High Rates of Malaria Microscopy but Low Turnaround of Test-results Among Inpatients in Tertiary Care: With Delayed Initiation, Monotherapy and Incomplete Dosing of Antimalarials

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Abstract

Objectives: To describe the patterns of malaria diagnosis and antimalarial use: monotherapy, missed Day 1 dosing and risk-factors.

Methods: Prospective cohort of consented adult inpatients on the medical and gynaecological wards of Uganda's 1790-bed Mulago National Referral Hospital.

Results: One in five (19%, 146/762; 95% confidence interval (CI): 16% to 22%) inpatients had an admitting or discharge malaria diagnosis or both. Microscopy was requested in 77% (108/141; 95% CI: 69% to 83%) of inpatients with an admitting malaria diagnosis; results were available for 46% (50/108; 95% CI: 37% to 56%), of whom 42% (21/50; 95% CI: 28% to 57%) were positive. Artesunate (AS) only (47%, 47/100; 95% CI: 37% to 57%) was the most frequently hospital-administered antimalarial followed by quinine (Q) only (23%, 95% CI: 15% to 32%). A quarter (25%, 25/100; 95% CI: 17% to 35%) of the inpatients missed their Day 1 dose of hospital-initiated antimalarials. Nearly half (47%, 95% CI: 34% to 61%) of 57 inpatients on AS and 18%(95% CI: 4% to 32%) of 28inpatients on Q missed at least one day of dosing in Days 1-3. Number of admitting diagnoses was a significant risk-factor for missed Day 1 dosing of hospital-initiated antimalarials (OR = 2.7, 95% CI: 1.53-4.54; *P*-value < 0.001).

Conclusions: Half the malaria microscopy results were not available; yet, the rate of testing was high. Improvement in laboratory services, procurement, prescription, dispensing and administration of antimalarials could curb missed treatment for confirmed malaria cases, monotherapy and delayed doses.

Background

Around 405,000 people died from malaria globally in 2018, 94% of whom were from the World Health Organization (WHO) African Region. Prompt detection and appropriate treatment of malaria prevents severe disease and death [1]. The risk of mortality from severe malaria is highest during the first 24 hours of hospitalization [2]. Yet, in most moderate- to high-malaria-transmission settings, long transit-time to a suitable health facility where appropriate intravenous antimalarials can be administered could delay the initiation of appropriate antimalarials and increase the risk of patient deterioration or death[2]. Other impediments to the timely initiation of appropriate antimalarials include the lack of timely laboratory diagnosis and drug stock-outs [2, 3].

World Health Organization recommends confirmation of malaria diagnosis by quality microscopy or malaria rapid diagnostic testing within 2 hours of patient presentation and before administration of antimalarials. Otherwise, the decision to treat should be taken on clinical grounds. If severe malaria is suspected, parasitological diagnosis should not delay initiation of antimalarials [2]. Adults with severe malaria, including pregnant women in all trimesters and breast-feeding mothers, should be treated with three doses of injectable artesunate (AS) for 24 hours minimum at 0, 12 and 24 hours regardless of whether the patient can tolerate oral treatment earlier. If unable to take oral medication, the patient should continue with injectable AS once daily, for a maximum of 7-days. If injectable AS is not available, once daily injectable artemether (AT) or 8-hourly quinine (Q) should be administered. Following injectable antimalarials, a full 3-day course (six doses) of oral artemisinin-based combination therapy (ACT) - mainly artemether-lumefantrine (AL) for Uganda – should be administered if the patient is able to take oral medication [2, 4–6]. Other recommended ACTs include artesunate-amodiaquine (AQ) and dihydroartemisinin-piperaquine (DP). If full treatment for severe malaria is not possible at a given health facility but injectables are available, adults and children should be given one intramuscular dose of AS or Q and referred to a suitable facility for appropriate management [2].

It is necessary for patients with severe malaria to access timely appropriate antimalarials, avoid antimalarial monotherapy and complete full courses of prescribed antimalarials, which promotes therapeutic success, reduces malaria-related mortality and prevents drug resistance [7–9]. However, SSA patients with severe malaria frequently receive incomplete doses of prescribed antimalarials, or monotherapy, and/or treatment meant for uncomplicated malaria [8, 10]. We have previously shown that one-third of hospitalized patients in our setting missed Day 1 of prescribed antibiotics [3], but similar data are scarce on antimalarial use. We aim to describe the patterns of malaria diagnosis and antimalarial use by extent of use, missed opportunity for treatment, frequency of administered-treatment, medication-use-cycle (prescription-dispensing-administration), missed-dose days (including missed Day 1 dosing) and mortality. We also evaluate patient-level risk-factors for missed Day 1 dosing of prescribed antimalarials and the relationship between missed Day 1 dosing of prescribed antimalarials and length of hospital stay among adult inpatients at Mulago Hospital.

Methods

Detailed account of the study design, setting, data collection and data management is documented elsewhere [3]. Briefly, key details are the following.

Study design and setting

A prospective cohort study was conducted among inpatients, 18 years and older, at Mulago National Referral Hospital with bed capacity of 1,790 and an annual inpatient turnover of 140,000 patients. Three medical wards and one Gynaecological ward were included, each with an official bed capacity of 54 and average of 5–25 patient admissions per day [3].

Details on the prescription, dispensing and administration of medicines are hand-recorded in the patients' charts. Hospital pharmacists dispense the prescribed free-of-charge injectable and/or oral antimalarials, as appropriate, to inpatients/caregivers in quantities that discourage misuse of medicines. However, the inpatients/caregivers are instructed to return to the pharmacy early enough for more medication to avoid missing treatment[3].

Data collection

The data were collected in December 2013 to April 2014 by trained research assistants. Study patients provided written informed consent and were enrolled using a systematic sampling procedure following a daily random start from the first two (Infectious Diseases and Gastrointestinal Illnesses ward), three (Haematology, Neurology and Endocrinology ward) and four (Cardiovascular, Pulmonology and Nephrology ward & Gynaecology ward) new admissions; and

subsequently every second, third and fourth admission, respectively. Patients were assessed at baseline (demographics, clinical conditions, medications) and on a daily basis (clinical conditions, medications) until discharge, transfer, death, or loss to follow-up. The data were collected daily from 8.00am to 6.00 pm from Monday to Friday and from10.00am to 6.00 pm on weekends and public holidays [3].

