Full title: A cohort-event monitoring study to describe the profile of adverse events in patients receiving treatment for malaria in urban Ghana

Short title: Adverse events in a pharmacovigilance cohort of malaria patients in Ghana

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Abstract

Background: Antimalarial treatment and strategies have changed much in the last 15 years, resulting in an increased variety of medicines available. Active pharmacovigilance methods are important for continued safety surveillance of these medicines, particularly in environments in which there is variability in treatments prescribed and limited confirmatory diagnostic capacity as well as limited ability of spontaneous reporting pharmacovigilance systems to generate much needed safety information quickly and efficiently.

Objective: To use the cohort-event monitoring (CEM) technique to gather drug utilisation and adverse event data for patients prescribed antimalarial medicines in an outpatient setting.

Methods: The characteristics of a large urban African cohort of outpatients (n=2,831) receiving antimalarial medications are described. The cohort was actively surveyed over the subsequent week to record adverse events, using follow-up phone calls, paper reports and/or voluntary return clinic visits. Adverse events reported in the cohort were analysed overall and by clinically-relevant age and medication groupings.

Results: At least one event was reported in 29.5% of patients. Adverse events were more likely to be reported in subjects older than 12 years of age, and by patients prescribed an artesunate-amodiaquine combination. A range of adverse events were reported, the most frequent higher level terms being asthenic conditions (10.1% of total cohort), neurological signs and symptoms (4.5%), headaches (3.1%), appetite disorders (2.1%) and disturbances in consciousness (1.6%). There were three reports of possible extrapyramidal events (2 cases of tremor "hand and back shaking all over" and one case of tongue protrusion), which may appear to be related to combinations including amodiaquine and an artemisinin.

Conclusion:

The use of the CEM methodology is a useful tool for monitoring the safety of widely available and utilised medicines, particularly in an urban environment where spontaneous reporting yields poor results and where the availability of various regimens and high levels of medicine usage can give valuable 'real-life' safety data. The types and frequencies of events reported reflected the types of events expected in patients prescribed antimalarials and nearly all events reported are listed in the summary of product characteristics of the medicines involved.

Word Count: 341

Key points:

1. Cohort event monitoring provides rapid real-life information on antimalarials as used in outpatient settings

2. Several adverse events reported after intake of antimalarial are similar to malaria symptoms necessitating large studies to identify real antimalarial associated events
3. Rare but important events e.g. extrapyramidal symptoms can be picked up during cohort event monitoring

Word Count: 5,796

1 Introduction

The last 15 years have seen a large change in the treatment strategy for malaria, particularly in sub-Saharan Africa. Rapidly rising drug resistance to standard treatments such as chloroquine and sulphadoxine-pyrimethamine and the consequent increase in morbidity and mortality has driven the development of a class of anti-malarials which combine artemisinin derivatives with long-acting partner drugs (artemisinin combination therapies- ACTs). [1,2] Due to the urgency of the situation, these new treatments have been widely deployed following pivotal trials demonstrating their efficacy and safety. [3-6]

This widespread introduction of ACTs provided an opportunity to pilot pharmacovigilance systems to assess safety in geographical populations within whom the medicines may not yet have been tested during the pre-marketing clinical trials. In addition, the focus of clinical trials on ACTs in Africa has been in children, as this population is at the highest risk of serious morbidity and mortality .[7] As a result, limited information is available on the adverse event profile in older children and adults and in children under 6 months of age. Pharmacovigilance data collected during post-marketing surveillance will therefore be important to fill this knowledge gap especially since the antimalarial trials in children under 5 are often powered to determine efficacy and the occurrence of frequent adverse events. Rarely are such studies powered to detect less common safety issues. In Ghana, the first-line treatment for malaria was changed by the Ministry of Health to artesunate-amodiaquine (ASAQ) in January 2005, and a cohort-event monitoring (CEM) study was designed to describe events following the use of anti-malarials and to explore the use of CEM methodology in this context.

Cohort-event monitoring is an adaptation of prescription-event monitoring (PEM), in which patients who are prescribed a drug are actively followed-up to gain information on adverse events (AEs) which occurred in an appropriate time-frame following treatment. [8] CEM, just like PEM, is therefore a form of active surveillance. In PEM studies, exposure and event data is collected directly from health professionals who have direct access to patient healthcare records, often extending over many years of the patients life. However, in countries such as Ghana, the majority of outpatient records, where they exist, are only in paper-format (electronic health records are all but absent) and held by the patients due to the fluidity of accessing healthcare from different providers, for example independent drug shops in addition to government or private health centres. CEM is therefore

adapted to source event data directly from patients, through direct patient contact or provision of patient reporting systems.

The pattern of drug utilisation observed in this setting in the CEM study and predictors of prescribing patterns have been described in an earlier paper. [9] This paper focuses on the safety data reported from this study, focussing on adverse event reports collected from patients who had received anti-malarial medicines from a prescription presented at a health facility pharmacy. The objective of the study was to capture adverse events to antimalarials when prescribed for the treatment of uncomplicated malaria in the community setting, through active procedures (CEM), which would illustrate the range and frequency of adverse events experienced by a naturalistic cohort following malaria treatment. The study also underlines the robustness of CEM methodology in monitoring safety of newly marketed community-prescribed medicines in such an environment and yields valuable information on the range and extent of events reported to individual antimalarial medicines.

2 Methods

Data presented in this article were collected between April and November 2006 through a prospective, longitudinal, observational cohort-event monitoring study in Accra and its environs in the Greater Accra Region of Ghana. The study source population covered approximately 4 million inhabitants (approximately 20% of the Ghanaian population at the time). The procedures for the recruitment and consenting of health centres and patients have been already described elsewhere. [9] In brief, 24 health institutions across Accra recruited patients prescribed anti-malarials consecutively from the pharmacy at the time of dispensing. 15 of these facilities were government hospitals/clinics whilst the rest were either private or quasi-government. Data collection at recruitment included demographics, contact details, method of diagnosis of malaria (health professional type and parasitological confirmation), anti-malarials prescribed and concomitant medications prescribed. As pointed out previously, [9] the original study design changed from a comparative study of the safety of artesuante-amodiaquine vs. chlorproguanil-dapsone; to a general descriptive study of the safety profile of prescribed anti-malarials due to WHO policy recommendations on treating uncomplicated malaria only with artemisinin-based combination therapy and the subsequent termination of the original study by the sponsor, WHO-TDR, in line with the WHO recommendations

