Ferrari et al. Malaria Journal (2015) 14:226
DOI 10.1186/s12936-015-0732-1

MALARIA JOURNAL

RESEARCH Open Access

An operational comparative study of quinine and artesunate for the treatment of severe malaria in hospitals and health centres in the Democratic Republic of Congo: the MATIAS study

Giovanfrancesco Ferrari[1,2*], Henry M. Ntuku[3], Christian Burri[1,2], Antoinette K. Tshefu[3], Stephan Duparc[4], Pierre Hugo[4], Didier K. Mitembo[1,2], Amanda Ross[1,2], Philippe L. Ngwala[5], Joseph N. Luwawu[6], Papa N. Musafiri[7], Symphorien E. Ngoie[8] and Christian Lengeler[1,2]

Abstract

Background: The Democratic Republic of the Congo (DRC) has the highest number of severe malaria cases in the world. In early 2012, the National Malaria Control Programme (NMCP) changed the policy for treating severe malaria in children and adults from injectable quinine to injectable artesunate. To inform the scaling up of injectable artesunate nationwide, operational research is needed to identify constraints and challenges in the DRC's specific setting.

Methods: The implementation of injectable quinine treatment in 350 patients aged 2 months or older in eight health facilities from October 2012 to January 2013 and injectable artesunate in 399 patients in the same facilities from April to June 2013 was compared. Since this was an implementation study, concurrent randomized controls were not possible. Four key components were evaluated during each phase: 1) clinical assessment, 2) time and motion, 3) feasibility and acceptability, and 4) financial cost.

Results: The time to discharge was lower in the artesunate (median = 2, 90 % central range 1–9) compared to the quinine group (3 (1–9) days; p <0.001). Similarly, the interval between admission and the start of intravenous (IV) treatment (2 (0–15) compared to 3 (0–20) hours; p <0.001) and parasite clearance time (23 (11–49) compared to 24 (10–82) hours; p <0.001) were lower in the artesunate group. The overall staff pre-administration time (13 (6–38) compared to 20 (7–50) minutes; p <0.001) and the personnel time spent on patient management (9 (1–24) compared to 12 (3–52) minutes; p <0.001) were lower in the artesunate group. In hospitals and health centres, the mean (standard deviation, SD) total cost per patient treated for severe malaria with injectable artesunate was USD 51.94 (16.20) and 19.51 (9.58); and USD 60.35 (17.73) and 20.36 (6.80) with injectable quinine.

Conclusions: This study demonstrates that injectable artesunate in the DRC is easier to use and it costs less than injectable quinine. These findings provide the basis for practical recommendations for rapid national deployment of injectable artesunate in the DRC.

Keywords: Malaria, Severe malaria, Democratic Republic of the Congo, DRC, Kinshasa, Injectable quinine, Injectable artesunate

* Correspondence: Giovanfrancesco.Ferrari@unibas.ch
[1]Swiss Tropical & Public Health Institute, Basel, Switzerland
[2]University of Basel, Basel, Switzerland
Full list of author information is available at the end of the article

Background

The Democratic Republic of the Congo (DRC) has the highest severe malaria burden in the world [1]. The combination of artesunate plus amodiaquine (AS-AQ) was adopted as a first-line treatment for uncomplicated malaria in 2005, with a second ACT, artemether plus lumefantrine (AL), added in 2010. Meanwhile, injectable quinine remained the recommended first-line drug for cases of treatment failure and for severe malaria.

In 2010, the AQUAMAT trial demonstrated that treating severe malaria with artesunate reduced the case fatality rate in African children (<15 years) by 22.5 % compared to treatment with injectable quinine [2]. Previously, the benefit of artesunate compared to quinine had been demonstrated in adults in the SEAQUAMAT trial carried out in Southeast Asia [3]. These results led to the recommendation of injectable artesunate as the treatment of first choice for severe malaria in children and adults in the WHO guidelines in 2011 [4]. Nevertheless, cases of delayed haemolytic anaemia secondary to injectable artesunate administration were reported and the causative role of artesunate is still controversial. Its long-term safety profile is under evaluation. In addition to its efficacy, injectable artesunate offers a number of programmatic advantages over quinine, such as eliminating the need for rate-controlled infusions or cardiac monitoring, and the risk of induced hypoglycaemia [4].

In 2012, the National Malaria Control Programme (NMCP) of the DRC, with support from the relevant ministry departments, decided to adopt the revised WHO severe malaria treatment guidelines, which strongly recommended injectable artesunate in preference to quinine or artemether as first-line treatment for severe malaria. An implementation period of three years to scale up injectable artesunate was included in the national strategic plan.

This transition will require many operational and clinical adaptations. To support this process, there is a need for locally derived operational experience addressing constraints and challenges, something that all implementing countries will have to consider. These data are essential for three reasons: 1) better planning of the implementation of the new treatment based on quantified operational parameters; 2) identifying constraints and pitfalls to guide the training of health care providers; and, 3) providing strong and locally relevant arguments in situations where the health staff are reluctant to accept the change of treatment.

The present MATIAS study ('MAlaria Treatment with Injectable ArteSunate') aims to support the national introduction of injectable artesunate as the first-line treatment of severe malaria in the DRC by assessing four key components: 1) clinical safety, 2) time and motion, 3) feasibility and acceptability, and 4) cost.

Methods

Study design

The MATIAS study was an observational implementation study of patients aged 2 months and older with severe malaria and included two successive phases. In the first phase, between October 2012 and January 2013, severe malaria patients were treated with intravenous (IV) quinine. Then, between April and June 2013, severe malaria patients were treated with IV artesunate.

