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ORIGINAL RESEARCH ARTICLE

Safety Experience During Real-World Use of Injectable Artesunate in Public Health Facilities in Ghana and Uganda: Outcomes of a Modified Cohort Event Monitoring Study (CEMISA)

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Abstract

Introduction Injectable artesunate (Inj AS) is the World Health Organization (WHO)-recommended product for treating severe malaria. However, despite widespread usage, there are few published safety studies involving large populations in real-world settings. In this study, we sought to assess the incidence of common adverse events (AEs) following the intake of Inj AS in real-life settings.

Methods This is a modified cohort event monitoring study involving patients who were administered with Inj AS at eight sites (four each in Ghana and Uganda) between May and December 2016. Patients were eligible for inclusion if they had severe/complicated malaria and were able and willing to participate in the study. Eligible patients were followed up by telephone or hospital or home visit on Days 7, 14, 21 and 28 after drug administration to document AEs and serious AEs (SAEs). Patients were also encouraged to report all AEs at any time during the study period. The Kaplan–Meier method was used to estimate the proportion of patients with any AEs by end of Day 28. Causality assessment was made on all AEs/SAEs using the WHO/UMC (Uppsala Monitoring Centre) causality method.

Results A total of 1103 eligible patients were administered Inj AS, of which 360 patients were in Ghana and 743 in Uganda. The incidence of any AE by the end of follow-up among patients treated with AS was estimated to be 17.9% (197/1103) (95% confidence interval [CI] 15.8–20.3). The median time-to-onset of any AEs was 9 days (interquartile range (IQR) = 4, 14). The top five AEs recorded among patients treated with AS were pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). Most of these top five AEs occurred in the first 14 days following treatment. Regarding the relatedness of these AEs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related. There were 17 SAEs including 13 deaths. Two of the deaths are 'possibly' related to Inj AS, as were three non-fatal SAEs: severe abdominal pain, failure of therapy and severe anaemia.

Conclusion The incidence of common AEs among patients treated with Inj AS in real-world settings was found to be relatively low. Future studies should consider larger cohorts to document rare AEs as well.

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Key Points

Injectable artesunate (Inj AS) is a life-saving medicine used to treat severe malaria.

There are few data on the safety of Inj AS when used in real-world settings, though it has been shown to be well-tolerated in clinical trials.

Safety data obtained from public health facilities in Ghana and Uganda support the safety findings from clinical trials and provide additional evidence for continued use of Inj AS in severe malaria.

1 Introduction

Severe malaria is a life-threatening condition responsible for a significant part of the 445,000 global malaria deaths that occurred in 2016 alone [1]. When not treated, the case fatality rate for severe malaria can be very high. Severe malaria is the harshest form of the disease. In addition to the symptoms of uncomplicated malaria such as fever, parasitaemia and malaise, severe malaria also manifests with one or more of the following: severe anaemia, acute renal failure, respiratory oedema, hypoglycaemia or coma. Published fatality rates for severe malaria vary widely due to study design, treatment practices and patient types. Fatality rates are typically around 16–20% but rates as low as 2% and high as 100% have been reported [2]. With prompt and effective treatment, case fatality rates can fall as low as 10% [2] or below. The current edition of the World Health Organization (WHO) *Guidelines for the Treatment of Malaria* (2015, third edition) [3] recommends injectable artesunate (Inj AS) (ATC [Anatomical Therapeutic Chemical] code P01BE03) as the treatment of choice for severe malaria. The SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial) [4] and AQUAMAT (Artesunate Versus Quinine in the Treatment of Severe Falciparum Malaria in African Children) [5] studies showed reductions in fatality of 34.7% and 22.5%, respectively, when Inj AS was used to treat severe malaria instead of injectable quinine. In these studies, the use of Inj AS was also associated with fewer adverse events (AEs) than quinine. Systematic reviews [6, 7] have also demonstrated lower case fatality rates and lower AE profiles with Inj AS than with quinine. For years, parenteral quinine remained the main drug for treating severe malaria, but its usage is associated with problems in reconstitution and administration [8]. Quinine needs to be administered slowly as a constant intravenous (IV) infusion, a process which is difficult in most settings. It may also be given intramuscularly (IM) but IM administration is associated with erratic availability and poor clinical outcomes. In addition to these, the use of quinine is associated with several AEs including cinchonism, rashes, rare cardiotoxicity, deafness, hypoglycaemia, dizziness, blindness and even death [9, 10]. These factors prompted the WHO policy change and subsequent recommendation for the use of Inj AS for treating severe malaria.