Data management

Epidata 3.1 software was programmed with checks to limit data entry errors and the electronic database password-secured to limit access only to authorized personnel.

Statistical analysis

Patterns of malaria diagnosis and antimalarial use

The proportions of inpatients who received antimalarials preadmission and during hospitalization were determined using, as numerator, the number of inpatients who received at least one antimalarial and, as denominator, the total number of study patients. We calculated proportions of inpatients who had malaria microscopy done and those who experienced antimalarial missed-dose days, including missed Day 1 dosing. See **Appendix** for details on time-to-first-dose and parenteral-to-oral-switch of antimalarials.

We used Chi-squared tests to screen univariate-level relationships between patient-level characteristics and antimalarial use during hospitalization (yes/no); and potential patient-level risk-factors for missed Day 1 antimalarials during hospitalization. Logistic regression was used to identify risk-factors for missed Day 1 antimalarials. Results were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). Poisson CIs were used for counts below 16. Stata 14.0 [11] was used for all the analyses.

Identification of missed Day 1 dosing of antimalarials

Among inpatients for whom an antimalarial was prescribed during hospitalization and at least one dose administered, missed Day 1 dosing was measured in two ways; i) calendar-day as proposed by Kiguba *et al* 2016 [3], see **Appendix**, and ii) 24-hour timescale using date-and-time of hospital admission and date-and-time of first in-hospital antimalarial dose.

Results

Study population

*Demographic and clinical characteristics:*The median age of 762 inpatients was 30 years (interquartile range, IQR, 24 to 42years), see **Table 1**.One in five (19%, 141/762; 95% CI: 16% to 21%) inpatients had an admittingmalariadiagnosis,see **Tables 1 & 2**: 11% (16/141; 95% CI: 7% to 18%) had malaria as their single admitting diagnosis. One in eight (12%, 88/762; 95% CI: 9% to 14%)inpatients had a discharge malaria diagnosis: 44% (39/88; 95% CI: 34% to 55%) had malaria as their single discharge diagnosis.One in five (19%, 146/762; 95% CI: 16% to 22%) had an admitting or discharge malaria diagnosis or both, see **Table 2**:21% (30/146; 95% CI: 14% to 28%) had malaria-in-pregnancy.

Table 1
Demographic and clinical characteristics of 762 inpatients, Uganda

Characteristic	Antimalarial Use during the Current Hospitalization		
	Yes	No	Overall
Age, years[a]	27 (21 -35)	30 (25 - 43)	30 (24 - 42)
Length of hospital stay, days[a]	4 (3 - 5)	4 (3 - 6)	4 (3 - 6)
Patient-days of observation	454	3,287	3,741
Extent of antimalarial use			
	Antimalarial Use during the Current Hospitalization, n (%)		
	Yes	No	Total
Pre-admissionantimalarials	97 (13)	665 (87)	762
In-hospitalantimalarials	100 (13)	662 (87)	762
Pre-admission antimalarials	38 (38)	62 (62)	100
Pre-/in-hospital co-trimoxazole	15 (15)	87 (87)	100
In-hospital antibiotics	61 (61)	39 (39)	100
In-hospital antiretrovirals	14 (14)	86 (86)	100
Pre-/in-hospital antimalarials	159 (21)	603 (79)	762
Subgroup analyses on key variables			
	Antimalarial Use, n (%)		Single factor analysis
	Yes	No	Total, [% col][b]	OR[c]	95% CI[d] for OR	*P*-value
Gender						
Male	20 (9)	208 (91)	228 [30]	1.0		
Female	80 (15)	454 (85)	534 [70]	1.8	1.09 - 3.07	0.022
Ward						
Gynaecological (GYN)	25 (13)	166 (87)	191 [25]	1.0		
Infectious Diseases and Gastrointestinal Illnesses (IDGI)	57 (18)	263 (82)	320 [42]	1.4	0.87 - 2.39	0.161
Haematology, Neurology and Endocrinology (HNE)	12 (10)	105 (90)	117 [15]	0.8	0.37 - 1.58	0.459
Cardiovascular, Pulmonology and Nephrology (CPN)	6 (4)	128 (96)	134 [18]	0.3	0.12 - 0.78	0.013
Number of working diagnoses						
One	16 (12)	122 (88)	138 [18]	1.0		
Two	31 (15)	177 (85)	208 [27]	1.3	0.70 - 2.55	0.380
Three	28 (15)	158 (85)	186 [24]	1.4	0.70 - 2.61	0.370
Four or more	25 (11)	205 (89)	230 [30]	0.9	0.48 - 1.81	0.831
Length of hospital stay, days						
Less than 5-days	64 (15)	368 (85)	432 [57]	1.0		
Five days or more	36 (11)	294 (89)	330 [43]	0.7	0.46 - 1.09	0.115
HIV-serostatus						
Negative	49 (14)	291 (86)	340 [45]	1.0		

[a]Median (Interquartile Range, IQR); [b]% Column; [c]OR = Odds Ratio; [d]confidence interval; [e]Not all HIV-positive patients had the immunosuppressed syndrome, ISS