2.1 Methods of surveillance

Two types of follow-up mechanisms were employed in this CEM study – active follow-up by phone or self-reporting by patients either directly to the study team or to the Outpatients Department of the Korle-Bu Teaching Polyclinic, a site dedicated for managing all adverse events occurring in patients taking part in the study from the day of recruitment and until 28 days later. Active follow-up was performed by trained research assistants by primarily telephone contact and some limited home visits to the patient, within 7 days after drug dispensing. Some patients had to be called more than twice as the contact phone number given belonged to a friend/relative/co-tenant who may not have been available at the time the call was made. Self-reporting to the research team or the Polyclinic was facilitated as follows. Each recruited patient was given a card which identified him/her as a participant in the study and thus eligible for free management at the Polyclinic from the day of recruitment till 28 days after (see Electronic Supplementary Material 1). A protocol for receiving and managing these patients and sending reports of their visit to the study team was also disseminated to all physicians and health workers at the Polyclinic. The card also had contact telephone numbers of key members of the study team for patients to call if needed. Patients were asked to report any events of medical concern (literally "anything that worries you") at any time during the 7 day follow-up whether or not they thought that the event could be due to the medicine. Six telephone lines were dedicated to the project and maintained by the study team, to which the patients could call or send a text message (to a cell phone) and then were immediately responded to by the research assistants. Patients were also advised to return to the facility from which they obtained the initial treatment in case of concern, (for example lack of improvement in their clinical condition or suspected adverse events) and also had the option of seeing research staff at the pre-defined treatment centre, i.e. the Korle-Bu Polyclinic. Patients were asked to report immediately to a health centre if they experienced any of the following signs: dark-coloured urine, rashes, sore throat, bruising or bleeding from any part of the body. Dark-coloured urine is a sign of haemolysis and the study team was keen to ensure that any patient with signs suggestive of haemolysis or any other serious event was promptly identified and managed appropriately. Patients requiring hospitalisation were given optimum care for their condition in line with the prevailing standard of care in Ghana. All such patients were managed by physicians at the Korle-Bu Polyclinic or the adjoining Korle-Bu Teaching hospital. Patients who suffered serious adverse events were followed up to determine outcome and any report of death investigated including results of autopsy. The study protocol for this study defined "serious adverse events" as those that result in death, are life-threatening, require in-patient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The study team developed a standard method for obtaining information from patients by phone and used a structured questionnaire modelled along the national spontaneous reporting form for collection of safety events post-treatment. Information was collected concerning the prescribed medications (posology, dates of treatment start and stop, source of drug), adverse events (description of event, date of onset, date of cessation, treatment or action taken, outcome (including death), previous use of the drug and any similar AEs), concomitant medications, other available details (e.g. past medical history, laboratory test results, allergies) (see Electronic Supplementary Material 2). The research team visited each participating institution twice every week to collect recruitment forms, information on spontaneous reports received and discuss study progress.

During the study period, additional community activities designed to increase awareness of the study and to promote reporting of adverse events through the national spontaneous reporting system were carried out; for example a short generic pharmacovigilance advertisement on Ghana TV, radio and newspapers, and logos and contact information were displayed on project vehicles.

2.2 Data management

Data were double-entered and verified on a Microsoft Access database (Microsoft Office 2003) and analysed using Stata (Version 10.1). Adverse event data was recorded according to how the patient or caregiver described the event, and then reviewed and coded using Medical Dictionary for Regulatory Activities (MedDRA®) (Version 13.1) terminology. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.

2.3 Analyses

Treatments were grouped into four main categories – artemisinin-based monotherapy (monotherapy ART, where ART is used as an abbreviation for artemisinin), non-artemisinin based monotherapy (monotherapy non-ART), artesunate-amodiaquine (ASAQ) and other artemisinin-combination therapies (ACTs). Univariate analyses using crude odds ratios (OR) were applied to describe the determinants of event reporting. In addition, multivariate analysis was conducted using logistic regression (reported as adjusted odds ratio (AOR) and 95% Wald Confidence intervals (CI)) to investigate the combined effect of patient characteristics in relation to whether or not events were reported. Variables significant at $p<0.1$ in univariate analyses were included in the logistic

regression model. Frequency of event reporting was also assessed and reported as percentages of treatment group. All events reported were grouped by MedDRA® higher level term (HLT) according to age group and therapy type. Events reported in patients under 5 years were grouped by treatment prescribed (amodiaquine; artemether; artemether+amodiaquine; artesunate; dihydroartemisinin; dihydroartemisinin+amodiaquine; artesunate+amodiaquine) and reported at MedDRA® preferred term (PT) level. Adverse events verbatim as reported by the patients or caregiver were also reviewed qualitatively.

Events that existed prior to treatment were not collected and there was no attempt to distinguish between new or worsening events in individual patients or the study cohort as a whole. All events recorded post-treatment were analysed statistically to determine the likely factors associated with the occurrence of adverse events following antimalarial treatment. There was no case-causality or relationship assessment of events reported as there were no obvious benefits of this exercise in the current study design.

2.4 Ethics

The study was approved by the Ethical and Protocol Review Committee of the University of Ghana Medical School. Patients were included in the study following signed and witnessed informed consent. A parent/guardian provided consent for patients under the age of 18 years.

3 Results

3.1 Cohort composition

Twenty-four health centres recruited patients for the study, resulting in a cohort of 2,831 eligible patients. The distribution of the baseline characteristics of the cohort and prescribing patterns are described fully in a previous paper, [9] and the type and frequency of anti-malarials prescribed are given in Table 1. Demographically, the recruited cohort included 59.9% (n=1,695) females, with increasing female numbers with increasing age. Children under 5 years comprised 21.6% (n=610) of the cohort, 11.2% (n=317) 5-12 years, 60.6% (n=1,716) 13-59 years and 5.5% (n=157) 60 years and above (1.1%, n=31, of unknown age). A total of 2,092 (73.9%) patients were followed-up after treatment. Figure 1 shows the distribution of patients by treatment group and the number in the cohort with a follow-up contact and at least one event reported. The distribution of characteristics of patients followed-up was similar to the baseline cohort. Paediatric patients (defined as age 12 years and below) comprised 31.6% (n=662) of followed-up patients. The female population of the cohort was 58.5% (n=1,224) and approximately 90% (n=1,882) of all prescriptions were resulting from a clinical diagnosis of malaria based on clinical signs and symptoms alone with no parasitological confirmation. Concomitant antibiotics were prescribed to 30.5% (n=639) of patients, clearly

indicating a high proportion of presumptive treatment of fevers for both malaria and possibly other infections contrary to national guidelines.

3.2 Reporting of events

Table 2 shows the results of univariate analysis and multivariate logistic regression to determine factors associated with the reporting of AEs. Results presented in the table indicate that the age group, treatment arm (anti-malarial drug administered) and concomitant antibiotic administration were associated with the report of AE in the univariate analyses. In the multivariate analysis, the odds of reporting AEs were more in subjects older than 12 years of age (AOR, 1.56 [95% CI, 1.24 – 1.96], p<0.001) compared with children <5 years. The odds of patients prescribed ASAQ to report an event was also higher (AOR, 1.51 [95% CI, 1.22- 1.87], p<0.001) compared with those prescribed non-artemisinin monotherapy (Table 2). Non-ASAQ ACTs showed a borderline association with event reporting (AOR 1.35 [95% CI, 0.98-1.86], p=0.063) compared with non-artemisinin monotherapy. There was no significant difference in reporting between males and females, mode of diagnosis (presumptive versus laboratory confirmed) or number of concomitant medications prescribed. Concomitant prescription with antibiotics was significantly associated with reporting of events in the univariate analysis, but not when adjusting for factors included in the multivariate analyses.

3.3 Description of reported events

At least one event was reported in 29.4% (n=616, [95% CI=27.5-31.5]) of patients who were successfully followed up. The majority of events did not require discontinuation of anti-malarial therapy and were resolved without additional treatment. A large proportion of reported events, including asthenia, nausea and vomiting, headache, lack of appetite, dizziness, fever, diarrhoea, musculoskeletal pain and cough were mild in intensity and overlapped with known malaria signs and symptoms. Commonly reported events also included undesirable effects known to be associated with certain anti-malarial therapies, for example asthenia, vertigo, sleep disturbance, pruritus, sensory abnormalities and rashes. [10] There was one death during follow-up of an adult male (aged 35 years) who had been prescribed ciprofloxacin in addition to ASAQ antimalarial therapy. Post-mortem results indicated that the patient died of complications related to typhoid fever.

The most commonly reported event was asthenia, often described by patients as ‘weakness’ or ‘generalized weakness’ (n=211, 10.1% of the follow-up cohort, [95% CI= 8.8-11.5]) (Table 3). The odds of reporting asthenia was higher in patients prescribed ASAQ compared with patients prescribed non-ASAQ ACTs (AOR, 1.69 [95% CI, 1.02-2.86]), artemisinin monotherapy (AOR,

2.17 [95% CI, 1.49-3.13]) or non-artemisinin monotherapy (AOR, 5.26 [95% CI, 1.92-14.29]). Asthenia was also associated with females more than with males (AOR 1.57 [95% CI, 1.13-2.18]).