The current data on the efficacy and clinical safety of Inj AS have all been obtained in well-controlled clinical trials or during operational research [6, 11–15]. The recruitment of patients in such settings is controlled and patient follow-up and management is stringent in these studies; hence, safety information obtained may not reflect what occurs in real life. There is a dearth of information on the safety of Inj AS when used in real-world (post-approval, routine healthcare practice) settings even though a signal—post-artesunate delayed haemolysis (PADH)—has been raised following identification of a number of delayed haemolysis cases after treatment with Inj AS [16–18].

Inj AS is an extremely important life-saving product in the treatment of severe malaria across all 91 malaria-endemic countries and across all malaria transmission zones [1, 19]. It is used extensively in imported or traveller's malaria in non-endemic countries, where it has been associated with very high reduction in mortality with few reports of drug-related AEs [20]. Despite the assurance given by the available studies on the safety of Inj AS, the absence of strong pharmacovigilance systems in countries that use millions of doses of the product annually makes it necessary to undertake appropriate post-authorisation studies in order to better understand its actual safety profile when used in real-world settings. This study was therefore conceived to obtain safety data in relation to Inj AS when used in real-world settings in public health facilities in two African countries where severe malaria may or may not be properly diagnosed (microscopy; rapid diagnostic tests [RDTs]; laboratory measurement of haemoglobin [Hb]) and where facilities for monitoring and follow-up are variable.

The specific objective of the study was to determine the incidence of any AEs that occur up to 28 days after administration of Inj AS for the treatment of severe/complicated malaria during the normal course of clinical practice in the participating health facilities. The findings from this study should contribute to the WHO global individual case safety report (ICSR) database VigiBase™ and facilitate quicker identification of safety signals. Currently, VigiBase™ has very little data from Africa that includes data on antimalarials [21, 22].

2 Methods

2.1 Study Design, Sites and Patient Recruitment

This was a prospective, longitudinal, modified cohort event monitoring study in sub-Saharan Africa (CEMISA) which utilises the principles of prescription event monitoring [23] but with cohorts smaller than the minimum 10,000 patients. The study recruits patients in secondary care settings similar to the approach adopted in specialised cohort event monitoring [24]. In this study, the cohort consisted of patients who were prescribed Inj AS for presumed or diagnosed severe malaria between May 2016 and December 2016 in two countries (Ghana and Uganda). The study was undertaken in four public health facilities in Ghana (Princess Marie Louise Hospital and Ridge Hospital, Accra; Kintampo Municipal Hospital, Kintampo and Agogo Medical Research Hospital, Agogo) and four public health facilities in Uganda (Mubende Regional Referral Hospital, Mubende; Jinja Referral Hospital, Jinja; Lira Regional Referral Hospital, Lira and Kagadi Hospital, Kagadi).

Patients were eligible for inclusion if they had severe/complicated malaria (*Plasmodia* of any species) presumed or diagnosed as per national policies and health facility practice/protocol [3]; if they were able and willing to participate in the study; and if they agreed to the schedule for follow-up contact or home visits. Patients were excluded if they had a serious concurrent illness. All eligible patients gave informed consent. For children, informed consent was obtained from parents or a caregiver/guardian.

Case Report Forms (CRFs) were used to record data on each study subject during the study as defined by the protocol. All events that happened in the study were fully documented in the CRF. The CRFs consisted of the day 1A form, drug administration form, follow-up forms (Days 7, 14, 21 and 28), AE form, SAE form and the end of study form. The day 1A form served as the enrolment form on the first day of the study. It was the form used after the participant or representative signed the informed consent to record demographic, medical history and laboratory data. The drug administration form was used to record the drug under investigation administered to the participant and all other concomitant medications. The AE form was used to record all AEs and the SAE form was used to record events that met the seriousness criteria. The Day 7 to Day 28 follow-up forms were used to record the participant's current health status and any new concomitant medications. Finally, the end of study form was used to record the primary reason for the termination from the study. A completed CRF after going through the various validations and data quality checks is then prepared for entry into the study database.