Four components were evaluated in each phase: 1) clinical safety, assessed on the basis of limited routine patient information; 2) time and motion parameters; 3) feasibility and acceptability; and 4) financial costs. The results of the feasibility and acceptability component required additional in-depth studies and are reported elsewhere (Ntuku *et al.*, personal communication).

Participants (population, inclusion, exclusion criteria)

The study population consisted of patients admitted with severe malaria to one of the study sites between October 2012 and June 2013. Patients were included in the study if they were older than 2 months, fulfilled the WHO criteria of severe *Plasmodium falciparum* malaria [5], had either a positive rapid diagnostic test (RDT) for *P. falciparum* (SD Bioline Malaria Antigen P.f/Pan Standard Diagnostics Inc, Yongin, South Korea) and/or a positive Giemsa-stained thick blood smear on admission, and they or their relative or guardian gave informed written consent. Patients were excluded if they had a known serious adverse reaction to quinine and/or artemisinin derivatives, or if there was a history of adequate anti-malarial treatment for more than 24 h before admission. Women with known or suspected pregnancy in all trimesters during the second (artesunate) phase were not included and were treated with quinine according to the national guidelines [6]. Pregnancy status was determined by details from the patient's history and/or by a positive pregnancy test.

Signed informed consent for participation was obtained in French or in the local language from all participants or from their relatives or guardians. Because of the life-threatening nature of the disease, an initial consent was obtained from the accompanying relative or guardian on behalf of the patient, if necessary, and final consent was solicited as soon as the patient was able to decide and respond. Since this was an observational study, investigators did not intervene in patient management, which was left to the discretion of the attending physicians. Ethical clearance for the study was obtained from the Ethics Committee of both Cantons of Basel, Switzerland (EKBB, Ref No 201/12) and from the Ethics Committee of the Kinshasa School of Public Health (KSPH Ethics Commission, Ref No 057/12), University

of Kinshasa, DRC. The study was registered in ClinicalTrials.gov (Identifier: NCT01828333).

Study settings

The study sites consisted of three hospitals and five health centres in one urban and three rural health zones (HZs) in the DRC, representative of typical health facilities in the country (Fig. 1). The sample included a large public health hospital (Institut Médical Evangélique, Kimpese, Bas Congo); one medium-sized, non-profit, missionary hospital (St Luc Kisantu); and a medium-sized, government hospital (Centre Hospitalier Roi Baudouin). In addition, five rural health centres were selected within the same HZs (Health Centre Bita, Health Centre Menkao, Health Centre Ngeba, Health Centre CECO, Health centre La Famille) (Fig. 1 and Additional file 1).

Interventions

During the first phase, patients receiving IV quinine were treated according to the national treatment guidelines. An initial loading dose of 20 mg of quinine salt/kg in 5–10 ml isotonic glucose solution (5 %) per kg body weight was infused over 4 h. Following a rest period of 8 and 12 h after administration of the loading dose began, a maintenance dose of 10 mg of quinine salt/kg was given. The maintenance dose was repeated every 12 h until the patient was able to swallow the oral treatment [5, 7]. Patients receiving artesunate (Guilin Pharmaceuticals, Shanghai, China) received doses intravenously at 2.4 mg/kg on admission, at 12 and 24 h, and then once daily until oral treatment could be swallowed [5]. The content of each 60 mg vial of artesunate powder was dissolved in 1 ml of sodium bicarbonate and then diluted with normal saline solution or dextrose 5 % before IV injection [8, 9]. At least three doses of artesunate had to be given before switching to a full course of oral treatment. The drugs used for the study were provided for free by the manufacturer (Artesunate, Guilin Pharmaceutical Co. Ltd, Shanghai, China) and by the funding agency, Medicines for Malaria Venture (MMV) (quinine).

Study outcomes

Outcome measures were defined for each of the four study components. For the clinical assessment component, the outcomes were: 1) duration of hospitalisation, defined as the time from hospital registration to discharge, (this was the primary study endpoint); 2) time from hospital admission to start of parenteral treatment; 3) time from initiation of parenteral treatment to initiation of oral treatment; 4) parasite clearance time (PCT), defined as the time from the initiation of a patient's parenteral treatment until the patient's first negative blood film; and 5) clinical status at discharge. For the time and motion component, the main outcome measure was the cumulative staff time required for all steps of drug preparation, administration and patient management. For the feasibility and acceptability component, the main outcomes were health-provider perceived feasibility of patient management, perceived ease of applying drug treatment, and perceived quality of case management by patient/caretaker. These results are reported separately (Ntuku *et al.* in prep). For the financial