The profile of reported events for ASAQ as the new first-line therapy at the time of the study was similar to that of other available treatments (Table 3). Of particular interest for the safety profile of this therapy are events of the nervous system. One case of paraesthesia (an event labelled as uncommon in the current Summary of Product Characteristics) was reported in a 46 year old male who was prescribed ASAQ concomitant with amoxicillin, paracetamol and chlorpheniramine (an antihistamine). Two reports of tremor were also reported in adult females (verbatim 'back and hand shaking', 'shaking all over'), and one dyskinesia (verbatim 'tongue protrusion'), reported together with tongue swelling.

Cardiac events reported included 10 reports of palpitations (6 in the ASAQ group). One adult patient on ASAQ experienced dizziness, collapsed and later recovered. No events diagnosed as hepatic toxicity were reported. Seven patients reported chromaturia (mapped to the Higher Level Term "Urinary abnormalities" in Table 4) – three aged <5 years (two ASAQ patients, one non-ASAQ ACT patient) and four adults (two ASAQ patients and two artemisinin monotherapy patients). Ocular icterus was reported in a patient under 5 years (non-ASAQ ACT) and an adult on artemisinin monotherapy (mapped to the Higher Level Term "Ocular disorders NEC" in Table 4).

The most commonly recorded events in patients under 5 years of age taking ASAQ (n=113) included general weakness (n=16, 14.2%, [95% CI=8.3-22.0]), vomiting (n=9, 8.0%, [95% CI=3.7-14.6]), anorexia (n=8, 7.1%, [95% CI=3.1-13.5]) and pyrexia (n=7, 6.2%, [95% CI=2.5-12.3]) in single episodes (Table 5). There was one report of pharyngolaryngeal pain (event occurred two days after commencement of treatment) in a boy aged 1 year 3 months who was administered ASAQ in addition to an antitussive and an antibiotic. One case of urticaria was reported in a 1 year-old boy prescribed ASAQ in addition to paracetamol and haematinic (event occurred on the same day of commencement of treatment).

Whilst a dihydroartemisinin (DHA)+AQ regimen was not commonly prescribed among the study cohort, some notable reactions were reported with DHA+AQ including loss of consciousness in a 1 year 8 months old female who was also prescribed antitussive, flucloxacillin and paracetamol (event occurred the same day of commencement of treatment). Skin discolouration as an event was reported to have occurred on the same day of start of drug administration in two female patients (aged 3 years and 1 year 4 months) who were both prescribed DHA+AQ in addition to paracetamol, folic acid plus oral rehydration salt in the 1st case and amoxicillin plus antitussive in the 2nd case.

Two cases of swollen eyes were reported (both events occurred a day after starting drug treatment) - the first case involving a 4 year old male patient prescribed artemether + AQ in addition to paracetamol and haematinic and the second case involved a 6 years old female prescribed only artemether. One case of musculoskeletal stiffness was reported (on the same day of start of drug administration) in a 16 year old female prescribed ASAQ plus paracetamol and haematinic.

3.4 Reports to hospital clinics

During recruitment, patients were given special cards with which they could access free medical care in the event of adverse events. Many of the adverse events reported during the follow-up calls had subsided at the time of the calls. Patients who were still experiencing adverse events at the time of follow-up calls were urged to report to Korle-Bu Polyclinic, the designated study clinic, for treatment. There were 60 patients who reported to the Out-Patients Department (OPD) of the Korle-Bu Polyclinic due to suspected adverse events (Table 6). There were 27 (3.1%) ASAQ patients who attended the hospital, 28 (3.1%) monotherapy patients and 5 (1.6%) who had taken non-ASAQ ACTs. In general, these patients felt they had events which were related to the anti-malarial intake which prompted the hospital contact. The most common event reported by the ASAQ patients to the Polyclinic was abdominal pain or discomfort reported by 11 patients (40.7%, [95% CI=22.4-61.2]). Palpitations were reported by 3 patients (11.1%, [95% CI=2.4– 29.2]) out of the 27 patients on ASAQ therapy who came to the Polyclinic. No neutropaenia was detected for any patient reporting to hospital though it must be stressed that few of the patients had laboratory investigations. All the patients reporting to hospital recovered fully without sequelae. The data from these patients are incorporated into the general analysis and such routine hospital attendance was not classified as "hospitalisation" and thus not considered "serious" events unless the events satisfied other criteria of "serious events" as defined in the methods section.

3.5 Qualitative aspects of event reports

Features of the verbatim reports from the patients provide indicators of the severity of the event, and could give clues as to the possible causality of events. For example, adult patients reported to research assistants that the type of 'weakness' they experienced after drug administration was quite different from the 'weakness' they associated with uncomplicated malaria. Temporality information can also add important context for causality assessments, for example 'felt dizzy and vomiting each time drug was taken', 'feeling of weakness after each dose of the drug', 'weak and has to sleep and then eat to become strong again (happens any time drug is taken)'. Culturally-based descriptions also required interpretation in context, for example 'headache, feeling dizzy in the sun, back, hand shaking, feet and hands feel heavy, sometimes stiffness'. However, most of the reported events were

possible to code directly and accurately using MedDRA®. Where it became necessary, complex culturally-based descriptions were broken down into groups of events and coded using MedDRA®.

4 Discussion

This study demonstrated that it is feasible to perform active safety monitoring, in this case CEM, as part of the pharmacovigilance activities in an urban African setting. The combination of actively solicited event data combined with the opportunity for patients to spontaneously report, elicited a large volume of event reports which reflects the safety of anti-malarials in real-life usage. Cohort event monitoring in sub-Saharan Africa has the potential to become an important tool in pharmacovigilance since the passive/spontaneous reporting rate is generally low. Some documented advantages of CEM include: a) effective in identifying signals at an early stage; b) ability to make accurate comparisons between medicines; and c) provides clinically significant results rapidly and hence stimulates interest in drug safety in general. [11]

4.1 Patterns of reporting

Adverse events were reported across age groups, with a higher rate of reporting in adults, who were also the group most likely to be prescribed ASAQ in this cohort. At the time of the study, ASAQ had recently been designated the first-line medication for treating uncomplicated malaria in Ghana, and a number of adverse events were widely reported in the media. Subsequently, a review of the ASAQ dosing regimen and inclusion of artemether + lumefantrine (AL) and dihydroartemisinin + piperaquine as additional first-line medications occurred. These actions may have made patients taking ACTs more attentive of their response to treatment, compared to non-ACTs – a situation similar to the well-known Weber effect. [12]

4.2 Adverse events

The most commonly reported events included asthenia, nausea and vomiting, headache, lack of appetite, abdominal pain, dizziness, fever, pruritus, increased temperature, diarrhoea, musculoskeletal pain and cough. These are commonly reported symptoms of clinical malaria, and thus could be indication-related events, and are similar to those reported in the recent CEM cohort performed in Nigeria. [13] Knowledge of clinical signs and symptoms at baseline could have assisted in distinguishing whether these events occurred newly after antimalarial administration or were associated with the diagnosis. Current CEM studies therefore collect baseline events. However, such data collection may not be feasible in all CEM studies, and therefore alternative methods of analysis need to be explored to determine whether such symptoms are presented in excess of what would be expected as a result of malaria morbidity. Comparative CEM studies with large numbers and different ACTs will thus yield valuable information in this regard as would meta-analyses of

individual CEM studies though the extremely low numbers of published studies precludes the latter option presently. No events of neutropaenia were reported in all the treatment groups. However, non-specific symptoms associated with neutropaenia due to amodiaquine toxicity, namely fever, lethargy, sore throat and weakness, were observed in patients prescribed amodiaquine either as monotherapy or as artemisinin combination therapy, but were not further investigated in the laboratory. Routine laboratory investigations for events such as this would be expensive to implement on a routine basis during pharmacovigilance activities, but an algorithm of event severity and risk could perhaps be considered in similar studies in the future. The cardiac events noted in the cohort, particularly in ASAQ patients, have been highlighted as a potential risk in a previous electrocardiogram study demonstrating increased risk of bradycardia on the second day of treatment with ASAQ. [14] Dystonic effects associated with amodiaquine+artesunate have, since the study concluded, been published as a signal of adverse events to amodiaquine-containing ACTs. [10] Interestingly, this signal represents the first drug-safety signal to be published from Africa based on data obtained solely from African passive spontaneous reporting systems. The summary of product characteristics (SPC) of amodiaquine+artesunate combinations has now been amended to include dystonia as a possible adverse reaction. The 2 reports of tremor reported in adult females (‘back and hand shaking’, ‘shaking all over’), and one report of dyskinesia (verbatim ‘tongue protrusion’) appear to fit within the general definition of dystonic events and adds to the growing body of evidence linking ASAQ to movement disorders.

