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ORIGINAL ARTICLE

Efficacy of artemether–lumefantrine versus dihydroartemisinin–piperaquine for the treatment of uncomplicated malaria among children in Rwanda: an open-label, randomized controlled trial

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Background: Artemisinin-based combination therapies (ACTs) have proven highly effective in reducing malaria morbidity in sub-Saharan Africa. Artemether–lumefantrine (AL) was introduced in 2005 as a first-line ACT for the treatment of uncomplicated malaria in Rwanda. Monitoring the therapeutic efficacy of ACTs is necessary to ensure effective malaria case management.

Methods: A comparative study on the efficacy of AL and dihydroartemisinin–piperaquine (DHP) was conducted in two sites, Masaka and Ruhuha, between September 2013 and December 2015. Clinical and parasitological responses were assessed at days 28 and 42.

Results: A total of 534 children were treated with AL (n=267) or DHP (n=267). After polymerase chain reaction (PCR) adjustment, 98.3% and 98.9% of children in the AL and DHP arms, respectively, achieved an adequate clinical and parasitological response (ACPR) at day 28. At day 42, PCR-adjusted ACPR proportions were 97.3% and 98.4% for AL and DHP, respectively. PCR-adjusted ACPR was 99% for both drugs at days 28 and 42 in Ruhuha. The PCR-adjusted ACPR proportions in Masaka were 97.3% for AL and 98.5% for DHP at day 28 and 95.2% for AL and 97.5% for DHP at day 42.

Conclusions: AL remains efficacious in Rwanda 10 y after its adoption. The probability of new infections occurring among patients in the DHP arm was significantly lower than those in the AL arm. DHP also demonstrated a greater post-treatment prophylactic effect against new infections compared with AL.

Keywords: antimalarial resistance monitoring, artemisinin-based combination therapy, malaria, Rwanda, sub-Saharan Africa

Introduction

Antimalarial chemotherapies remain one of the most powerful tools for limiting malaria morbidity and mortality in sub-Saharan Africa.[1] Artemether–lumefantrine (AL) was introduced in Rwanda in 2005 for the treatment of uncomplicated *Plasmodium falciparum* malaria.[2] AL is now available in all Rwandan health facilities and has recently been approved for dispensing by community health workers to all individuals >6 months of age following a positive malaria test as part of the expanded home-based management of malaria strategy.[3] In addition to its adoption in Rwanda, AL is also being used as a first-line treatment throughout much of sub-Saharan Africa.[4]

Increased drug pressure has been identified as the main cause behind the development of resistance to antimalarial drugs in *P. falciparum*.[5,6] Following the development of resistance to chloroquine, sulphadoxine–pyrimethamine and amodiaquine,[7] these drugs are no longer prescribed as first-line

treatments and the World Health Organization (WHO) now recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* infection.[8] Pairing a fast-acting artemisinin derivative with a more slowly eliminated partner drug is intended to rapidly reduce parasite biomass and provide protection against the development of resistance.[9] Additionally, oral ACT formulations are generally well tolerated and highly effective for treating uncomplicated malaria when the recommended dosage regimens are adhered to.[10–12]

Multidrug resistance and ACT treatment failure have been recently reported in the Mekong subregion of Southeast Asia[13–16] and there is a claim that artemisinin resistance was detected in a patient infected in Africa.[17] Once the therapeutic efficacy of a first-line ACT has declined below 90%, the WHO recommends the treatment be replaced and an ACT with a demonstrated cure rate of at least 95% be adopted.[18] Continuously monitoring the efficacy of first-line ACTs as well as those under consideration for future use is critical to inform treatment policy.[19]

To our knowledge, only a single trial evaluating the efficacy of ACTs has been conducted in Rwanda.[20] The trial was part of a multicountry study conducted from 2007 to 2009 and demonstrated that AL and dihydroartemisinin–piperaquine (DHP) were highly efficacious in Rwanda. Monitoring the efficacy of the nationally recommended ACTs in Rwanda is critical to the continued success of these drugs and policymakers require up-to-date evidence to determine if the pharmacotherapies provided in Rwanda have retained their ability to treat uncomplicated malaria appropriately.