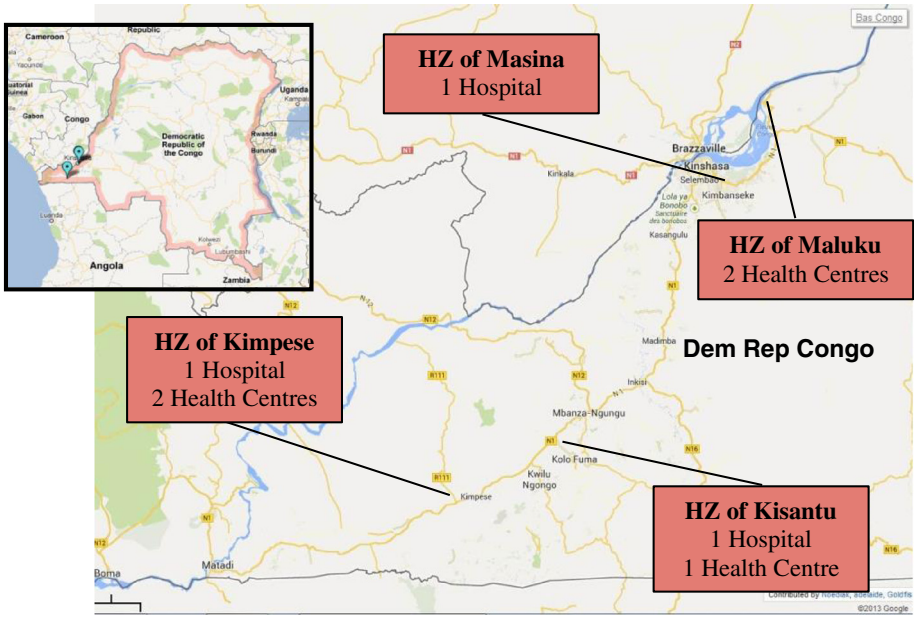

Fig. 1 Map showing the location of the study sites and the selected health zones

cost component, the main outcome was the total financial cost of patient management, including treatment.

Sample size calculation

The study sample size was calculated based on seven centres, a mean hospitalisation of 2.23 days (standard deviation of 1.64) [3], 80 % power and an assumed 20 % shorter hospital stay with injectable artesunate. This calculation yielded 25 patients per centre and study period. Under the assumption of an effect variation by centre with a standard deviation of 0.05, the required number per centre was corrected to 27. This effect was presumed to be moderate, as each centre acted as its own control in the study. The two-phase study design was selected to fit the implementation strategy in this area. To ensure a safety margin and to aid disaggregation of the data by centre, the number of patients to be recruited was finally set to 50 patients of all ages from each centre and per study phase. One of the sites initially selected was removed due to difficulties in initiating the study. However, due to recruitment numbers slightly below expectations during the quinine phase, two additional study centres were added. This amendment increased the number of treatment centres to eight.

Statistical methods

Continuous outcomes were described using their mean and standard deviation, or median and 90 % central range if the distribution was skewed. Dichotomous outcomes were summarized as proportions. Clinical characteristics are presented by age groups < 5 years and ≥ 5 years. Skewed data, such as the time to event outcomes, were compared using the non-parametric Wilcoxon rank sum test. The paper-based questionnaires were double-entered and validated in EpiData version 3.1 software (The EpiData Association, Odense, Denmark) and analysed in Stata version 12.1 (Stata Corp, College Station, TX, USA).

Key procedures

Prior to the first study phase, all investigators and staff involved in the study in each hospital/health centre participated in a 3-day training on study procedures. Laboratory technicians received a refresher course on thick blood smear preparation/reading and, before the second phase, a refresher course on haemoglobin (Hb) measurement with the HemoCue 201 plus system (Angelholm, Sweden). Simulated interviews were conducted to practice obtaining informed consent. Local principal investigators took part in practical sessions on filling in the case report forms (CRF). Nurses and doctors attended a separate training on reporting serious adverse events (SAE). Nurses also participated in piloting the time and motion study tool, which included observing and timing the activities related to drug preparation/administration prior to the first data collection. Upon completion of the first phase, hospital and health centre personnel involved in the study convened in Kinshasa for a 2-day training on preparing and administering injectable artesunate. Job aids and training tools developed by MMV were used for this training [9]. In addition, each site received ten doses of injectable artesunate for training purposes, allowing health care providers to become familiar with the new drug prior to patient recruitment. Weekly supervision visits to each site throughout the duration of the study ensured regular monitoring of the study team.

Patient assessment

Demographic information and limited routine clinical history data were collected for each patient and local study physicians (hospitals) or nurses (health centres) performed basic routine clinical assessments. A Giemsa-stained thick blood smear was performed and examined every 12 h during the first 24 h and then every 24 h until negative or until patient discharge. For PCT calculations, thick blood smears were later reread for quality control by experienced microscopists at the KSPH, blinded to the results of the first reading and to the RDT results. Hb levels were systematically assessed with a HemoCue 201 plus + photometer (Angelholm, Sweden) during the second study phase, at hospital admission, at discharge and at follow-up visits on days 7, 14, 21, and 28. The HemoCue testing resulted in a change in study protocol because of reports of haemolytic anaemia following artesunate treatment [10]. The results of that extension are presented elsewhere [11]. To ensure the proper functioning of the photometer, high and low Hb liquid controls (HemoCue Eurotrol HemoTrol) were run weekly at each site. Given the observational nature of the study, laboratory tests were not systematically performed and were left to the discretion of the physician or treating nurse, except for parasitological tests required for inclusion in the study and the Hb assessment during the second phase. Time of admission, time of start and end of parenteral treatment, and time to discharge were also recorded for every patient during both phases.

Parenteral treatment was completed by administering a full course of the recommended first-line, oral, combination therapy AS-AQ or AL in the artesunate phase, or with quinine tablets or the standard treatment practiced by the centre in the quinine phase. The first dose of the oral treatment was administered at the health facility in the presence of the nurse responsible. Subsequent doses were administered at home, according to the instructions given to parents and guardians. Patients were discharged at the discretion of the attending physician/nurse, after a final clinical assessment. During the first study phase, patients were asked to return to the hospital/health centre for follow-up 7 days after discharge to

assess their clinical status and their adherence to oral therapy. In the second study phase, patients were asked to return on days 7, 14, 21, and 28 after discharge to assess the clinical status and adherence to oral therapy and to determine their Hb levels at these time points.