Overall, events reported were within the expected type and frequency based on the summary of product characteristics of the medications prescribed and from other literature.

4.3 Limitations

Overall, the cohort size was not large enough to be able to detect rare events (occurring in ≥ 0.01% and < 0.1% of the population treated). The sample size of just under 3000 would thus be expected to record only events occurring at or more than rates of 1 in 1000. The proportion of patients lost to follow-up in the study was relatively high (26.1%) but this is not unusual in studies of this nature and compares favourably with results obtained in other studies carried out in Ghana with similar methodologies. [15,16] It highlights one of the challenges in retaining a large cohort of patients in such an environment where certain population groups may have less access to telecommunications, and homes may be difficult to locate in the absence of established demographic data. This may have introduced bias in reporting as those less likely to have telephone availability could have been in particular socioeconomic or educational groups which could also be related to treatment options and

also event-reporting characteristics, although there does not appear to have been any disproportionate loss to follow-up in terms of age, gender or proximity to the designated healthcare centre for hospital reports. There are virtually no electronic health records in Ghana thus classical PEM studies could not have been undertaken. This observational study was also not blinded, and therefore both the reporter and the data collector were aware of the treatment taken, and may have prompted additional reporting according to knowledge of the regimen. However, reporting of many common events which could also be related to malaria, such as nausea and vomiting, was fairly consistent across treatment and age groups.

One of the ways in which event reporting in PEM and some CEM studies differs from those in clinical trials is that it is not possible to determine baseline events in these large observational studies, and therefore events which are reported may or may not be truly 'new' events. This has an impact on considerations of causality of events in relation to the medicine, and may also mean that indication-related events appear at a high rate during the observation period, although these may have been present prior to treatment. In view of these limitations and considering the study design, case-causality assessment was not undertaken for individual events.

Pharmacovigilance is further complicated by lack of resources to definitively diagnose malaria or treatment practices where practitioners refuse to diagnose malaria using rapid-diagnostic tests or microscopy contrary to national or international guidelines. The high level of antibiotic prescribing (30.8%) coupled with the clinical rather than microscopical diagnosis of malaria [9] may indicate uncertainty in diagnosing the cause of the presenting complaints, especially fever, and hence an attempt to treat both for malaria and any suspected underlying infection(s). Medication use in adults without a definitive malaria diagnosis could also result in events related to un-investigated or undiagnosed alternative conditions, and therefore pharmacovigilance reports may also reflect burden and complications from other diseases, rather than medication-related events. Clinicians likely to have only one contact with a patient, especially for whom there is a possibility that they have a disease which can be fatal if untreated, are likely to treat all potential causes even though current WHO guidelines and national malaria treatment policies clearly indicate the need to test before treating except in rare situations where testing facilities are not available. Presumptive diagnosis and treatment of malaria with multiple medicines and antibiotics is not uncommon in most malaria endemic countries in Africa [9, 17], but the practice poses challenges for safety monitoring and case causality assessment as reported events could reflect aspects of a combination of diseases, drug-drug interactions or drug-related events. For example, reported rashes may be interpreted as a sign of

hypersensitivity to medication, but could also reflect symptoms of viral infection. This is, however, 'real life medical practice' in Africa, and needs to be considered when assessing the safety profile of medicines in the community setting. The current WHO malaria treatment guideline which strongly recommends testing using microscopy or rapid diagnostic tests before treating malaria may go a long way to improve availability of diagnostic aids and thus reduce the presumptive treatment of malaria in Africa though there is no published evidence that this is actually happening yet.

Previous antimalarial therapies taken within the past month were not recorded. Data on repeat courses of curative doses of antimalarials is scarce, but this is key information for pharmacovigilance activities, particularly as previous adverse experiences with particular treatments may have also influenced the choice of a current treatment and may indicate a particular susceptibility to certain adverse reactions. Since this study was non-interventional and did not require laboratory investigations post-treatment, it might miss important events like anaemia that may occur up to 2 weeks after treatment. Identification of such events may require other study designs though the routine deployment of electronic health records (see section 4.5) could facilitate identification of such important signals.

4.4 Applicability

It is likely that the design of this study would be more difficult to replicate in an area with a more sparsely distributed population with less telecommunications networks coverage and access to electronic media. Prescribing practices in urban areas, and therefore likely event reports, are likely to differ from rural areas, in part due to availability of medications, diagnostic equipment and level of health worker expertise. However, with expanding mobile networks throughout the continent, the potential for such a follow-up model to be feasible over a wider geographical area is on the horizon.

4.5 Costs of technique and benefits

This study has demonstrated the benefits of active follow-up studies like CEM in collecting large amounts of safety data quickly in the period immediately following the deployment of a new medicine, vaccine or treatment regimen. Such data is useful for policy makers, programme managers and patients alike as it permits rapid assessment of real-life safety of products. A large cohort size of 10,000 is however needed in order to detect events occurring at or more frequently than 1 in 3000. Such large cohort sizes comes with a cost component which may nonetheless prove cost-effective. The cost of initiating a new CEM study in Africa is anywhere between US$75000 – US$100,000 including cost of a vehicle, equipment, consumables, staff and patient management costs in case of adverse events. These studies are non-interventional and the costs do not include laboratory

examinations except in cases of adverse events. Subsequent studies may cost less as the equipment and vehicles could be re-used. This relatively high cost is however justifiable when one considers that the routine spontaneous reporting systems employed by nearly all malaria-endemic countries yield very little results in terms of adverse reaction reports to antimalarials in particular [18] and all medicines in general. Newer approaches like the routine use of electronic health records may offer cost-effective means of collecting long-term data on the safety of antimalarial in real-life usage. The deployment of electronic health records, even in just a few sentinel clinics or hospitals, will also go a long way to strengthen existing health systems in malaria-endemic countries and provide the much needed baseline information on diseases and events often absent in most phase IV studies conducted in Africa. It will also provide longitudinal data that may lend themselves to epidemiological analysis as well as comparison of future studies with current data.

Conclusions

The profile of adverse events recorded in this study following prescription of antimalarials for uncomplicated malaria were similar to the symptoms of malaria. The most commonly reported event was asthenia, often described by patients as 'weakness' or 'generalized weakness' This was reported more frequently in patients prescribed ASAQ and was also more associated with females more than with males. There were three cases of dystonic reactions (reported as "back and hand shaking" in two cases and "tongue protrusion" in one case). There were 10 reports of palpitations and 7 reports of chromaturia. The findings in this study lay the ground for larger comparative studies of the real-life safety of antimalarials in general and ACTs in particular, especially in the current era of multiple ACTs. The study shows that cohort-event monitoring (CEM) implemented in an urban community is a feasible active safety monitoring approach to reinforce pharmacovigilance activities. The combined follow-up model, including active phone interviews, spontaneous patient reporting and the option for return to the prescribing clinic/hospital, enriches the quality and completeness of the data, and should be recommended practice. With regards to the safety data obtained from this CEM study, the safety profile of the drugs under monitoring is consistent with safety profile expected for the medicines concerned. This study has also added to the growing body of evidence linking amodiaquine-based regimen with movement and/or dystonic adverse events.