Positive	23 (10)	209 (90)	232 [30]	0.7	0.39 - 1.11	0.113
Unknown	28 (15)	162 (85)	190 [25]	1.0	0.62 - 1.70	0.919
Hospitalization in past 3-months						
No	75 (14)	455 (86)	532 [70]	1.0		
Yes	25 (11)	205 (89)	230 [30]	0.7	0.46 - 1.20	0.227
Charlson's co-morbidity index score						
Zero	64 (16)	329 (84)	393 [52]	1.0		
One or more	36 (10)	333 (90)	369 [48]	0.6	0.36 - 0.86	0.008
Antiretroviral therapy use						
No	86 (14)	549 (86)	635 [83]	1.0		
Yes	14 (11)	113 (89)	127 [17]	0.8	0.43-1.44	0.444
Microscopy - Malaria Parasitaemia Results Available						
No	62 (62)	616 (93)	678 [89]	1.0		
Yes	38 (38)	46 (7)	84 [11]	8.2	4.81-14.0	<0.001
Major admitting diagnosis						
Malaria						
No	17 (3)	604 (97)	621 [81]	1.0		
Yes	83 (59)	58 (41)	141 [19]	50	28.3-91.5	<0.001
Immunosuppressed syndrome (ISS) or HIV/AIDS[e]						
No	86 (14)	524 (86)	610 [80]	1.0		
Yes	14 (9)	14 (91)	152 [20]	0.6	0.34 - 1.12	0.113
Tuberculosis (TB)						
No	92 (14)	548 (86)	640 [84]	1.0		
Yes	8(7)	114 (93)	122 [16]	0.4	0.20 - 0.88	0.023
Sepsis-related working diagnosis						
No	81 (12)	597 (88)	678 [89]	1.0		
Yes	19 (23)	65 (77)	84 [11]	2.2	1.23 - 3.78	0.007
Respiratory Conditions except TB						
No	85 (13)	547 (87)	632 [83]	1.0		
Yes	15 (12)	115 (88)	130 [17]	0.8	0.47 - 1.51	0.557
Miscellaneous infections						
No	78 (12)	571 (88)	649 [85]	1.0		
Yes	22 (19)	91 (81)	113 [15]	1.8	1.05 - 2.98	0.032

[a]Median (Interquartile Range, IQR); [b]% Column; [c]OR = Odds Ratio; [d]confidence interval; [e]Not all HIV-positive patients had the immunosuppressed syndrome, ISS

Table 2

Malaria detection by laboratory diagnosis among 762 hospitalized

Malaria suspected at admission~																	Malaria not susp
Malaria at discharge (n = 83)								No malaria at discharge (n = 58)									Malaria at discha
Microscopy requested, n (%)¥																	
Yes						No		Yes								Yes	
Returned Positive		Returned Negative		Not Returned		Not Requested		Returned Positive		Returned Negative		Not Returned		Not Requested		Returned Positive	
21 (25)		13 (16)		31 (37)		18 (22)		0 (0)		16 (28)		27 (47)		15 (26)		1 (20)	
In-hospital administration of antimalarials, n (%)																	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
20 (95)	1(5)	11(85)	2(15)	26 (84)	5(16)	15(83)	3(17)	0(0)	0(0)	5(31)	11(69)	3 (11)	24(89)	3(20)	12(80)	1 (100)	0 (0)
Single admitting diagnosis of malaria, n (%)																	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
5 (24)	16 (76)	0 (0)	13 (100)	5 (16)	26 (84)	4 (22)	14 (78)	0 (0)	0 (0)	1 (6)	15 (94)	1 (4)	26 (96)	0 (0)	15 (100)	0 (0)	1 (100)
Received antimalarials during the 4-weeks preadmission, n (%)																	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
7 (33)	14 (67)	5 (38)	8 (62)	8 (26)	23 (74)	7 (39)	11 (61)	0 (0)	0 (0)	5 (31)	11 (69)	8 (30)	19 (70)	3 (20)	12 (80)	0 (0)	1 (100)
Single discharge diagnosis of malaria, n (%)																	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
9 (43)	12 (57)	3 (23)	10 (77)	16 (52)	15 (48)	11 (61)	7 (39)	0 (0)	0 (0)	0 (0)	16 (100)	0 (0)	27 (100)	0 (100)	15 (0)	0 (0)	1 (100)

‡19% (146/762; 95% confidence interval (CI): 16% to 22%) of inpatients had either an admitting or discharge malaria diagnosis or both;~19% (141/762; 95% C requests had concurrent malaria rapid diagnostic testing (mRDT) done. However, mRDT results were available for only one inpatient, who tested positive.

Laboratory diagnosis of malaria:Microscopy was requested in 26% (201/762) of inpatients; laboratory results were available for 42% (84/201; 95% CI: 34% to 48%) of them,30% (25/84; 95% CI: 20% to 41%) tested positive. Microscopy was requested in 77% (108/141; 95% CI: 69% to 83%) of inpatients with an admitting malaria diagnosis; laboratoryresults were available for 46% (50/108; 95% CI: 37% to 56%) of them,42% (21/50; 95% CI: 28% to 57%) tested positive, see **Appendix**.At bivariate level, inpatients with an admitting malaria-in-pregnancy diagnosis were ten-fold more likely to test positive for malaria when compared with non-pregnancy-related malaria inpatients (odds ratio, OR = 10.1; 95% CI: 1.55 to 65.96; 1 degree of freedom, df; $\chi 2 = 9$; *P*-value = 0.003) i.e. [82% (9/11; 95% CI: 48% to 98%) vs. 31% (12/39; 95% CI: 17% to 48%)], respectively.

Extent of antimalarial use

Thirteen percent (97/762; 95% CI: 10% to 15%) of inpatients received antimalarials during the 4-weekspre-admission, see **Table 1**:of whom 44% (43/97; 95% CI: 34% to 55%) had an admitting malariadiagnosis. Thirteen percent (100/762; 95% CI: 11% to 16%) of inpatients received antimalarials during the current hospitalization, see **Table 1**:of whom 83% (83/100; 95% CI: 74% to 90%) had an admitting malaria diagnosis, see **Table 1**.

Missed opportunity for hospital-initiated antimalarials

Four of 25 (16%, 95% CI: 5% to 36%) inpatients with a positive malaria test did not receive in-hospital antimalarials; none of the fourdied while in hospital, see **Box 1,** and none had malaria-in-pregnancy.

Frequency of administered antimalarials

Four-week preadmission period:At *patient-level,*oral artemether-lumefantrine (AL) only (52%, 50/97; 95% CI: 41% to 62%) was most frequently administered followed by injectablequinine (Q) only (23%, 22/97; 95% CI: 15% to 32%), see **Table 3** and **Appendix**.

Current hospitalization:At *patient-level,* AS only (47%, 47/100; 95% CI: 37% to 57%) was the most frequently administered followed by Q only (23%, 23/100; 95% CI: 15% to 32%), AL only (15%, 15/100; 95% CI: 9% to 24%) and AS + AL only (8%, 8/100; 95% CI: 4% to 15%), among others; see **Table 3** and **Appendix**.