Time and motion

The time and motion methodology consisted of 1) dividing a process into key tasks, and 2) observing each task to assess the average time required to perform it. The sum of the average times spent on each task was used to compute the total average time to complete the process. In each of the three participating hospitals, an external study nurse supervised the time and motion component and was present throughout the study. In the five health centres, the health centre personnel were responsible for the measurements. Therefore, the number of patients followed up was limited as a second nurse was not always available. Observed activities included: 1) pre-administration tasks (preparation of all materials and injectable solution, searching for the vein, setting the infusion in case of quinine), 2) drug administration, and 3) all other activities related to patient management. Observations were made by the nurses using digital stopwatches and a checklist to record the time taken for each task. Inter-observer agreement was not formally assessed. Materials required for all tasks were also recorded on the same observer checklist and this information was used later to calculate financial costs.

Cost of treatment component

A financial cost analysis was carried out from the provider's perspective, accounting only for costs incurred by the hospitals and the health centres. Complete unit cost data on resources used were recorded for 386 patients under quinine and for 333 patients under artesunate. To estimate the mean unit cost, the 2014 average exchange rate (USD 0.00107 to the Congolese Franc) was adopted [12]. Health care costs were divided into four main categories: 1) drug costs (parenteral quinine and artesunate, oral therapy), 2) diagnostic costs (blood smear), 3) administration equipment costs (infusion set, IV solution, syringes), and 4) in-patient costs (consultation cost, bed occupancy, blood transfusion, and nursing care). Administration equipment, blood smear and parenteral quinine unit costs were estimated from the hospital/health centre price lists, as well as in-patient costs. The full dose costs for both parenteral quinine and artesunate were applied, since the recommendation given in the study was to avoid re-using the drug once it was opened, and hence partially used ampoules had to be discarded. Artesunate was used in the 60-mg vial, the WHO pre-qualified formulation at the time. Costs of oral treatment with AS-AQ/AL were included in the analysis despite being subsidized by the Global Fund to Fight AIDS, TB and Malaria (GFATM) in the selected health facilities. Costs of artesunate and of AS-AQ/AL were obtained from the Management Sciences for Health (MSH) *International Drug Price Indicator Guide* [13].

Additional treatments and diagnostic costs, other than the parenteral drug and the thick blood smear, were not included in the analysis. Specific costs associated with co-morbidities, with the exception of blood transfusions (severe anaemia), were not considered in the analysis because they would have required a level of clinical monitoring that was not possible in this study. In two sites (referral hospital Saint Luc and Health Centre Ngeba), a lump sum health care payment system was in place, thus unit costs were unavailable. The decision was made to reflect as closely as possible the local practice and to generate nationally relevant data rather than internationally, fully costed estimates. Hence, the lump sum estimates were taken for this analysis. However, the two sites were analysed separately to take these differences into account, since lump sums are likely to underestimate the full cost of treatment, especially if there is a central subsidy by an external donor, as in the case of these two facilities.

Results

Clinical assessment

A total of 749 patients were recruited from eight sites, 399 in the quinine group from October 2012 to January 2013 (study phase one), and 350 in the artesunate group from April to July 2013 (study phase two). The quinine group consisted of 248 (62 %) children between 2 and 59 months, and 151 (38 %) individuals aged 5 years and above. The artesunate group consisted of 215 (61 %) children between 2 and 59 months and 135 (39 %) individuals aged 5 years and above. The demographic and baseline characteristics were similar for the two study groups (Table 1). All patients tested positive for malaria, either by thick blood smear or RDT on the day of inclusion. Overall mortality was 2.8 % (21/749), with 3.8 % for patients treated with quinine (15/399) and 1.7 % for patients treated with artesunate (6/350) ($p = 0.110$). The majority of deaths (13 of 21, 62 %) occurred within the first 24 h after admission, of which nine of 15 were in the quinine group (with two dying before receiving the treatment) and four of six were in the artesunate group (zero before receiving the treatment). Of the eight deaths that occurred after 24 h, six occurred in the quinine group and two in the artesunate group. Prostration was the most frequent manifestation of severe malaria at admission in children between 2 and 59 months in the quinine (204/248, 82 %) and artesunate groups (171/215, 80 %), as well as in individuals 5 years and above (122/151, 81 % and 120/135, 90 %). Respiratory distress and