Several challenges were identified throughout the study that, once addressed, can improve CEM in these settings. These include: i) improving malaria diagnostic test availability, ii) expansion of information technology and telecommunications capacity and general infrastructure, iii) knowledge and understanding of local and cultural context of patient-reported events, iv) improving cohort retention and minimize loss to follow up by leveraging media channels and diversify individual reminders channels. Given the complexity and flexibility of prescribing patterns, it is also apparent that the capacity and sustainability of pharmacovigilance projects can be enhanced by widening the scope of monitoring beyond a single disease or drug. International collaboration, both with the WHO and the Uppsala Monitoring Centre (UMC) in Sweden as well as across regions in Africa can also augment the feasibility and value of the safety information acquired. Studies such as these will complement the dearth of information on the real life safety of antimalarials. [18] The well known drawbacks of spontaneous reporting, typically under-reporting, is likely to be worse in resource-constrained environments and pharmacovigilance studies such as this will increasingly become the main source of Phase IV drug safety information.

There are many areas that can therefore be identified for future research, both around the methods of collection of adverse event data in this context, its transferability to a more rural environment, and

also the type of data collected. Benefits of educating medicine-users and prescribers to acknowledge the potential harms of medicines and report concerns could impact on both service user and prescriber behaviour, resulting in more rational drug use which may benefit the individual and have a wider-ranging public health benefit in the long term.

Competing interests

Germano Ferreira has been employed by Sanofi Pasteur and GSK Vaccines over the period of preparation of the manuscript, but the work on the manuscript was performed in his personal capacity and time, and bears no relation to Sanofi or GSK projects nor funding. Alexander Dodoo, Carole Fogg, Edmund Nartey, Germano Ferreira, George Obeng Adjei, William Kudzi, Abdul Malik Sulley, Augustina Kodua and David Ofori-Adjei have no conflicts of interest that are directly related to the content of this study.

Authors' contributions

AD, DO-A were the co-investigators for this study and designed the project proposal and oversaw the project. ETN, GOA and WK were responsible for database design, data entry and pre-analysis management. AMS and AK were the research associates implementing the study, managing the data collectors and visiting the various project sites. CF and GLCF performed statistical analysis. CF and AD drafted the manuscript, and all authors read and approved the final manuscript

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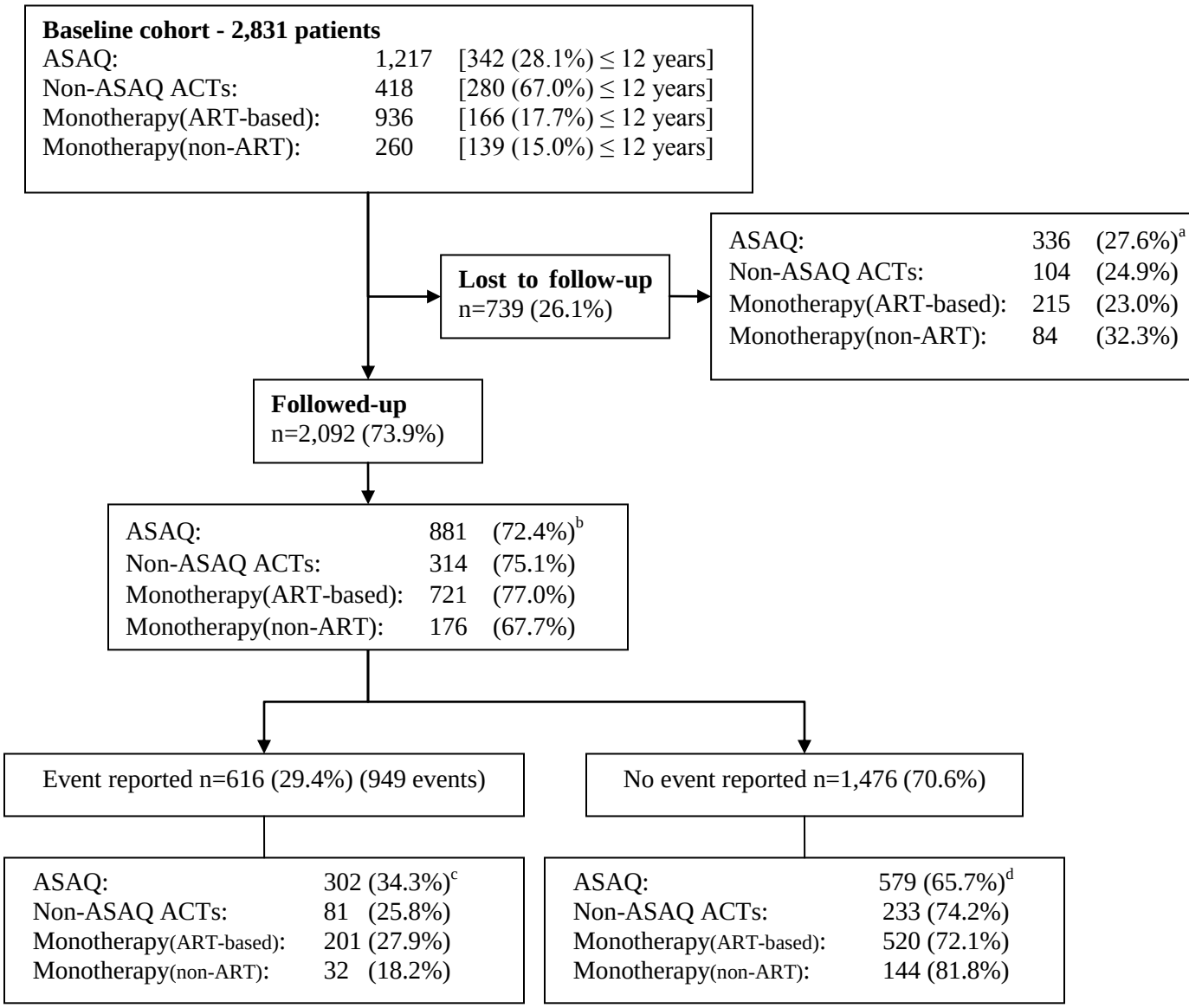
Figure 1.Patient flow



[a]Percentage of treatment group lost to follow-up
[b]Percentage of treatment group who were followed-up
[c]Percentage of patients followed-up who had an event according to treatment group
[d]Percentage of patients followed-up who did not have an event according to treatment group

NOTE: percentage a + b = 100% for each treatment group

Abbreviations:
ART – artemisinin
ASAQ – artesunate-amodiaquine
ACT – artemisinin combination therapy

Table 1. Anti-malarial treatment prescribed

Drug group/treatment		N (%)
1st line therapy (ASAQ)		1, 217 (43.0)
ACT-Other		418 (14.8)
	DHA+AQ	240 (8.5)
	Artemether+AQ	77 (2.7)
	Artemether+lumefantrine	58 (2.1)
	DHA+pyrimethamine-sulphametopirazine	13 (0.5)
	Artesunate+SP	12 (0.4)
	DHA+SP	6 (0.2)
	DHA+chloroquine	5 (0.2)
	Artesunate+chloroquine	3 (0.1)
	Artemether+pyrimethamine-sulphametopirazine	1 (0.04)
	Artemether+quinine	1 (0.04)
	Artesunate+ quinine	1 (0.04)
	DHA+artemether+lumefantrine	1 (0.04)
Monotherapy-ART based		936 (33.1)
	DHA	577 (20.4)
	Artesunate	293 (10.4)
	Artemether	55 (1.9
	Artesunate/artemether	10 (0.4)
	Artemether/DHA	1 (0.04)
Monotherapy – non ART		260 (9.2)
	Amodiaquine	133 (4.7)
	SP	78 (2.8)
	Pyrimethamine-sulphametopirazine	32 (1.1)
	Chloroquine	14 (0.5)
	Quinine	3 (0.1)
Total		**2831**