Table 3
Frequency of antimalarials usedbyhospitalized patients, Uganda, 2014

Antimalarial	Number: n, %	
Patient-level		
Pre-admission, n = 97		
Artemether-Lumefantrine only	50	52%
Quinine only	22	23%
Sulfadoxine-Pyrimethamine only	9	9%
Artesunate only	5	5%
Coartem + Quinine only	4	4%
Duocotexcin only	2	2%
Artemether only	1	1%
Artesunate + Duocotexcin only	1	1%
P-alaxin + Quinine only	1	1%
Artemether + Quinine + Doxycycline only	1	1%
Dihydroartemisinin-Piperaquine only	1	1%
In-hospital, n = 100		
Artesunate only[±]	47	47%
Quinine only~	23	23%
Artemether-Lumefantrine only	15	15%
Artesunate + Artemether-Lumefantrine only	8	8%
Quinine + Artemether/Lumefantrine only	3	3%
Sulfadoxine-Pyrimethamine only	2	2%
Artesunate + Quinine only	2	2%
Drug-level		
Pre-admission, n = 105		
Artemether-Lumefantrine	54	51%
Quinine	28	27%
Sulfadoxine-Pyrimethamine	9	9%
Artesunate	6	6%
Duocotexcin	3	3%
Artemether	2	2%
Dihydroartemisinin-Piperaquine	2	2%
Doxycycline	1	1%
In-hospital, n = 113		
Artesunate	57	50%
Quinine	28	25%
Artemether-Lumefantrine	26	23%
Sulfadoxine-Pyrimethamine	2	2%

[±]68% (32/47) o-the inpatients presented with both admitting and discharge malaria diagnoses [median length of hospital stay: 4 (IQR, 3 to 5) days];
~91% (21/23)of the inpatients had both admitting and discharge malaria diagnoses [median length of hospital stay: 3 (IQR, 2 to 4) days]

Medication-use-cycle

Overview of prescription, dispensing and administration of antimalarials

Overall: Antimalarials were prescribed for 15% (114/762) of inpatients, dispensed to 79% (90/114), yet, administered in 100 inpatients (93 of 100had an antimalarial prescription), see **Appendix** for details on AS, Q and AL.

Incomplete dosing of in-hospital antimalarials

*Artesunate:*25% (14/57; 95% CI: 14% to 38%) of inpatients in whom *in-hospital AS was administered*received<3 doses of *both dispensed and administered AS* irrespective of pregnancy, see **Appendix**.

Quinine: 21% (6/28; 95% CI: 8% to 41%) of inpatients in whom *in-hospital Q was administered*received<3 doses of *both dispensed and administered Q* irrespective of pregnancy, see **Appendix**.

Artemether-Lumefantrine: 71% (20/28; 95% CI: 51% to 87%) of inpatients in whom *in-hospital AL was administered*received <6 doses of *administered AL*.

Missed Day 1 dosing of hospital-prescribed antimalarials

Calendar-day: A quarter (25%, 25/100; 95% CI: 17% to 35%) of inpatients who received antimalarials during the current hospitalization missed their Day 1 dose of hospital-initiated antimalarials based on calendar-day. Similar results of missed Day 1 dosing were obtainedbased on *post-admission 24-hour-delay*, see **Appendix**.

Missed-dose days of the most frequently administered hospital-prescribed antimalarials

*Artesunate:*Around a quarter (28%, 16/57; 95% CI: 17% to 42%) of inpatients who initiated antimalarials with AS missed their Day 1 dose(s) based on calendar-day; 19% (10/52; 95% CI: 10% to 32%) missed Day 2 and 27% (8/30; 95% CI: 12% to 46%) missed Day 3. Nearly half (47%, 27/57; 95% CI: 34% to 61%) the inpatients missed at least one day of AS dosing in Days 1-3, see **Table 4**.

Table 4

Missed dose-days of artesunate injection among 57 hospitalized patients who received in-hospital intravenous artesunate, Ugand

fileno	Length of stay, days	Preadmission antimalarial use	Admitting MalariaDiagnosis	Discharge Malaria Diagnosis	AL co-prescribed	Switched to AL	AS Doses Prescribed	AS Doses Received	Day 1	Day 2	Day 3	Day
6	3	No	Yes	No	No	No	3	1		1 dose		
20	3	No	Yes	Yes	Yes	No	2	3	1 dose	2 doses		
75	4	No	Yes	Yes	No	No	6	2	1 dose	1 dose		
77	5	No	Yes	Yes	Yes	No	3	3	1 dose	1 dose	1 dose	
90	2	No	Yes	Yes	Yes	No	2	1	1 dose			
109	4	Yes	Yes	Yes	Yes	No	10	3	1 dose		1 dose	1 dose
112	5	No	No	No	No	No	3	2		2 doses		
125	2	No	Yes	Yes	Yes	Yes	3	2	2 doses			
128	4	No	Yes	No	Yes	Yes	3	2	1 dose	1 dose		
130	5	Yes	Yes	Yes	Yes	Yes	3	1	1 dose			
169	4	No	Yes	Yes	Yes	No	3	2	1 dose	1 dose		
174	5	No	Yes	Yes	No	No	3	4		1 dose	2 doses	1 dose
215	5	No	Yes	Yes	No	No	3	3	1 dose	1 dose	1 dose	
218	5	No	Yes	No	No	No	3	3		1 dose	1 dose	1 dose
233	10	Yes	Yes	No	No	No	3	2	1 dose	1 dose		
251	3	Yes	No	No	No	No	2	3	1 dose	2 doses		
253	5	Yes	Yes	Yes	Yes	No	2	2	1 dose	1 dose		
291	2	No	Yes	Yes	Yes	No	3	2	1 dose	1 dose		
294	3	No	Yes	Yes	Yes	No	2	3	2 doses	1 dose		
295	10	No	No	No	No	No	3	4		1 dose	1 dose	2 dose
299	3	No	Yes	Yes	Yes	No	3	2		2 doses		
300	5	No	No	Yes	Yes	No	2	3		1 dose	1 dose	1 dose
303	2	No	Yes	Yes	Yes	No	4	1	1 dose			
305	3	Yes	Yes	Yes	Yes	No	4	3	1 dose	1 dose	1 dose	
313	3	No	Yes	Yes	Yes	No	3	3	1 dose	2 doses		