Patients were followed up to document the occurrence of any AEs using standard questions on the follow-up CRFs. Patients were followed up by telephone or hospital or home visit, when possible, on Days 7, 14, 21 and 28 after drug intake (index date) and were asked to report all AEs at any time during the 28-day follow-up period. The 28-day follow-up period was adopted in line with the follow-up period adopted for malaria clinical trials [25] as well as previous studies on the safety of antimalarials [26]. No attempt was made to intervene in routine care of any of the recruited patients in the study apart from monitoring the safety of the antimalarial agents administered by the treating clinicians by collecting data from consenting patients directly and sometimes also from their clinical notes. Hb levels, when measured, were also recorded. Any patient with AEs was managed in line with existing standard of care in each of the participating facilities.

2.2 Definitions

The following definitions are based on the European Union's Guidelines on Good Pharmacovigilance Practice.

2.2.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical investigation participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

2.2.2 Serious AE (SAE)

An SAE means an AE that results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

2.3 Data Collection, Drug Prescription and Dosing

Routine clinical practice in malaria-endemic countries requires immediate treatment of patients with suspected clinical malaria in line with WHO *Guidelines for the Treatment of Malaria* [3]. Treatment of severe malaria occurs usually in in-patient settings. All study participants were recruited from hospitals. The implication for this study, therefore, was that most patients had started

treatment before being recruited into the study. IM/IV artesunate was administered as per normal practice in the treating institutions. The actual dosage and duration of treatment as well as any concomitant medications were extracted from the patient's clinical notes and recorded on the study CRFs. The WHO recommendation [3] for treating severe malaria is to "treat all adults and children with severe malaria (including infants, pregnant women in all trimesters, lactating women) with intravenous or intramuscular artesunate for at least 24 h. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT [artemisinin-based combination therapy]". We also collected data on mode of malaria diagnosis (i.e. clinically, microscopically or by the use of RDTs). Other co-variables collected included laboratory investigations conducted (including Hb measurements). Data were entered, managed and stored in a specially created version of MedSpina™, an in-house electronic health records system that allows clinicians and other health workers to collect patients' data, including laboratory results, to facilitate patient care.

2.4 Outcome and Causality Measurement

The outcomes measured in the study were all AEs temporarily associated with the intake of Inj AS, including deaths and other SAEs. Assessment of causality included, where available, the level of parasitaemia as well as any concomitant medications administered. Since this was a non-interventional study, there was no systematic laboratory investigation to document AEs. However, all events reported or available in the patient's notes, including laboratory data, were extracted and recorded in the CRFs. Using the WHO/UMC (Uppsala Monitoring Centre) causality method, a physician and a pharmacist not involved in the direct care of the participants assessed the relatedness and causal link of the medicine to the AEs.

2.5 Sample Size Calculation

The study was powered to estimate the incidence of AEs with a certain level of precision in Ghana and Uganda. We assumed that the incidence of any AEs in the Ghanaian and Ugandan population was, on average, 20%. We therefore required a total of 3164 patients in the two countries to produce a two-sided 95% confidence interval (CI) for the ratio of population proportions with a width that is equal to 0.200 when the estimated sample proportion decreases to 0.12 and the ratio of the sample proportions is 0.60. Due to available funding, we planned to enrol a cumulative sample size of 1000 patients receiving Inj AS from all participating countries in the first part of this study with the additional number of 2164 expected in the second part. The 1000 patients produces a two-sided 95% CI with a width equal to 0.050 when the incidence of any AE is 20% as we have assumed.

2.6 Data Analysis

We summarized patients' characteristics using proportion (nominal scale variables) and mean or median (interval scale variables). We calculated the incidence of any AEs as the total number of any AEs recorded by end of follow-up divided by the total number of patients treated with AS and who completed the study. The Kaplan–Meier method was used to estimate the proportion of patients with any AEs by the end of Day 28. The date of treatment was considered as the origin (i.e. the date the patient was at risk of any AE). The patient was censored at the date the patient was last seen (i.e. lost to follow-up) or at the end of the study without any AE.

Since the study was designed to have a cumulative sample size of 1000 patients on Inj AS from all participating countries (Part 1), with the eventual number of 3164 expected in Part 2, we considered site (country) as a fixed effect and therefore we did not present results for each country. All analyses were performed using STATA® 14 MP (StataCorp, College Station, TX, USA). Case summaries were also presented for all SAEs, including deaths and their relatedness to Inj AS as well as the causality assessment gradings.