Table 1 Characteristics and clinical presentation of patients at recruitment

	Quinine (*N* = 399)		Artesunate (*N* = 350)	
	2–59 months (*N* = 248)	>5 years (*N* = 151)	2–59 months (*N* = 215)	>5 years (*N* = 135)
Sex				
Female	122 (49 %)	72 (48 %)	115 (53 %)	71 (53 %)
Age	24 (7–53)	10 (5–48)	24 (7–48)	8 (5–48)
Medical history (past 30 days)				
Other malaria episode	18 (7 %)	7 (5 %)	16 (7 %)	16 (12 %)
Fever (*N* = 398)	90 (37 %)	78 (52 %)	59 (27 %)	76 (56 %)
Pretreatment with anti-malarial	31 (12 %)	20 (13 %)	20 (9 %)	20 (15 %)
Other treatment(s) received	113 (46 %)	75 (50 %)	98 (46 %)	83 (61 %)
Other major health problem(s)	6 (2 %)	3 (2 %)	0 (0 %)	4 (3 %)
Episode of convulsion (*N* = 394)	34 (14 %)	10 (7 %)	13 (6 %)	11 (8 %)
Known hypersensitivity to other drugs	0 (0 %)	5 (3 %)	2 (1 %)	5 (7 %)
Signs and symptoms on admission				
Fever	220 (89 %)	129 (85 %)	197 (92 %)	121 (90 %)
Fever before enrolment (days and range)	3 (2–4)	3 (2–5)	3 (1–7)	3 (1–7)
Vomiting	100 (40 %)	78 (52 %)	113 (53 %)	78 (58 %)
Coma	23 (9 %)	12 (8 %)	5 (2 %)	11 (8 %)
Reported convulsions	72 (29 %)	19 (13 %)	59 (27 %)	14 (10 %)
Blantyre coma score (8–24 months)	3 (2–5)	–	4 (3–8)	–
Glasgow coma score (>2 years)	10.5 (5–13)	10 (8–15)	7.5 (4–5)	NA
Pallor	NA	NA	77 (36 %)	20 (15 %)
Jaundice	3 (1 %)	4 (3 %)	7 (3 %)	2 (1 %)
Shock	10 (4 %)	2 (1 %)	2 (1 %)	2 (1 %)
Respiratory distress	128 (52 %)	58 (38 %)	96 (45 %)	64 (47 %)
Severe anaemia (<5 g/dl) (*N* = 326 Q; 334 A)	8.1 (3 %) [a]	9.1 (2 %) [a]	15 (7 %) [b]	1 (1 %) [b]
Parasite count (per μl); geometric mean (95 % CI)	17 068 (12 119-24 038) [c]	12 022 (7 040-20 527) [c]	22 289 (15 498-32 057) [c]	12 346 (7 812-19 511) [c]
Prostration	204 (82 %)	122 (81 %)	171 (79 %)	120 (89 %)
Urine colouration (*N* = 391)	2 (1 %)	2 (1 %)	10 (5 %)	8 (6 %)
Clinical examination on admission				
Weight (kg and SD)	11.1 (3.0)	33.2 (17)	11.2 (4)	27.6 (15)
Temperature (°C and SD) (*N* = 398)	38.1 (1)	38.3 (1)	38.1 (1)	38.4 (1)
Pulse	125 (70–180)	102 (64–148)	119 (60–171)	94 (60–140)
Respiratory rate per minute	42.5 (28–72)	39.0 (24–60)	40 (24–72)	40 (20–58)
Co-morbidity	82 (34 %)	51 (34 %)	80 (37 %)	58 (43 %)

Data are summarized as numbers (%), median (90 % central range) or mean (SD)
NA not available
[a] Clinical assessment only
[b] HemoCue
[c] The initial parasitaemia was calculated only for those patients for whom the biological confirmation was done by thick blood smear

convulsions were also frequent symptoms at admission in both groups. The total number of patients who received a blood transfusion was 214 (29 %), with 128 (32 %) and 88 (25 %) in the quinine and artesunate groups, respectively. Five per cent of the patients under the quinine regimen had persistent symptoms at discharge, compared to 3 % under the artesunate regimen (Table 2). A decrease in Hb levels at one of the follow-up visits was a frequent SAE reported during the artesunate regimen [11]. A 7-day oral quinine course was the most frequently prescribed oral medication to complete treatment after the initial injectable quinine regimen (92 %), whereas AS-AQ was the most prescribed oral medication (97 %) after injectable artesunate for all ages.

Table 2 Clinical examination at discharge

	Quinine		Artesunate	
	2–59 months (*N* = 226)	>5 years (*N* = 144)	2–59 months (*N* = 208)	>5 years (*N* = 131)
Weight (kg)	11.1 (3.0)	32.8 (16.7)	11.2 (4.3)	27.2 (14.9)
Temperature (°C)	36.7 (0.5)	36.6 (0.5)	36.7 (0.4)	36.5 (0.4)
Pulse	100 (70–128)	90 (41–120)	90 (64–124)	85.4 (18.8)
Respiratory rate per minute	35 (22–40)	28 (16–48)	31.8 (6.6)	29.2 (8.0)
Persistence of signs at discharge	12 (5.4 %)	6 (4.3 %)	7 (3.4 %)	4 (3.0 %)

Data are summarized as numbers (%), median (90 % central range) or mean (SD)

Patient adherence was assessed by the duration of oral treatment and the reported number of tablets taken. Following injectable quinine and injectable artesunate, 236 (85 %) and 308 (99 %) patients fully adhered to the treatment, respectively.

The time to discharge was slightly lower in the artesunate group compared to the quinine group, with a median of two (90 % central range 1–9) *versus* three (1–9) days, respectively (p <0.001). Given that mortality was slightly higher in the quinine group, this would have led to a shorter hospital stay but the effect would be minimal because of the low case fatality rate. The interval between admission and start of parenteral treatment was significantly shorter in the artesunate group compared to the quinine group, two (0–15) *versus* three (0–20) hours (p <0.001). The interval from beginning parenteral treatment initiating oral treatment was slightly longer in the artesunate group (45 (32–56) *versus* 39 (12–67) hours in the quinine group, p <0.001). Parasite clearance time was 23 (11–49) hours for artesunate *versus* 24 (10–82) hours for quinine (p <0.001) (Table 3).

Time and motion study

Administration times by task are shown in Tables 4 and 5. There was a reduction in the staff time required for all tasks during the artesunate phase. The total median personnel time for pre-administration and patient management tasks was 33 (10–60) for artesunate and 36 (13–92) minutes for quinine. The median cumulative staff time for observed drug pre-administration tasks per patient per drug session was 13 (6–38) for artesunate and 20 (7–50) minutes for quinine. Cumulative median personnel time spent for patient management was 9 (1–24) for artesunate and 12 (3–52) minutes for quinine.