[±]The variation from 1 to 2 AS doses depends on time of day that an inpatient initiates treatment. Injectable AS is given at 0, 12, 24 hourstheninpatient is swit might receive 1 to 2 AS doses per calendar-day - very rarely 3 AS doses. *N = [(The 57 artesunate users) – (Number of inpatients who did not have artesunate confidence intervals for theestimates are 28% (17% to 42%), 19% (10% to 32%), 27% (12% to 46%), 7% (0% to 36%) and 20% (0% to 72%). Nearly half (47%, 27 inpatients on AS missed at least one day of AS dosing in Days 1-3.

fileno	Length of stay, days	Preadmission antimalarial use	Admitting MalariaDiagnosis	Discharge Malaria Diagnosis	AL co-prescribed	Switched to AL	AS Doses Prescribed	AS Doses Received	Day 1	Day 2	Day 3	Day
314	3	Yes	Yes	Yes	No	No	3	3	1 dose	1 dose	1 dose	
315	3	Yes	Yes	Yes	Yes	No	3	2	1 dose	1 dose		
320	5	Yes	Yes	Yes	Yes	No	3	4	1 dose	1 dose	1 dose	1 dose
326	4	Yes	Yes	Yes	Yes	No	3	3	1 dose	1 dose	1 dose	
328	3	Yes	Yes	Yes	Yes	No	3	3	1 dose	1 dose	1 dose	
335	5	Yes	Yes	Yes	Yes	No	3	3	1 dose		1 dose	1 dose
348	7	Yes	Yes	Yes	Yes	Yes	3	3	1 dose			
353	5	No	No	No	Yes	No	3	3		1 dose	1 dose	1 dose
354	3	Yes	Yes	Yes	Yes	No	3	2	1 dose	1 dose		
361	4	No	Yes	Yes	No	No	3	2	1 dose	1 dose		
385	2	No	Yes	Yes	Yes	No	3	1	1 dose			
389	9	No	Yes	Yes	No	No	3	2	1 dose	1 dose		
400	6	No	Yes	Yes	No	No	3	3				1 dose
420	3	Yes	No	No	Yes	No	3	1	1 dose			
424	4	No	Yes	Yes	Yes	No	3	3		1 dose	2 doses	
425	3	Yes	Yes	No	Yes	No	3	3	1 dose	2 doses		
437	4	No	Yes	Yes	No	No	3	3	1 dose	1 dose	1 dose	
441	3	Yes	No	Yes	Yes	No	3	3	1 dose	2 doses		
445	4	Yes	Yes	Yes	Yes	No	3	3		1 dose	2 doses	
447	9	No	Yes	Yes	Yes	Yes	4	3			1 dose	1 dose
466	4	Yes	Yes	No	Yes	Yes	2	3		2 doses	1 dose	
475	4	No	Yes	Yes	Yes	No	6	2			1 dose	1 dose
520	3	No	Yes	Yes	Yes	Yes	1	1	1 dose			
545	16	Yes	Yes	No	No	No	3	3	1 dose	2 doses		
571	4	No	Yes	Yes	No	No	3	1	1 dose			
584	6	No	Yes	No	No	No	3	4	1 dose	1 dose	2 doses	

[±]The variation from 1 to 2 AS doses depends on time of day that an inpatient initiates treatment. Injectable AS is given at 0, 12, 24 hourstheninpatient is swit might receive 1 to 2 AS doses per calendar-day - very rarely 3 AS doses. *N = [(The 57 artesunate users) – (Number of inpatients who did not have artesunate confidence intervals for theestimates are 28% (17% to 42%), 19% (10% to 32%), 27% (12% to 46%), 7% (0% to 36%) and 20% (0% to 72%). Nearly half (47%, 27 inpatients on AS missed at least one day of AS dosing in Days 1-3.

623	5	No	Yes	Yes	Yes	No	3	3		2 doses	1 dose	
637	3	No	Yes	No	No	No	1	1	1 dose			
644	3	No	Yes	Yes	Yes	No	3	1		1 dose		
645	4	Yes	No	No	No	No	2	2	1 dose	1 dose		
699	15	Yes	No	Yes	No	No	3	8	1 dose	2 doses		1 dose
754	1	No	Yes	Yes	Yes	No	2	2	1 dose	1 dose		
Missed-dose day, n									16	10	8	1
Dose-day data unavailable, n1									0	5	27	44
Dose-day data available, N*									57	52	30	13
Proportion of inpatients with missed-dose day, n/N~									28%	19%	27%	7%

[±]The variation from 1 to 2 AS doses depends on time of day that an inpatient initiates treatment. Injectable AS is given at 0, 12, 24 hourstheninpatient is swit might receive 1 to 2 AS doses per calendar-day - very rarely 3 AS doses. *N = [(The 57 artesunate users) – (Number of inpatients who did not have artesunate confidence intervals for theestimates are 28% (17% to 42%), 19% (10% to 32%), 27% (12% to 46%), 7% (0% to 36%) and 20% (0% to 72%). Nearly half (47%, 27 inpatients on AS missed at least one day of AS dosing in Days 1-3.

Quinine: One in five (18%, 5/28; 95% CI: 6% to 37%) of inpatients who initiated antimalarials with Q missed Day 1 doses based on calendar-day; 10% (2/20; 95% CI: 1% to 32%) missed Day 2 and 14% (1/7; 95% CI: 0% to 58%) missed Day 3.One in five (18%, 5/28; 95% CI: 4% to 32%) inpatients missed at least one day of Q dosing in Days 1-3, see **Table 5**.