ASAQ= artesunate-amodiaquine; ACT= artemisinin combination therapy ; ART= artemisinin; DHA = dihydroartemisinine; AQ = amodiaquine; SP = sulphadoxine-pyrimethamine

This table has been reproduced from reference [9]

Table 2. Patient characteristics in relation to whether one or more events were reported

Characteristic	Event(s) N=616 *n, (%)*	Univariate Analysis Crude OR [95% CI]	p-value	Multivariate[a] An Adjusted OR [95
Age Group				
<5 years (N=443)	106(23.9)	Ref		Ref
5- 12 years (N=219)	46(21.0)	0.84[0.57 – 1.25]	0.4	-
>12 years (N=1,415)	460(32.5)	1.50 [1.20 – 2.00]	0.001	1.56 [1.24 – 1.9
Unknown (N=15)	*4 (26.7)*			
Gender				--
Male (N=868)	246(28.3)	Ref		
Female (N=1,224)	370(30.2)	1.10 [0.90 – 1.32]	0.35	
Mode of diagnosis				--
Presumptive (N=1,882)	573(30.5)17(27.0)	Ref		
Laboratory confirmed (N=63)	*26 (17.7)*	0.84 [0.48 – 1.49]	0.56	
Unknown (N=147)				
Anti-malarial drug administered				
Monotherapy (Non-ART based) (N=176)	32(18.2)	Ref		Ref
Monotherapy (ART based) (N=721)	201(27.9)	1.74 [1.14 – 2.64]	0.009	-
ASAQ (N=881)	302(34.3)	2.35 [1.56 – 3.53]	<0.001	1.51 [1.22 – 1.8
Non-ASAQ ACTs (N=314)	81(25.8)	1.56 [0.99 – 2.48]	0.056	1.35 [0.98 – 1.8
Concomitant antibiotic administration				
No (N=1,453)	447(30.8)	Ref		-
Yes (N=639)	169(26.5)	0.81 [0.66 – 0.99]	0.046	-
Number of concomitant medications prescribed				
3 or less (N=1201)	256(28.0)	Ref		
4 and above (N=1630)	360(30.5)	1.13 [0.93 – 1.36]	0.214	-

[a]N=1923. Patients with unknown age (n=15) and/or unknown mode of diagnosis (n=148) were excluded from the multivariate analyses. Only variables significant at p<0.1 were included in the final model.

Abbreviations: OR: odds ratio; CI: confidence interval; ART: artemisinin; ASAQ: artesunate-amodiaquine; ACT: artemisinin combination therapy

Table 3. Events reported grouped by MedDRA® Higher Level Term (HLT) according to therapy type

MedDRA® Higher Level Term	Total cohort N=2092 n(%)	ASAQ N=881 n(%)	ACT other N=314 n(%)	Monotherapy ART N=721 n(%)	Monotherapy non-ART N=176 n(%)
Anaemias NEC	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Anal and rectal signs and symptoms	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Anxiety symptoms	4(0.19%)	3(0.34%)	0(0%)	0(0%)	1(0.57%)
Apocrine and eccrine gland disorders	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Appetite disorders	44(2.1%)	26(2.95%)	9(2.87%)	8(1.11%)	1(0.57%)
Asthenic conditions	211(10.09%)	124(14.07%)	24(7.64%)	58(8.04%)	5(2.84%)
Bladder and urethral symptoms	4(0.19%)	2(0.23%)	0(0%)	2(0.28%)	0(0%)
Bone related signs and symptoms	2(0.1%)	1(0.11%)	0(0%)	1(0.14%)	0(0%)
Breast signs and symptoms	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Breathing abnormalities	4(0.19%)	3(0.34%)	0(0%)	1(0.14%)	0(0%)
Cardiac signs and symptoms NEC	10(0.48%)	6(0.68%)	0(0%)	3(0.42%)	1(0.57%)
Circulatory collapse and shock	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Coughing and associated symptoms	9(0.43%)	4(0.45%)	2(0.64%)	1(0.14%)	2(1.14%)
Dermal and epidermal conditions NEC	6(0.29%)	2(0.23%)	1(0.32%)	3(0.42%)	0(0%)
Dermatitis and eczema	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Diarrhoea (excl infective)	25(1.2%)	12(1.36%)	7(2.23%)	4(0.55%)	2(1.14%)
Disturbances in consciousness NEC	33(1.58%)	17(1.93%)	5(1.59%)	7(0.97%)	4(2.27%)
Disturbances in initiating and maintaining sleep	14(0.67%)	7(0.79%)	3(0.96%)	1(0.14%)	3(1.7%)
Dyspeptic signs and symptoms	13(0.62%)	10(1.14%)	0(0%)	3(0.42%)	0(0%)
Ear disorders NEC	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Faecal abnormalities NEC	3(0.14%)	1(0.11%)	1(0.32%)	1(0.14%)	0(0%)
Febrile disorders	20(0.96%)	11(1.25%)	1(0.32%)	5(0.69%)	3(1.7%)
Feelings and sensations NEC	27(1.29%)	13(1.48%)	4(1.27%)	8(1.11%)	2(1.14%)
Flatulence, bloating and distension	2(0.1%)	0(0%)	1(0.32%)	1(0.14%)	0(0%)
Fluid intake decreased	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Gastrointestinal and abdominal pains (excl oral and throat)	40(1.91%)	15(1.7%)	7(2.23%)	13(1.8%)	5(2.84%)
Gastrointestinal atonic and hypomotility disorders NEC	3(0.14%)	3(0.34%)	0(0%)	0(0%)	0(0%)
Gastrointestinal signs and symptoms NEC	7(0.33%)	2(0.23%)	0(0%)	5(0.69%)	0(0%)
General signs and symptoms NEC	2(0.1%)	0(0%)	1(0.32%)	1(0.14%)	0(0%)