Table 3 Key time intervals

	Quinine	Artesunate	p-value
Time to discharge (days)	3 (1–9)	2 (1–9)	p <0.001
Interval between admission and beginning of parenteral treatment (hours)	3 (0–20)	2 (0–15)	p <0.001
Interval between beginning of parenteral treatment and oral treatment (hours)	39 (12–67)	45 (32–56)	p <0.001
Parasite clearance time (hours)	24 (10–82)	23 (11–49)	p <0.001

Median and 90 % central range

Table 4 Personnel time (in minutes) required to complete pre-administration tasks, by drug type

Quinine (*N* = 832)		Artesunate (*N* = 795)	
Material preparation	6 (2–18)	Material preparation	4 (1–10)
Drug preparation	4 (1–14)	Reconstitution	3 (1–8)
Search for the vein	5 (1–14)	Dilution	2 (1–10)
Perfusion regulation	4 (1–10)	Dose verification	2 (1–6)
–		Search for the vein	3 (1–10)

Median and 90 % central range

Cost analysis

In hospitals and health centres, the mean (SD) total costs per patient treated for severe malaria with injectable artesunate were USD 51.94 (16.20) and 19.51 (9.58); and USD 60.35 (17.73) and 20.36 (6.80) with injectable quinine. Costing details for individual study sites are given in Table 6.

Discussion

This study is the first to quantify key operational parameters in the management of patients with severe malaria treated with injectable artesunate. Injectable artesunate was superior to quinine for almost all of the parameters assessed. Furthermore, from the provider's perspective, overall costs were lower for injectable artesunate in hospitals and similar in health centres. The aim of the study was to assess operational aspects rather than safety and efficacy. However, there was no indication for any of the outcomes obtained from available clinical charts that patients fared worse with injectable artesunate compared to parenteral quinine, concurring with available data on the efficacy and safety of the use of injectable artesunate in the DRC [2].

Table 5 Overall cumulative personnel time (in minutes)

	Quinine	Artesunate	p-value
Overall personnel pre-administration time	20 (7–50)	13 (6–38)	p <0.001
Overall personnel patient management time	12 (3–52)	9 (1–24)	p <0.001
Overall personnel time	36 (13–92)	33 (10–60)	p <0.001

Median and 90 % central range

Table 6 Mean cost (with SD) for treating one episode of severe malaria in patients admitted to hospitals and health centres in the Democratic Republic of Congo

Hospital/Health centre	Mean length of stay, days (SD)		Blood smear unit cost		Mean injectable drug cost		Mean oral drug cost[a]		Mean administration cost		Mean inpatient cost		Mean total cost per patient	
	QNN	ART	QNN	ART	QNN	ART	QNN	ART	QNN	ART	QNN	ART	QNN	ART
Kimpese referral hospital	7.12 (4.43)	6.26 (5.01)	2.94	2.94	0.45 (0.22)	7.72 (3.28)	0.66 (0.38)	0.48 (0.06)	1.89 (0.83)	1.39 (0.48)	49.56 (18.04)	47.25 (19.82)	61.58 (18.72)	59.57 (20.97)
Centre Hospitalier Roi Baudouin	4.09 (3.41)	3.72 (2.17)	3.21	3.21	0.78 (0.17)	3.24 (1.51)	0.97 (0.30)	0.56 (0.21)	6.59 (1.56)	0.90 (0.83)	38.60 (12.99)	38.76 (8.32)	53.29 (7.86)	46.58 (8.55)
Hôpital St Luc Kisantu	3.13 (1.06)	6.68 (4.00)	NA	NA	NA	3.87 (1.72)	0.70 (0.23)	0.50 (0.18)	NA	NA	NA	NA	50.34 (9.98) [b]	55.44 (11.81) [b]
Health Centre CECO	3.96 (2.35)	4.28 (3.36)	1.07	1.07	0.57 (0.14)	7.19 (2.51)	1.00 (0.49)	0.48 (0.13)	2.10 (0.34)	1.62 (0.45)	40.28 (10.32)	41.62 (14.47)	32.53 (14.25) [c]	28.21 (9.41) [c]
Health Centre La Famille	3.80 (1.54)	2.58 (1.50)	1.07	1.07	0.94 (0.43)	7.26 (3.95)	1.58 (0.59)	0.66 (0.30)	3.89 (1.59)	1.22 (0.45)	10.48 (3.63)	8.19 (3.21)	19.35 (4.46)	18.21 (5.02)
Health Centre Bita	2.18 (0.68)	1.99 (0.11)	1.07	1.07	1.49 (0.33)	7.30 (2.68)	1.99 (0.78)	0.49 (0.17)	6.48 (1.23)	1.51 (0.23)	6.71 (2.07)	6.39 (0.30)	21.97 (2.73)	16.56 (2.87)
Health Centre Menkao	1.78 (0.97)	1.27 (1.34)	1.07	1.07	1.81 (0.72)	9.12 (5.09)	1.05 (0.45)	0.63 (0.24)	5.10 (1.19)	2.60 (0.73)	3.15 (1.29)	2.49 (1.76)	13.92 (2.59)	15.66 (5.84)
Health Centre Ngeba	4.6 (2.59)	2.7 (0.98)	NA	NA	NA	5.87 (1.95)	0.97 (0.30)	0.43 (0.04)	NA	NA	NA	NA	6.86 (0.84) [b]	4.47 (0.10) [b]

In 2014 USD; *NA* not available

[a] Mean cost for oral quinine and AS-AQ

[b] Unit costs not available. Lump sum payment system. All exams and drugs other than anti-malarial are included. Patients pay a part of the total costs; the rest is supported by a partner