Table 5
Missed dose-days of quinine injection among 28 hospitalized patients who received in-hospital intravenous quinine, Uganda, 2014

fileno	Length of stay, days	Preadmission antimalarial use	Admitting Malaria Diagnosis	Discharge Malaria Diagnosis	AL co-prescribed	Switched to AL	Doses Prescribed	Doses Received	Day 1	Day 2	Day 3	Day 4
5	2	No	Yes	Yes	1		3	2	1 dose	1 dose		
28	6	Yes	Yes	Yes	1		3	3	1 dose		1 dose	1 dose
66	8	Yes	No	No	0		3	1	1 dose			
99	4	Yes	Yes	Yes	0		3	3	1 dose	1 dose	1 dose	
142	3	No	Yes	Yes	0		3	3	1 dose	2 doses		
143	4	No	Yes	Yes	0		3	1	1 dose			
165	3	No	Yes	Yes	0		3	2	1 dose	1 dose		
296	2	Yes	Yes	Yes	0		3	2	1 dose	1 dose		
343	2	Yes	Yes	Yes	1		3	1	1 dose			
376	3	No	Yes	Yes	1		3	2	1 dose	1 dose		
415	5	Yes	Yes	Yes	0		3	3	2 doses	1 dose		
416	3	Yes	Yes	Yes	0		9	3	1 dose	1 dose	1 dose	
417	4	No	Yes	Yes	0		3	3	1 dose	1 dose	1 dose	
419	3	No	Yes	Yes	1	0	3	3	1 dose	2 doses		
437	4	No	Yes	Yes	0		6	2	1 dose	1 dose		
462	8	No	Yes	Yes	0		3	3	1 dose	2 doses		
479	5	Yes	Yes	Yes	1	1	3	3	1 dose		1 dose	1 dose
484	4	Yes	Yes	Yes	1		3	3	3 doses			
489	3	Yes	Yes	Yes	0		9	3	2 doses	1 dose		
491	2	No	Yes	Yes	0		3	2	1 dose	1 dose		
fileno	**Length of stay, days**	**Preadmission antimalarial use**	**Admitting Malaria Diagnosis**	**Discharge Malaria Diagnosis**	**AL co-prescribed**	**Switched to AL**	**Doses Prescribed**	**Doses Received**	**Day 1**	**Day 2**	**Day 3**	**Day 4**
598	9	No	Yes	No	0		6	3		2 doses	1 dose	
633	3	No	Yes	Yes	1		21	3	2 doses	1 dose		
674	2	No	Yes	Yes	1			1	1 dose			
680	10	No	Yes	Yes	1	1	6	3	2 doses	1 dose		

*N = [(The 28 quinine users) – (Number of inpatients without quinine dose-day data)] or (28-n1); ~95% confidence intervals for the estimates are 18% (6% to 37%), 10% (1% to 32%), 14% (0% to 58%).One in five (18%, 5/28; 95% CI: 4% to 32%) inpatients missed at least one day of Q dosing in Days 1-3.

699	15	Yes	No	Yes	0		21	3			2 doses	1 dose
713	2	No	Yes	Yes	0		3	2	1 dose	1 dose		
721	2	No	Yes	Yes	0		3	2	1 dose	1 dose		
761	6	No	Yes	Yes	1	1	3	2	1 dose	1 dose		
Missed-dose day, n									5	2	1	
Dose-day data unavailable, n1									0	8	21	
Dose-day data available, N *									28	20	7	
Proportion of inpatients with missed-dose day, n/N ~									18	10	14	
*N = [(The 28 quinine users) – (Number of inpatients without quinine dose-day data)] or (28-n1); ~95% confidence intervals for the estimates are 18% (6% to 37%), 10% (1% to 32%), 14% (0% to 58%).One in five (18%, 5/28; 95% CI: 4% to 32%) inpatients missed at least one day of Q dosing in Days 1-3.												

Artesunate vs. Quinine: The frequency of missing at least one day of antimalarials in Days 1-3 was significantly higher among inpatients who received AS vs. inpatients who received Q (difference of 29%; 95% CI: 7% to 45%; 1 df; $\chi 2$ =6.7; *P*-value = 0.010).

Malaria-in-pregnancy: For both AS and Q, there was no significant difference in frequency of missed-dose days based on pregnancy-status, see **Appendix**.

Mortality among inpatients who received in-hospital antimalarials

Four of 100 inpatients who received in-hospital antimalarials died during hospitalization. All four inpatients had clinically-diagnosed malaria: microscopy was requested is three inpatients, but results were not available, see **Box 2**.Unconscious 88-year-old female of unknown HIV-status presented with a single admitting diagnosis of severe malaria and pulse rate of 98 beats per minute. She received a pre-referral intramuscular Q dose 23 hours preadmission and two Qdoses 11 hours apartafter admission. She died on Day 2 of hospitalization. The other three cases had multiple diagnoses, see **Box 2**.

Patient-level risk-factors for missed Day 1 dosing of antimalarials

Number of admitting diagnoses was a statistically significant risk-factor for missed Day 1 dosing of hospital-initiated antimalarialsbased on calendar-day (OR = 2.7, 95% CI: 1.53-4.54; *P*-value < 0.001), see **Table 6**. Similar results of missed Day 1 risk-factorwere obtained based on *post-admission 24-hour-delay*, see **Table S1**.Malaria-in-pregnancy was not significantly relatedto missed Day 1 dosing of antimalarials.

Missed Day 1 dosing of hospital-initiated antimalarials versus length of hospital stay

Nostatistically significant association was observedbetween missed Day 1dosing of antimalarials and length of hospital stay (OR = 1.1, 95% CI: 0.91-1.27; *P*-value <0.396).Mean length of hospital stay for missed Day 1 cases was 4.7 (SD=1.7) days versus 4.2 (SD=2.5) days for non-cases.