Headaches NEC	65(3.11%)	26(2.95%)	9(2.87%)	26(3.61%)	4(2.27%)
Heart rate and pulse investigations	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Increased physical activity levels	8(0.38%)	7(0.79%)	0(0%)	1(0.14%)	0(0%)
Joint related signs and symptoms	3(0.14%)	0(0%)	0(0%)	3(0.42%)	0(0%)
Lacrimal disorders	2(0.1%)	1(0.11%)	0(0%)	1(0.14%)	0(0%)
Mental impairment (excl dementia and memory loss)	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Migraine headaches	2(0.1%)	2(0.23%)	0(0%)	0(0%)	0(0%)
Muscle tone abnormalities	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Muscle weakness conditions	2(0.1%)	2(0.23%)	0(0%)	0(0%)	0(0%)
Musculoskeletal and connective tissue pain and discomfort	10(0.48%)	5(0.57%)	0(0%)	4(0.55%)	1(0.57%)
Musculoskeletal and connective tissue signs and symptoms NEC	1(0.05%)	0(0%)	1(0.32%)	0(0%)	0(0%)
Nasal congestion and inflammations	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Nausea and vomiting symptoms	76(3.63%)	32(3.63%)	15(4.78%)	26(3.61%)	3(1.7%)
Neurological signs and symptoms NEC	93(4.45%)	51(5.79%)	5(1.59%)	33(4.58%)	4(2.27%)
Ocular disorders NEC	5(0.24%)	0(0%)	2(0.64%)	2(0.28%)	1(0.57%)
Ocular infections, inflammations and associated manifestations	4(0.19%)	1(0.11%)	3(0.96%)	0(0%)	0(0%)
Oedema NEC	2(0.1%)	1(0.11%)	0(0%)	1(0.14%)	(0%)
Oral soft tissue pain and paraesthesia	4(0.19%)	2(0.23%)	1(0.32%)	10(1.39%)	1(0.57%)
Pain and discomfort NEC	30(1.43%)	18(2.04%)	1(0.32%)	0(0%)	1(0.57%)
Paraesthesias and dysaesthesias	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Physical examination procedures	23(1.1%)	10(1.14%)	5(1.59%)	5(0.69%)	3(1.7%)
Pruritus NEC	41(1.96%)	22(2.5%)	3(0.96%)	14(1.94%)	2(1.14%)
Rashes, eruptions and exanthems NEC	14(0.67%)	7(0.79%)	1(0.32%)	5(0.69%)	1(0.57%)
Rate and rhythm disorders NEC	4(0.19%)	4(0.45%)	0(0%)	0(0%)	0(0%)
Rubeola viral infections	1(0.05%)	0(0%)	1(0.32%)	0(0%)	0(0%)
Salivary gland disorders NEC	2(0.1%)	1(0.11%)	0(0%)	0(0%)	1(0.57%)
Sensory abnormalities NEC	15(0.72%)	4(0.45%)	0(0%)	10(1.39%)	1(0.57%)
Site specific vascular disorders NEC	2(0.1%)	0(0%)	2(0.64%)	2(0.28%)	0(0%)
Skin structures and soft tissue infections	2(0.1%)	0(0%)	0(0%)	0(0%)	0(0%)
Social issues	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Soft tissue disorders NEC	2(0.1%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Speech and language abnormalities	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Therapeutic and nontherapeutic responses	11(0.53%)	2(0.23%)	3(0.96%)	5(0.69%)	1(0.57%)
Tongue disorders	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)

Tongue signs and symptoms	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)
Tremor (excl congenital)	2(0.1%)	2(0.23%)	0(0%)	0(0%)	0(0%)
Upper respiratory tract infections	7(0.33%)	1(0.11%)	2(0.64%)	4(0.55%)	0(0%)
Upper respiratory tract signs and symptoms	4(0.19%)	3(0.34%)	0(0%)	1(0.14%)	0(0%)
Urinary abnormalities	8(0.38%)	4(0.45%)	1(0.32%)	3(0.42%)	0(0%)
Urinary tract signs and symptoms NEC	1(0.05%)	0(0%)	0(0%)	1(0.14%)	0(0%)
Urticarias	2(0.1%)	1(0.11%)	0(0%)	1(0.14%)	0(0%)
Visual disorders NEC	1(0.05%)	1(0.11%)	0(0%)	0(0%)	0(0%)

Abbreviations: ART: artemisinin; ASAQ: artesunate-amodiaquine; ACT: artemisinin combination therapy; NEC: not elsewhere classified

Table 4. Events reported grouped by MedDRA® Higher Level Term (HLT) according to age group

MedDRA® Higher Level Term	Total cohort N=2092 n(%)	<5 years N=443 n(%)	5-12 years N=219 n(%)	>12 years N=1415 n(%)
Anaemias NEC	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Anal and rectal signs and symptoms	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Anxiety symptoms	4(0.19%)	1(0.23%)	0(0%)	3(0.21%)
Apocrine and eccrine gland disorders	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Appetite disorders	44(2.1%)	17(3.84%)	5(2.28%)	22(1.55%)
Asthenic conditions	211(10.09%)	38(8.58%)	15(6.85%)	158(11.17%)
Bladder and urethral symptoms	4(0.19%)	0(0%)	0(0%)	4(0.28%)
Bone related signs and symptoms	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Breast signs and symptoms	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Breathing abnormalities	4(0.19%)	0(0%)	0(0%)	4(0.28%)
Cardiac signs and symptoms NEC	10(0.48%)	0(0%)	0(0%)	9(0.64%)
Circulatory collapse and shock	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Coughing and associated symptoms	9(0.43%)	6(1.35%)	0(0%)	3(0.21%)
Dermal and epidermal conditions NEC	6(0.29%)	2(0.45%)	1(0.46%)	3(0.21%)
Dermatitis and eczema	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Diarrhoea (excl infective)	25(1.2%)	8(1.81%)	3(1.37%)	14(0.99%)
Disturbances in consciousness NEC	33(1.58%)	6(1.35%)	4(1.83%)	23(1.63%)
Disturbances in initiating and maintaining sleep	14(0.67%)	4(0.9%)	1(0.46%)	8(0.57%)
Dyspeptic signs and symptoms	13(0.62%)	0(0%)	0(0%)	13(0.92%)
Ear disorders NEC	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Faecal abnormalities NEC	3(0.14%)	1(0.23%)	0(0%)	2(0.14%)
Febrile disorders	20(0.96%)	2(0.45%)	3(1.37%)	14(0.99%)
Feelings and sensations NEC	27(1.29%)	5(1.13%)	0(0%)	22(1.55%)
Flatulence, bloating and distension	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Fluid intake decreased	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Gastrointestinal and abdominal pains (excl oral and throat)	40(1.91%)	2(0.45%)	2(0.91%)	35(2.47%)
Gastrointestinal atonic and hypomotility disorders NEC	3(0.14%)	1(0.23%)	0(0%)	2(0.14%)
Gastrointestinal signs and symptoms NEC	7(0.33%)	0(0%)	1(0.46%)	6(0.42%)
General signs and symptoms NEC	2(0.1%)	2(0.45%)	0(0%)	0(0%)

Headaches NEC	65(3.11%)	4(0.9%)	4(1.83%)	57(4.03%)
Heart rate and pulse investigations	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Increased physical activity levels	8(0.38%)	0(0%)	0(0%)	6(0.42%)
Joint related signs and symptoms	3(0.14%)	0(0%)	0(0%)	3(0.21%)
Lacrimal disorders	2(0.1%)	0(0%)	0(0%)	1(0.07%)
Mental impairment (excl dementia and memory loss)	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Migraine headaches	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Muscle tone abnormalities	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Muscle weakness conditions	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Musculoskeletal and connective tissue pain and discomfort	10(0.48%)	0(0%)	1(0.46%)	9(0.64%)
Musculoskeletal and connective tissue signs and symptoms NEC	1(0.05%)	1(0.23%)	0(0%)	0(0%)
Nasal congestion and inflammations	1(0.05%)	0(0%)	1(0.46%)	0(0%)
Nausea and vomiting symptoms	76(3.63%)	24(5.42%)	10(4.57%)	42(2.97%)
Neurological signs and symptoms NEC	93(4.45%)	2(0.45%)	4(1.83%)	86(6.08%)
Ocular disorders NEC	5(0.24%)	3(0.68%)	1(0.46%)	1(0.07%)
Ocular infections, inflammations and associated manifestations	4(0.19%)	3(0.68%)	0(0%)	1(0.07%)
Oedema NEC	2(0.1%)	0(0%)	0(0%)	1(0.07%)
Oral soft tissue pain and paraesthesia	4(0.19%)	2(0.45%)	1(0.46%)	1(0.07%)
Pain and discomfort NEC	30(1.43%)	0(0%)	0(0%)	29(2.05%)
Paraesthesias and dysaesthesias	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Physical examination procedures	23(1.1%)	15(3.39%)	4(1.83%)	4(0.28%)
Pruritus NEC	41(1.96%)	1(0.23%)	4(1.83%)	36(2.54%)
Rashes, eruptions and exanthems NEC	14(0.67%)	3(0.68%)	1(0.46%)	10(0.71%)
Rate and rhythm disorders NEC	4(0.19%)	0(0%)	0(0%)	3(0.21%)
Rubeola viral infections	1(0.05%)	1(0.23%)	0(0%)	0(0%)
Salivary gland disorders NEC	2(0.1%)	0(0%)	1(0.46%)	1(0.07%)
Sensory abnormalities NEC	15(0.72%)	0(0%)	0(0%)	15(1.06%)
Site specific vascular disorders NEC	2(0.1%)	2(0.45%)	0(0%)	0(0%)
Skin structures and soft tissue infections	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Social issues	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Soft tissue disorders NEC	2(0.1%)	0(0%)	1(0.46%)	1(0.07%)
Speech and language abnormalities	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Therapeutic and non-therapeutic responses	11(0.53%)	1(0.23%)	4(1.83%)	6(0.42%)
Tongue disorders	1(0.05%)	0(0%)	0(0%)	1(0.07%)