[c] Among health centres, blood transfusion was only performed in CECO. To allow cost comparison with the other health centres, costs of blood transfusion were not included in the total costs. Mean total costs for CECO under ART and QNN are USD47.47 (9.41) and USD51.79 (14.25) respectively if blood transfusion is included

A major reason for conducting the study in two phases was the need for comparative operational data between the new regimen and the old regimen. Because many aspects in health services are setting-specific, it was thought that the best controls would be the facilities themselves. The strongest study design would include a randomized concurrent control trial with enough health facilities to account for inter-facility variability, however, time and logistical reasons precluded such an approach for the current study. The design outlined here was the best suited to the Ministry of Health's current plan for scaling up artesunate. The operational parameters of treating severe malaria are unlikely to be sensitive to seasonal effects, and also unlikely to change much in a given facility over time periods equal to that of the study. Hence, although not randomized, this design allowed a reasonable comparison of the two regimens in real-world implementation settings. Although injectable quinine has been the mainstay for treating severe malaria for many years, there are virtually no existing data in the literature quantifying the operational parameters of interest.

In this study, patients admitted with severe malaria experienced a median delay of 3 h before receiving their initial quinine dose compared to 2 h with artesunate (Table 3). This time delay depended on several factors that should be further investigated. In particular, it could reflect the difficulties of promptly and safely administering quinine via IV. Although comparable in its preparation, quinine is a difficult drug to administer because of its unfavourable safety profile; it requires correct dose calculation, taking into account previous quinine treatment to avoid overdosing and serious consequences for the patient.

In the AQUAMAT trial [2], the risk of children dying while waiting to receive quinine was almost four times higher than the risk in children treated with artesunate. This delay adds to the time needed for referral, during which the condition of the patient can deteriorate [14]. In this study, 2 patients died before receiving quinine compared to none in the artesunate group. Although this delay is still critical for both regimens, it can be expected to decrease further for injectable artesunate as skills and confidence are acquired through repeated administration and preparation by health personnel.

The well-known difficulties in administering quinine may also explain the difference observed in the time interval between the beginning of the parenteral treatment and the initiation of oral treatment. Lack of confidence or uncertainty in reconstructing the history of previous treatments with quinine could potentially limit the number of doses a patient receives. According to the national DRC directives on the treatment of severe malaria [6], the number of doses of quinine administered

should be minimized until the patient can tolerate an oral medication. Under the artesunate regimen in this study, the WHO's recommendations of a minimum of three injections during the first 24 h, irrespective of the patient's ability to tolerate oral medication were strictly followed. This is one possible explanation for the prolonged time interval to the initiation of oral therapy.

The artesunate regimen achieved parasite clearance faster than the quinine regimen, which likely accounts for the shorter hospital stay. The reduction in median hospital stay by a day reduces costs of malaria treatment and minimizes socio-economic impacts on patients and their families. This is especially important for poorer and more vulnerable segments of the population.

The estimated costs of treating a patient with severe malaria in this study are similar to those calculated in previous studies [15, 16], although lower than those reported by Kyaw *et al.*, which used a more detailed cost analysis approach [17]. The costs were highly variable, depending on the level and type of facility (public, private or missionary). The mean pooled estimate total cost was found to be similar for artesunate compared to quinine in health centres, USD 19.51 (9.58) and 20.36 (6.80), while lower in hospitals, USD 51.94 (16.20) to USD 60.35 (17.73). Inpatient costs were the major driver costs for the difference observed between hospitals and health centres. Less standardized inpatient costs are established by each hospital and health centre and take into account a number of parameters, which include cost of labour, and the organisation of the health service. Since it was not possible to analyse all patient costs, particularly the cost related to supportive measures and the presence of co-morbidities, the total treatment costs are clearly underestimated. For the purpose of this study, a new vial of quinine was used for every dose, but this is not necessarily the case in the real world. As a result, drug costs were likely overestimated. However, not all sessions of drug preparation and administration were included due to understaffed health centres and the inability to reliably observe the most severe cases in need of prompt treatment.

The results show that the overall time spent on pre-administration tasks and on direct post-treatment patient care was slightly lower in the artesunate compared to the quinine group. Although statistically significant, this time difference is smaller than expected considering that artesunate is easier to use. This could be explained by the fact that health personnel had a limited time to get used to preparing and administering artesunate before starting patient enrolment in the second phase. Therefore, it could be that the overall difference in the pre-administration times will increase over time, in favour of artesunate. The overall personnel time spent on patient care was lower with artesunate administration compared to quinine. This is likely to have resulted in more time to care for other patients, leading to a positive effect on the overall quality of care. This was consistent with health care providers' higher satisfaction when using artesunate, as described elsewhere (Ntuku *et al.*, personal communication).

Conclusions

This study provides for the first time descriptive evidence of the effectiveness and practicability of using injectable artesunate for treating severe malaria in hospitals and health centres in the DRC. For most operational and cost parameters, injectable artesunate was found to be superior to injectable quinine. Combined with its higher efficacy, these findings support the rapid switch-over in the country. These findings also provide some useful operational and cost data for national authorities and for local health care managers involved in planning the transition.

Training health personnel is obviously a key factor for a successful transition, including a change in the attitudes and behaviours of providers.

The MATIAS study has contributed further evidence that injectable artesunate is a better treatment option than injectable quinine for patients with severe malaria. The findings suggest that transition to the new drug should be accelerated as quickly as possible. The Ministry of Health of the DRC is currently scaling up the use of injectable artesunate in the public sector, with the support of the GFATM and the other partners, which will enable 100 % coverage of in-patient cases within a 3-year period.