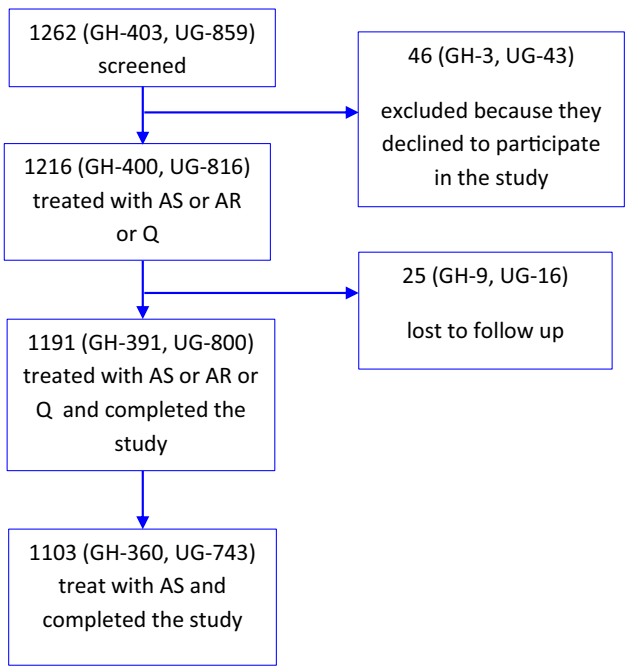

Fig. 1 Patient flow. *AE* adverse event, *AR* artemether, *AS* artesunate, *GH* Ghana, *Q* quinine, *UG* Uganda

3 Results

3.1 Characteristics of Participants and Treatment Received

A total of 1262 patients were screened, of whom 46 were excluded for declining to participate in the study (Fig. 1). Of the 1216 eligible patients, 25 were lost to follow-up and 88 were treated with either artemether or quinine, making them ineligible for analysis. There were 1103 patients who were treated with Inj AS (360 in Ghana and 743 in Uganda) (Table 1) and completed the study. The median age of patients was 3.9 years (interquartile range [IQR] = 2.1, 9) and the median weight was 13 kg (IQR = 10, 20) (Table 1).

3.2 Patient Follow-Up and Recording of Haemoglobin Readings

Most patients were followed-up by way of telephone calls. Of the 1103 individuals treated with Inj AS, 894 (81.1%) were followed up by telephone calls, 88 (8.0%) by home visits and 63 (5.7%) by hospital visits. In 58 (5.3%) follow-ups, the mode was not indicated. In relation to Day 14 follow-ups, 874 (79.2%) were by telephone calls, with 88 (8.0%) and 82 (7.4%) being by way of home visits or in hospital, respectively. Day 21 follow-ups followed a similar pattern, with 932 (84.5%) by telephone calls, 82 (7.4%) by home visits and 38 (3.4%) by hospital visits. In relation to Hb readings, there was marked differences between Ghana and Uganda. In the Ghana sites, baseline Hb was measured for 327 of the 360 patients, representing 90.8% of the patients. Seven patients in Ghana had Hb values recorded on both Day 0 and Day 14, and in all these cases the Hb values rose from baseline, indicating remission of anaemia. In Uganda, only 106 (14.3%) of the 743 patients had Day 0 Hb recorded and only one patient had Day 14 Hb recorded.

3.3 Incidence of Any AEs

The incidence of any AE by the end of follow-up among patients treated with Inj AS was estimated to be 17.9 (i.e. 197 of 1103) (95% CI 15.8–20.3) (Table 1 and Fig. 2). The

Table 1 Incidence of any adverse events by baseline characteristics of patients, 2016

Characteristics	Median (IQR)	Number of patients (% of total)	*n* (%) who had any AE	95% CI
Sex				
Female		540 (49.0)	96 (17.8)	14.8–21.2
Male		563 (51.0)	102 (18.1)	15.1–21.5
Age (years)	3.9 (2, 9)			
< 5		654 (59.3)	115 (17.6)	14.8–20.7
5–9		186 (16.9)	24 (12.9)	8.8–18.5
10–19		61 (5.5)	10 (16.4)	9.0–27.9
15–19		40 (3.6)	10 (25.0)	14.0–40.6
20–24		46 (4.2)	10 (21.7)	12.1–35.9
25+		114 (10.3)	29 (25.4)	18.3–34.2
Missing		2 (0.2)		
Weight (kg)	13 (10, 20)			
< 10		255 (23.1)	49 (19.2)	14.8–24.5
10–19		470 (42.6)	72 (15.3)	12.3–18.9
20–29		105 (9.5)	14 (13.3)	8.1–21.3
30+		184 (16.7)	36 (19.6)	14.4–25.9
Missing		89 (8.1)		
Time-to-onset of AE (days)	9 (4, 14)			
Site				
Ghana		360 (32.6)	125 (16.8)	14.3–19.7
Uganda		743 (67.4)	73 (20.3)	16.4–24.8
Pregnant				
No		1067 (96.7)	193 (18.1)	15.9–20.5
Yes		68 (3.3)	5 (13.9)	5.9–29.3
Total		1103 (100)	197 (17.9)	15.8–20.3