Table 6
Patient-level risk-factors for missed Day 1 dosing of administered antimalarials based on calendar-day delay among inpatients with an admitting malaria diagnosis, Uganda, 2014

Missed Day 1 dosing of antimalarials by calendar-day, n (%); (N = 83)									
Factor	**Missed Calendar-Day 1 dosing**			**Crude Analysis**			**Adjusted Analysis**		
	Yes	**No**	**Total, [% col][a]**	OR[b]	95% for CI[c]	*P*-value	OR[b]	95% for CI[c]	*P*-value
Antiretroviral therapy use									
No	15 (20)	59 (80)	74 [89]	1.0			1.0		
Yes	5 (56)	4 (44)	9 [11]	4.9	1.17-20.6	0.029	5.0	0.92-26.9	0.062
Malaria microscopytest results available									
No	8 (17)	39 (83)	47 [57]	1.0			1.0		
Yes	12 (33)	24 (67)	36 [43]	2.4	0.87-6.82	0.090	2.5	0.72-8.71	0.146
Linear on number of working									
Diagnoses	20	63	83	2.6	1.56-4.35	<0.001	2.7	1.53-4.64	0.001

[a]% Column; [b]OR = Odds Ratio; [c]confidence interval

Box 1: Missed opportunity for hospital-initiated antimalarial treatmentfor four inpatients with malaria parasitaemia as confirmed by microscopy, Uganda.	
Particulars	**Clinical notes**
Patient 1	A 60-year-old female with unknown HIV-status, 6-year history of hypertension and type 2 diabetes mellitus (DM) presented with poorly controlled DM having defaulted on DM treatment for 8-months. Microscopy for malaria parasites was requested on the day of admission (Day 1). Results were returned on Day 1 with confirmed malaria parasitaemia. AL and paracetamol were prescribed on Day 2 but not dispensed. The patient was discharged on Day 3 without antimalarial treatment.
Patient 2	A 24-year-old female with unknown HIV-status was referred from a clinic where she had been treated for suspected malaria and typhoid with no improvement. She presented with poorly treated malaria and a request for microscopy for malaria parasites was made on Day 1. Results were returned on Day 2 with confirmed malaria parasitaemia. AL and paracetamol were prescribed on Day 2 but not dispensedand the patient was discharged on Day 2 without antimalarial treatment.
Patient 3	A 44-year-old HIV-negative male was transferred from a referral hospital. He presented with an admitting diagnosis of chronic lymphocytic leukaemia and confirmed malaria parasitaemia by microscopy. No fresh request for malaria microscopy was made during the current admission. The patient did not receive any antimalarial treatment prescription and/or administration both prior to admission and throughout the current hospitalization. He was transferred to Uganda Cancer Institute on Day 3.
Patient 4	A 43-year-old HIV-positive female with history of DM and receiving second-line antiretroviral therapy, ART (tenofovir, lamivudine, lopinavir/ritonavir) and co-trimoxazole presented with an admitting diagnosis of colon cancer. Microscopy for malaria parasites was requested on Day 2 and results were returned the same day with confirmed malaria parasitaemia. No antimalarial treatment was prescribed, dispensed or administered during hospitalization though the patient continued to receive her ARTP and co-trimoxazole. The patient was transferred to Uganda Cancer Institute on Day 17.

Box 2: Mortality of four inpatients who received in-hospital antimalarial treatment, Uganda.	
Particulars	**Clinical notes**
Quinine	One inpatient who received Q during admission died in hospital.
Patient 1-Q	An 88-year-old female of unknown HIV-status presented with a single admitting diagnosis of severe malaria which manifested with fever, chills and unconsciousness. She was referred from a clinic for further management after receiving an initial intramuscular dose of quinine (23 hours prior to the current admission). Her vitals on admission were: pulse rate (98 beats per minute); blood pressure (116/63 mmHg); temperature (35.9 ^{o}C). Microscopy for malaria parasites was requested on admission (Day 1) but the results were not returned by Day 2. She received 2-doses of Q which were administered 11 hours apart, the first dose being 2 hours after admission on Day 1. The patient died on Day 2 of hospitalization.
Artesunate	Two inpatients who received AS during admission died in hospital. None of the two inpatients presented with either an admitting or a discharge malaria diagnosis:
Patient 1-AS	A 20-year-old female of unknown HIV-status was admitted with suspected severe sepsis of chest focus, bacterial pneumonia, urinary tract infection (UTI), salmonellosis and acute gastroenteritis. Microscopy for malaria parasites was requested on Day 1 but the results were not returned. She missed Day 1 dosing of AS and subsequently received 4 doses of AS. Her discharge diagnoses were UTI, pneumonia and salmonellosis. She died on Day 4.
Patient 2-AS	A 24-year-old HIV-positive female presented with severe immunosuppression, sepsis, disseminated tuberculosis and/or tuberculous meningitis, atypical measles syndrome and toxoplasmosis. Microscopy for malaria parasites was not requested on admission. She received 2 doses of AS and never missed Day 1 dosing. Her discharge diagnosis was severe immunosuppression. She died on Day 10.
Artemether + Lumefantrine	One inpatient who received AL in hospital died.
Patient 1-AL	A 23-year-old HIV-positive female presented with working diagnoses of immunosuppression, malaria, septicaemia, urinary tract infection and anaemia. Microscopy for malaria parasites was requested on admission (Day 1) but the results were not returned. Duocotexcin (DP) was prescribed on Day 1 but was neither dispensed nor administered. One dose of AL was administered on Day 3. Her discharge diagnoses were immunosuppression and malaria. She died on Day 6.

Discussion

Malaria microscopy was requested in 77% of inpatients with an admitting malaria diagnosis, similar to estimates for the public sector (80%) in moderate- to high-transmission countries in sub-Saharan Africa (SSA) [1]. Unfortunately, only half the microscopy results were available to guide appropriate antimalarial treatment. Thus, despite decent microscopy rates, healthcare professionals still rely on clinical judgement to treat half the suspected malaria cases. Clinical judgement increases the risk of unnecessary antimalarial treatment and, in turn, depletes antimalarial stocks for inpatients who truly need them; and increases the incidence of associated adverse drug reactions and drug resistance [2]. Seven in ten inpatients with suspected non-pregnancy-related malaria tested negative for malaria and would therefore not need antimalarials; compared with only two in ten inpatients with suspected malaria-in-pregnancy. The value of a confirmed malaria diagnosis depends on prompt availability of parasitology results and whether the clinician uses the results to decide how to manage the patient. Malaria negative test-results as confirmed by microscopy - the gold standard - should prompt clinicians to examine patients for other causes of illness and treat them accordingly [2]. However, the interpretation of negative microscopy results should take into account the high rates of antimalarial pre-treatment, which was as high as one in three admitted patients with suspected malaria in this patient cohort. A rapid diagnostic test (RDT), in addition to microscopy, could be used to detect the *HRP2* malaria antigen in patients who recently received antimalarials and whose blood films are, thus, likely to show no malaria parasitaemia [2]. RDTs can give positive results for up to 1-month after parasite clearance [2].