Additional file

Additional file 1: Location and characteristics of the eight study sites.

Abbreviations

ACT: Artemisinin-based combination therapy; AL: Artemether plus lumefantrine; AS-AQ: Artesunate plus amodiaquine; CI: Confidence interval; CRF: Case report form; DRC: Democratic Republic of the Congo; EKBB: Ethikkommission Beider Basel; KSPH: Kinshasa School of Public Health; GFATM: Global Fund to fight AIDS TB and Malaria; Hb: Haemoglobin; HZ: Health zone; IV: Intravenous; MATIAS: MAlaria Treatment with Injectable ArteSunate; MMV: Medicines for Malaria Venture; MSH: Management Science for Health; NGO: Non-governmental organization; NMCP: National Malaria Control Programme; PCT: Parasite clearance time; RDT: Rapid diagnostic test; SAE: Severe adverse event; SP: Sulphadoxine-pyrimethamine; UNICEF: United Nations International Children's Emergency Fund; WHO: World Health Organization.

Competing interests

SD and PH are employees of MMV.

Authors' contributions

CL, CHB, ATK, SD, and PH conceived the study and revised the manuscript. GF, HMN and DKM conducted the fieldwork and provided supervision throughout the duration of the study. GF and HMN contributed to

managing, analysing and interpreting the data. GF drafted the manuscript. AR assisted in the statistical analysis and revised the manuscript. PLN, JJNL, PNM, and SEN were the medical doctors *chefs de zone de santé* and key persons facilitating the collaboration and contributed to supervising the data collection. All authors contributed to writing the manuscript and endorse the recommendations of this work. All authors read and approved the final manuscript.

Acknowledgements
We would like to thank the staff at all participating sites for assisting in data collection and for their excellent work. We are also grateful to all patients and parents for their collaboration. A special thank goes to the MATIAS study team for their hard work and commitment to the study. We are grateful to Ministry of Health authorities and to the National Malaria Control Programme staff, who facilitated the study. We also would like to thank the numerous participants from the relevant directorates of the Ministry of Health, the WHO and the NGOs for their active participation in the two stakeholders' meetings. A special thank goes also to Ecaterina Galactionova for her valuable advices in the analysis of costs of severe malaria. The study was supported financially and technically by MMV.

Author details
[1]Swiss Tropical & Public Health Institute, Basel, Switzerland. [2]University of Basel, Basel, Switzerland. [3]Kinshasa School of Public Health, Kinshasa, Democratic Republic of the Congo. [4]Medicines for Malaria Venture, Geneva, Switzerland. [5]Zone de Santé de Kimpese, Kimpese, Democratic Republic of the Congo. [6]Zone de Santé Rurale de Kisantu, Kisantu, Democratic Republic of the Congo. [7]Zone de Santé de Maluku, Maluku, Democratic Republic of the Congo. [8]Centre Hospitalier Roi Baudouin 1er Masina, Kinshasa, Democratic Republic of the Congo.

Received: 11 December 2014 Accepted: 20 February 2015
Published online: 30 May 2015

References

1. WHO. World malaria report. Geneva: World Health Organization; 2011.
2. Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate *versus* quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376:1647–57.
3. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate *versus* quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005;366:717–25.
4. WHO. Guidelines for the Teatment of Malaria. 2nd edition – Rev. 1. Geneva: World Health Organization; 2011.
5. WHO. Management of severe malaria – A practical handbook. 3rd ed. Geneva: World Health Organization; 2013.
6. PNLP. Directives nationales de traitement du paludisme en République Démocratique du Congo (Draft). Kinshasa: Ministère de la Santé; 2012.
7. PNLP. Guide technique de formation en prevention et prise en charge du paludisme (Hopital General de reference). RDC.
8. World Health Organization Public Assessment Reports (WHOPARs). [http://apps.who.int/prequal/whopar/whoparproducts/MA044part6v1.pdf].
9. Medicines for Malaria Venture. [http://www.mmv.org/access/injectable-artesunate-tool-kit].
10. CDC. Published reports of delayed hemolytic anemia after treatment with artesunate for severe malaria-worldwide, 2010–2012. MMWR. 2013;62:5–8.
11. Burri C, Ferrari G, Ntuku HM, Kitoto AT, Duparc S, Hugo P, et al. Delayed anemia after treatment with injectable artesunate in the democratic republic of the congo: a manageable issue. Am J Trop Med Hyg. 2014;91:821–3.
12. OANDA. Currency converter. http://www.oanda.com [accessed 07 August 2014].
13. MSH (Management Sciences for Health). International Drug Price Indicator Guide, 2013 Edition. Medford: Mass: MSH; 2014. Updated annually.
14. WHO. Guidelines for the treatment of malaria. 2nd ed. Geneva: World health Organization; 2010.
15. Lubell Y, Yeung S, Dondorp AM, Day NP, Nosten F, Tjitra E, et al. Cost-effectiveness of artesunate for the treatment of severe malaria. Trop Med Int Health. 2009;14:332–7.
16. Lubell Y, Riewpaiboon A, Dondorp AM, von Seidlein L, Mokuolu OA, Nansumba M, et al. Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa. Bull World Health Organ. 2011;89:504–12.
17. Kyaw SS, Drake T, Ruangveerayuth R, Chierakul W, White NJ, Newton PN, et al. Cost of treating inpatient falciparum malaria on the Thai-Myanmar border. Malar J. 2014;13:416.