sample size. However, we were not able to take any corrective action because these stockouts were beyond the control of the research staff.

Thirdly, estimation of the incidence of AEs did not systematically take into consideration anomalies in biological parameters, because the study was designed to monitor mainly the occurrence of clinical AEs in peripheral health facilities in the rural setting, where there is no access to laboratory equipment and expertise.

Finally, the enrolment procedure (based on study inclusion and non-inclusion) resulted in the non-inclusion of many participants. This highlights the difficulties of implementing PV studies in African countries, and could be partly explained in our context mainly by the mobility of the population for their daily activities, the lack of interest of the population in reporting an ADR and the fact that our study was conducted in a rural community where the literacy rate is low (difficulty in finding an impartial witness for consent). This non-inclusion of certain participants could result in underestimation or overestimation of the incidence of ADRs. Continuous sensitization would certainly have improved this rate, but that was beyond the scope of our study. However, the final sample size was adequate to detect "rare" AEs (incidence occurring at a frequency of 1 out of 1000 patients or more) with a 95% probability.

Conclusion

Active surveillance through an HDSS platform seems to be an achievable approach to collect safety data in rural areas without major loss to follow-up, but this requires extra resources that are difficult to afford in resource-limited settings. The two surveillance systems were able to report many ADRs over a period of 2 years, although they did not report any new ADRs related to ASAQ. This shows that the HDSS platform could be a useful tool for the national PV system to monitor the safety of medicines, particularly in a rural environment where the use of newer technologies, such as web applications on tablets and smartphones, to report AEs may be very difficult to integrate. However, it is important to notice that the passive surveillance approach, which is more likely to be implemented by malaria control programs, seems to be more relevant in the SSA context, where health facilities have scarce human resources and insufficient funds to operate an active PV system. A few cases of exposure in the first trimester of pregnancy were reported, emphasizing the crucial need to develop a specific maternal and newborn health surveillance system (pregnancy exposure registry), which could contribute toward improving the assessment of maternal and neonatal outcomes.

Data Sharing Statement

All data generated or analyzed during this study are available at Clinical Research Unit of Nanoro data repository and shareable upon request addressed to the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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