AE adverse event, *CI* confidence interval, *IQR* interquartile range

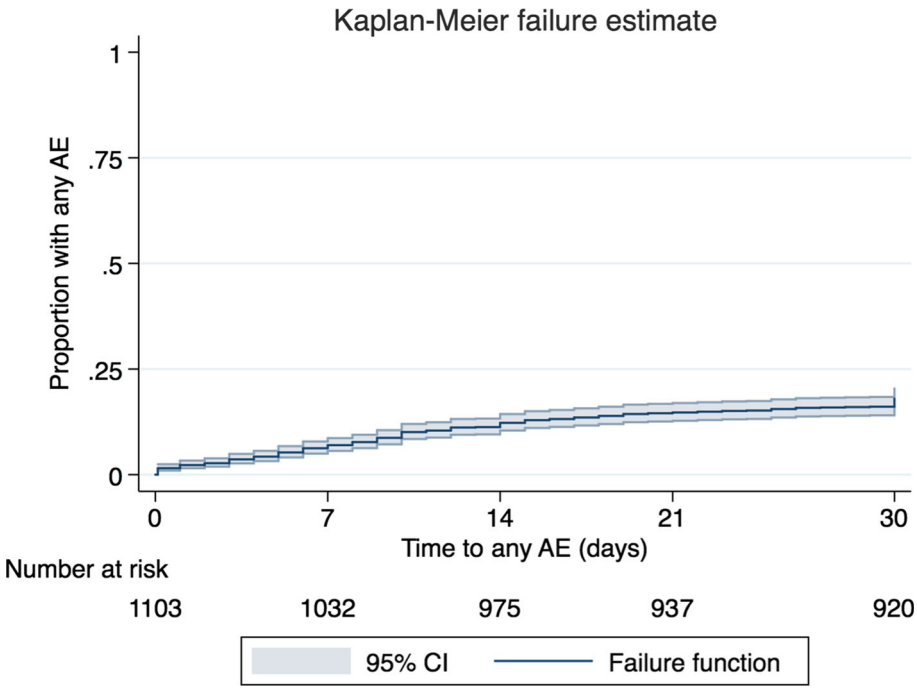

Fig. 2 Proportion of patients with any adverse events by time, 2016: Kaplan–Meier failure estimate. *AE* adverse event, *CI* confidence interval

Table 2 Top five adverse events by sex and time-to-onset among patients treated with injectable artesunate at all sites, 2016

	Number of patients treated with Inj AS	AE [*n* (%)]				
		Pyrexia	Abdominal pain	Diarrhoea	Cough	Asthenia
Sex	1103					
Female	540	16 (3.0)	13 (2.4)	6 (1.1)	9 (1.7)	8 (1.5)
Male	563	22 (3.9)	14 (2.5)	13 (2.3)	7 (1.2)	8 (1.4)
Time-to-onset of AE (days)	198					
0–7	77	11 (14.3)	12 (15.6)	6 (7.8)	5 (6.5)	9 (11.7)
8–14	58	12 (20.7)	4 (6.9)	8 (13.8)	5 (8.6)	6 (10.3)
15–21	27	7 (25.9)	2 (7.4)	3 (11.1)	4 (14.8)	1 (3.7)
22–28	36	8 (22.2)	9 (25.0)	2 (5.6)	2 (5.6)	0 (0.0)
Total	1103	38 (3.5)	27 (2.5)	19 (1.7)	16 (1.5)	16 (1.5)

AE adverse event, *Inj AS* injectable artesunate

median time-to-onset of any AEs was 9 days (IQR = 4, 14) (Table 1). The top five AEs recorded among patients treated with Inj AS were pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%) (Table 2 and Fig. 3). Most of these top five AEs occurred in the first 14 days following treatment (Table 2). Regarding the relatedness of these AEs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of abdominal pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related.