Tongue signs and symptoms	1(0.05%)	0(0%)	0(0%)	1(0.07%)
Tremor (excl congenital)	2(0.1%)	0(0%)	0(0%)	2(0.14%)
Upper respiratory tract infections	7(0.33%)	2(0.45%)	0(0%)	5(0.35%)
Upper respiratory tract signs and symptoms	4(0.19%)	1(0.23%)	0(0%)	3(0.21%)
Urinary abnormalities	8(0.38%)	3(0.68%)	0(0%)	5(0.35%)
Urinary tract signs and symptoms NEC	1(0.05%)	0(0%)	1(0.46%)	0(0%)
Urticarias	2(0.1%)	1(0.23%)	0(0%)	1(0.07%)
Visual disorders NEC	1(0.05%)	0(0%)	0(0%)	1(0.07%)

Abbreviations: ART: artemisinin; ASAQ: artesunate-amodiaquine; ACT: artemisinin-combination therapy; NEC: not elsewhere classified

Table 5. Events (MedDRA®- Preferred Term) reported in under-5's according to the treatment prescribed

Preferred Term	Total N=441[a]	AQ n=70 *n (%)*[b]	Artemether n=13 *n (%)*	Artemether +AQ n=41 *n (%)*	AS n=3 *n (%)*	DHA n=61 *n (%)*	DHA + AQ n=138 *n (%)*	ASAQ n=113 *n (%)*
Asthenia	**35**	3 (4.3)	1 (7.7)	1 (2.4)	1 (33.3)	3 (4.9)	10 (7.2)	16 (14.2)
Vomiting	**24**	1 (1.4)	1 (7.7)	-	-	4 (6.6)	9 (6.5)	9 (8.0)
Anorexia	**17**	-	-	1 (2.4)	-	2 (3.3)	6 (4.3)	8 (7.1)
Pyrexia	**14**	2 (2.9)	-	1 (2.4)	-	2 (3.3)	2 (1.4)	7 (6.2)
Diarrhoea	**8**	1 (1.4)	-	4 (9.8)	-	1 (1.6)	2 (1.4)	-
Cough	**6**	2 (2.9)	-	-	-	1 (1.6)	2 (1.4)	1 (0.9)
Feeling of body temperature change	**4**	1 (1.4)	-	1 (2.4)	-	-	1 (0.7)	1 (0.9)
Headache	**4**	1 (1.4)	-	1 (2.4)	-	1 (1.6)	-	1 (0.9)
Insomnia	**4**	2 (2.9)	-	-	-	-	2 (1.4)	-
Sedation	**3**	2 (2.9)	-	-	-	-	1 (0.7)	-
Malaise	**2**	-	-	1 (2.4)		1 (1.6)	-	-
Ocular hyperaemia	**2**	-	-	1 (2.4)	-	-	1 (0.7)	-
Oral pain	**2**	1 (1.4)	-	-	-	-	1 (0.7)	-
Pruritus	**2**	-	-	-	-	-	1 (0.7)	1 (0.9)
Rash generalised	**2**	1 (1.4)	-	-	-	-	1 (0.7)	-
Pallor	**2**	-	-	-	-	-	2 (1.4)	-
Nasopharyngitis	**2**	-	-	-	-	-	2 (1.4)	-
Abdominal pain upper	**1**	-	-	-	-	-	1 (0.7)	-
Anxiety	**1**	1 (1.4)	-	-	-	-	-	-
Crying	**1**	-	-	-	-	-	-	1 (0.9)
Dizziness	**1**	-	-	-	-	-	-	1 (0.9)
Eye swelling	**1**	-	-	1 (2.4)	-	-	-	-
Faeces discoloured	**1**	-	-	1 (2.4)	-	-	-	-
Fatigue	**1**	1 (1.4)	-	-	-	-	-	-
Feeling hot	**1**	1 (1.4)	-	-	-	-	-	-
Loss of consciousness	**1**	-	-	-	-	-	1 (0.7)	-
Measles	**1**	-		-	-	-	1 (0.7)	-
Musculoskeletal stiffness	**1**	-	-	1 (2.4)	-	-	-	-
Ocular icterus	**1**	-	-	-	-	-	1 (0.7)	-
Pain of skin	**1**	-	-	-	-	-	-	1 (0.9)
Pharyngolaryngeal pain	**1**	-	-	-	-	-	-	1 (0.9)
Skin discolouration	**1**	-	-	-	-	-	1 (0.7)	-
Somnolence	**1**	-	-	-	-	-	1 (0.7)	-
Urticaria	**1**	-	-	-	-	-	-	1 (0.9)
Weight decreased	**1**	-	-	-	-	-	1 (0.7)	-

[a]Chloroquine (n=1) and DHA + artemether + lumefantrine (n=1) were administered but patients did not report of experiencing any AE; [b]% are percentages of adverse events (n) reported within each treatment group; ASAQ= artesunate-amodiaquine; DHA = dihydroartemisinine; AQ = amodiaquine; AS=artesunate

Table 6. Event terms reported by patients to the hospital and MedDRA®- Preferred Term.

Reported term	**Preferred Term**	**Total N=60**	**ASAQ** n=27	**Non-ASAQ ACTs** n=5	**Monotherapy** n=28
Dizziness	Dizziness	**17**	8	2	7
Abdominal pain upper	Abdominal pain upper	**15**	11	-	4
Pyrexia	Pyrexia	**13**	5	-	8
Vomiting	Vomiting	**12**	2	3	7
Bodily aches and pains	Pain	**11**	8	-	3
Headache	Headache	**10**	3	-	6
Diarrhoea	Diarrhoea	**9**	5	2	2
Cough	Cough	**9**	3	-	6
General weakness	Asthenia	**8**	3	2	3
Rash generalised	Rash generalised	**7**	2	1	4
Loss of appetite	Anorexia	**7**	2	1	4
Bitterness in mouth	Dysgeusia	**4**	3	-	1
Palpitation	Palpitation	**4**	3	-	1
Nausea	Nausea	**4**	2	-	2
Insomnia	Insomnia	**3**	1	-	2
Pruritus	Pruritus	**3**	2	-	1
Chills	Chills	**3**	3	-	-
Waist pain	Myalgia	**3**	2	-	1
Yellow-coloured urine	Chromaturia	**2**	-	1	1
Jaundice	Ocular icterus	**1**	-	1	-
Numbness of fingers	Hypoesthesia	**1**	1	-	-
Sore mouth	Oral pain	**1**	1	-	-
Tremor	Tremor	**1**	1	-	-
Feeling cold	Feeling cold	**1**	1	-	-
Fainting	Loss of consciousness	**1**	1	-	-
Salivary hypersecretion	Salivary hypersecretion	**1**	-	-	1
Constipation	Constipation	**1**	1	-	-
Chest pains	Chest pains	**1**	1	-	-
Ear pain	Ear pain	**1**	1	-	-
Weight decreased	Weight decreased	**1**	1	-	-
Back pain	Back pain	**1**	1	-	-