One in six cases of confirmed malaria did not receive antimalarials during the current hospitalization, which raises concern over the safety of inpatient care at this tertiary care hospital. Poor coordination between the laboratory and clinicians is likely, which is exacerbated by high inpatient loads of up to 80 admissions in wards with official bed capacity of 54 [3]. Introducing an integrated electronic health record (EHR) system to track inpatient care could significantly improve the flow of information between different hospital departments and, in so doing, promote efficient clinical management of inpatients [12].

One in four inpatients who received at least one in-hospital dose of prescribed antimalarials missed the first day of their antimalarials, which is relatively frequent. Also, monotherapy and incomplete dosing primarily associated with injectable AS and Q were common, possibly fuelled by observed disparities in prescribed, dispensed and administered antimalarials –similar to observations made elsewhere [8, 10]. Possible reasons for these system lapses include; i) drug stock-outs, ii) poor communication between clinician and patient/caregiver and, iii) work overload [3]. The hospital should improve its stock forecasting for in-demand antimalarials, continue to promote intern-pharmacist-led bedside dispensing to reduce the clinicians' workload during drug administration and improve supervision of junior and mid-level clinicians to promote accountability to inpatients and the hospital [3].

Each additional admitting diagnosis increases by more than two-fold the odds of missed Day 1 dosing of prescribed antimalarials, which underlines the need for prompt availability of malaria test-results to promote the timely initiation of antimalarials. Prompt and complete antimalarial treatment rapidly eliminates malaria parasites from a patient's bloodstream [13]. Patients with severe malaria should access timely appropriate antimalarials, avoid antimalarial monotherapy and complete full courses of prescribed antimalarials to promote therapeutic success, reduce malaria-related morbidity and mortality, and prevent the emergence and spread of drug resistance [7–9].

Inpatients with an admitting malaria-in-pregnancy diagnosis seemed more likely to have a microscopically-confirmed malaria diagnosis than inpatients with other admitting malaria diagnoses. This comparative advantage at diagnosis did not translate into better antimalarial treatment because no pregnancy-related difference was observed in the prescription, dispensing and administration of antimalarials. Improvement in the antimalarial medication-use-cycle should target systemic weaknesses.

Unlike Q, the hospital frequently encounters drug stock-outs of in-demand, free-of-charge AS and AL, which inpatients must purchase from private community pharmacies to prevent lapses in prescribed treatment. Drugs bought from private community pharmacies are not recorded as dispensed in the hospital register [3], which explains why the reported number of inpatients with administered AS and AL exceeds the number of inpatients to whom these two drugs are dispensed. AS and AL are more in demand than Q because; i) AS is the drug of choice for its faster parasite clearance, less tedious administration regime, and safer profile and, ii) AL is administered after both injectable AS and Q as the continuation of antimalarial treatment in severe malaria [2].

Death could be attributed to severe malaria and/or quinine-related treatment in the 88-year-old female with a single admitting severe malaria diagnosis. The caveat to this malaria-related attribution is malaria based on clinical judgement only (in the absence of microscopy results), unknown HIV-serostatus, advanced age, unknown random blood sugar levels and other comorbidities – especially cardiovascular comorbidities. That notwithstanding, Q was poorly administered at intervals of 25 hours (between first and second doses) and 11 hours (between second and third doses). Yet, 8-hourly intervals of injectable Q administration for at least 24 hours are recommended until the patient is able to take oral medication [2]. The unconsciousness manifested in this inpatient is a known key sign of hypoglycaemia in severe falciparum malaria and carries a high risk of mortality [2]. Unfortunately, hypoglycaemia can result from both severe malaria and quinine-induced hyperinsulinaemia. Thus, blood sugar levels should be checked frequently in severe malaria inpatients who receive Q [2]. Also, this inpatient had tachycardia which could have resulted from Q use and/or hypoglyaemia. With hindsight, this elderly inpatient should have been treated with injectable AS instead, although the frequent unavailability of in-demand AS, and its associated higher cost, often dictates treatment with Q. This fatal case of suspected severe malaria underpins the need for the rapid turnaround of microscopy test-results and the hospital's investment in routine random blood sugar testing to improve the clinical management of inpatients with severe malaria.

In conclusion, half the malaria microscopy results were not available to guide the clinical management of malaria despite that the rate of testing was high. Laboratory services should improve to promote the treatment of malaria based on confirmed diagnosis as opposed to clinical judgement only, which could reduce the unnecessary use of antimalarials. System-level improvement is required in the procurement, prescription, dispensing and administration of antimalarials to curb the rampant missed opportunities for antimalarial treatment, monotherapy especially with injectable antimalarials and delayed/missed antimalarial doses.

The study's limitations have been reported elsewhere [3]. Briefly, the study was conducted at Uganda's National Referral and Teaching Hospital and the results might not be generalizable to facilities with lower calibres of inpatient care. Also, antimalarials that were purchased from private community pharmacies were not documented as dispensed in the hospital register so we obtained this dispensing information by interviewing the inpatients and/or their caregivers [3].

Declarations

Ethics approval and consent to participate:

Ethical approval was granted by the School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences (REC REF No. 2011 – 113), Mulago Hospital Research and Ethics Committee (MREC 253), and Uganda National Council for Science and Technology (HS 1151). All participants gave written informed consent.

Consent for publication:

Consent to publish this work was sought during the informed consent process.

Availability of data and materials:

The dataset for this publication is available on reasonable request from the corresponding author.

Competing interests:

SMB. holds GSK shares. RK and CK have nothing to declare.

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Authors' contributions:

RK conceived the study, supervised data collection and conducted data analysis. RK, SMB and CK designed the study, participated in interpretation of results and manuscript writing. All authors read and approved the final draft of the manuscript.

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