3.4 SAEs Including Deaths

During the study, 17 AEs were considered to be serious; 13 of these led to death. The deaths and the four other SAEs are described in Table 3. Four of the deaths occurred in seriously ill patients who were transferred from the hospital to their home with no further follow-up information due to the reluctance of carers/guardians and/or family members to provide any further information. Two others had no post-mortem information even though follow-up information with family members confirmed death.

4 Discussion

This is the first large-scale post-approval safety study on Inj AS. It involved over 1100 patients who were exposed to at least one dose of Inj AS in the participating public health facilities in Ghana and Uganda. The majority of the

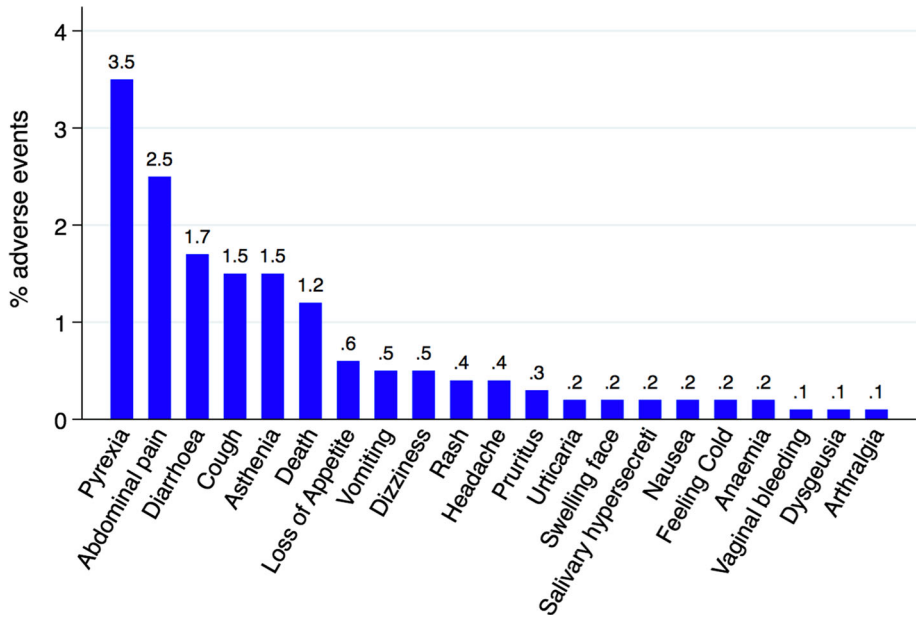

Fig. 3 Adverse events among patients treated with injectable artesunate at all sites, 2016

Table 3 Deaths and other serious adverse events reported in patients treated with injectable artesunate

Event type	*n*	Relationship to Inj AS intake
Deaths	13	4 of the 13 deaths did not have SAE specified and patients died outside the hospital with little information on follow-up. These reports are classified as 'unassessable'. 2 of the remaining 9 fatal SAEs (severe anaemia in a 22-month-old female and severe anaemia in a 20-month-old female) are causally assessed as 'possible' in relation to Inj AS intake. These SAEs are classified as 'related' to Inj AS, though disease and other conditions could also explain these SAEs. The remaining 7 fatal SAEs (multi-organ failure, severe respiratory distress, abdominal distension, asthenia, sickle cell disease, severe anaemia, pulmonary tuberculosis) are unrelated to Inj AS intake
Other SAEs	4	3 of the 4 SAEs—severe abdominal pain in a 42-year-old female; failure of therapy and severe anaemia in a sickle cell disease patient—are causally assessed as 'possible' in relation to Inj AS intake and thus related to Inj AS. 1 case—threatened abortion—is considered to be causally assessed as 'unlikely' to be attributable Inj AS intake and is thus unrelated

Inj AS injectable artesunate, *SAE* serious adverse event

participants were children, with 59.3% being less than 5 years old. Inj AS was very well-tolerated among the study population even though nearly one-fifth of participants reported at least one mild to moderate AE. The most common AEs reported in both countries included pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). The relationship between Inj AS and most of these events were classified as 'possible' following case causality assessment. There were 13 all-cause deaths reported in this study, giving an all-cause death rate of 1.2% (13/1103). Two of the deaths could be 'possibly' related to Inj AS. There were four other SAEs in addition to the deaths. Three of the non-fatal SAEs were 'possibly' related to Inj AS. Overall, the safety profile of Inj AS in the study population was favourable and comparable to that documented in the SEAQUAMAT and AQUAMAT studies.

The results obtained from this study are similar to the findings from clinical trials of Inj AS, including the SEAQUAMAT and AQUAMAT studies. The overall incidence of AE is similar to that listed in the public assessment reports (PARs; Part 4: Summary of Product Characteristics) for Inj AS, as published by the WHO [27]. The PAR lists the following among the possible common (1–10 in 100 patients) AEs related to Inj AS: cough, diarrhoea, abdominal pain and 'flu-like' effects (including fever, tiredness, bone and muscle pain). These AEs are, however, also symptoms of malaria and severe malaria, making case causality assessment complex. Nonetheless, the study findings provide validation for the safety profile of Inj AS as recorded in the PAR. This study recorded a lower proportion of deaths than the AQUAMAT and SEAQUAMAT studies. In the AQUAMAT study, 8.5% of the 2712 patients in the artesunate arm died (230 African children), whilst 15% of the 730 patients in the artesunate arm of the SEAQUAMAT study died (107 Asian patients) [4, 5]. It is important to state that, in contrast to our study, the SEAQUAMAT and AQUAMAT studies involved

patients who had been clinically diagnosed with severe malaria. In our study we did not apply a strict definition of diagnosis of severe malaria as the aim was to follow patients who had been administered Inj AS in the 'normal course of clinical practice'. It is, therefore, possible that several of the cases in our study are not necessarily severe malaria, a serious disease with relatively high mortality. The lower mortality of 1.1% obtained in this study compares with a similar study [28] in Africa where an overall mortality of 1.03% (2/194) was recorded, though it must be stressed that reported mortality in severe malaria varies widely due to differences in practices, including not applying strict criteria for the definition of severe malaria [29]. Our study had two reports of severe anaemia which may be potential cases of PADH. PADH occurs 14 days after artesunate intake and has other features. However, the absence of pre-Day 14 Hb readings in the two cases made a definite diagnosis of PADH fundamentally impossible.

This work has provided evidence indicating a favourable toxicity profile of Inj AS in real-world settings and one that is similar to that observed in earlier studies. However, it suffered from the limitations of most real-world studies. For instance, patients were enrolled if they had been administered at least one dose of Inj AS, presumably for the treatment of severe malaria. However, the majority of the patients were enrolled without any Hb readings and diagnosis of severe malaria was purely based on RDT and/or microscopy. Even in cases where microscopy or RDT showed absence of malaria parasites, the patients were still administered Inj AS. The safety profile of Inj AS would not necessarily be expected to be different in patients with the potentially deadly severe malaria than in patients without severe malaria, though the outcomes of treatment may differ. Another limitation of the study was the absence of baseline and Day 14 Hb values. Whilst there were 327 (91%) Day 0 Hb readings in Ghana, there were only seven (1.8%) Day 14 Hb readings in this same cohort. In Uganda, there were only 106 (14.3%) Day 0 Hb readings and one (0.1%) Day 14 Hb reading. Thus, in most of the participating facilities, most patients did not have more than one recorded Hb reading from the time of administration of Inj AS to the time the patient exited the study. This made it impossible to know whether there had been any drug-related changes in Hb values post-administration. Thus, even though very low levels of Hb were recorded in a few patients on Day 14, it was impossible to know whether this represented an existing severe anaemia or an actual fall due to Inj AS and which could thus have been a potential case of PADH. Another challenge in this real-world study was not being able to obtain follow-up information on four patients who died at home. The family/carers were not willing to provide any information, making it impossible to make any causal relationship. Finally, this study was not powered to detect rare AEs since the sample size of 1103 can only detect common AEs. It will be important to expand the study further in order to capture rare AEs in real-world settings. However, this follow-up study should, as a matter of ethics and for public health considerations, include a revision in the protocol for Hb readings to be made at baseline or soon thereafter and also at Day 14 to capture essential data to address the issue of PADH, which is a signal that has been raised in association with Inj AS use.

This study has provided additional information on the safety of Inj AS to that given in the pivotal studies that led to the WHO recommendation for its use as the medicine of choice in severe malaria. The incidence and types of AEs and SAEs observed in this study validates the WHO recommendation.

5 Conclusion

The incidence of common AEs among patients treated with Inj AS in real-world settings was relatively low. The overall safety profile of Inj AS among the treatment cohort was favourable. An interventional study to address PADH would be useful. Future studies should consider larger cohort to document rare AEs as well.

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