In the current study, the Rwanda National Malaria Control Program compared the efficacy of AL with DHP for the treatment of children with uncomplicated *P. falciparum* malaria as a part of their national drug-resistance monitoring initiative. DHP is currently not prescribed in Rwanda and represents a potential replacement for AL. The objective of the study was to determine and compare the efficacy of these two ACTs in treating uncomplicated malaria among children. Secondary objectives included comparing treatment efficacy across study sites and examining the protective effect of the two drugs against new infections. The results of this study are intended to provide the empirical evidence needed to inform antimalarial drug policy in Rwanda.

Methods

Study design and sites

This open-label, randomized trial was implemented by the Rwanda National Malaria Program to compare the efficacy of AL and DHP for the treatment of uncomplicated *P. falciparum* malaria among children (ages 1–14 y).[21] The study was conducted at the Masaka and Ruhuha health centres in the Bugesera and Kicukiro Districts, respectively (Figure 1) from September 2013 to December 2015. The Masaka health centre, adjacent to the capital city of Kigali, was selected as a study site due to its urban/peri-urban location. The Ruhuha health centre is located in a rural region within Rwanda's Eastern Province and was selected because of the continued increase in malaria cases recorded here even after indoor residual spraying had been implemented throughout the district. Both areas are characterized by moderate malaria transmission with two seasons: May–July and November–December. *P. falciparum* is the predominant malaria species within the two study areas, accounting for approximately 95% of malaria cases.

Ethical approval

The study received ethical approval from the Rwanda National Ethics Committee on 16 May 2012 (RNEC129/RNEC/2012). Written informed consent was obtained from the parent/caretaker of eligible children before enrolment in the study. If the parent/caretaker was illiterate, a witness' signature and the thumbprint of the participant's parent/caretaker were required.

Study population

Children 1–14 y of age presenting at the Masaka or Ruhuha health centres with fever (temperature ≥37.5°C) and/or a history of fever within the past 24 h and microscopy-confirmed *P. falciparum* mono-infection with asexual parasitaemia of 1000–100 000/μl were eligible for enrolment. Other inclusion criteria were the ability to attend follow-up visits and informed consent provided by a parent/caretaker. Children were excluded if they displayed symptoms of severe malaria,[22] comorbid infection, severe anaemia, epilepsy, history of drug allergy, treatment with any antimalarial drugs over the previous 2 weeks or enrolment in any other malaria-related study.

Sample size

Sample size calculations were informed by results from the 2009 study on AL and DHP conducted in Rwanda.[20] Using a two-sided type I error rate of 0.05 and an 80% power to detect a 5% difference between treatments, a sample of 268 patients per treatment arm was used. The total sample for each treatment arm was split evenly between the two study sites.

Study procedure

Children first underwent a medical examination and a blood sample was drawn. Once *P. falciparum* infection and eligibility criteria were confirmed, the purpose of the study was presented by a member of the study team and consent from the parent/caretaker was obtained. Treatment assignment was randomized and blinded through sealed envelopes that were opened after informed consent was obtained, stratified by health centre.

Oral treatments were administered to patients under direct supervision over 3 consecutive days according to the patient's body weight. AL was administered twice per day while DHP was given once daily, in line with the manufacture's dosing schedule. In case of vomiting within 30 min of treatment administration, a full dose of the drug was re-administered. The parent/caretaker of the participating child was asked to return with the participant for follow-up visits and blood draws on days 1, 2, 3, 7, 14, 21, 28, 35 and 42 or on any unscheduled day if malaria-like symptoms emerged. Thick blood smears were prepared for each patient during follow-up visits and examined to assess the parasitological response, as per WHO protocol.[21] Children received rescue treatment according to the national treatment guidelines if treatment failure was observed. Filter paper blood

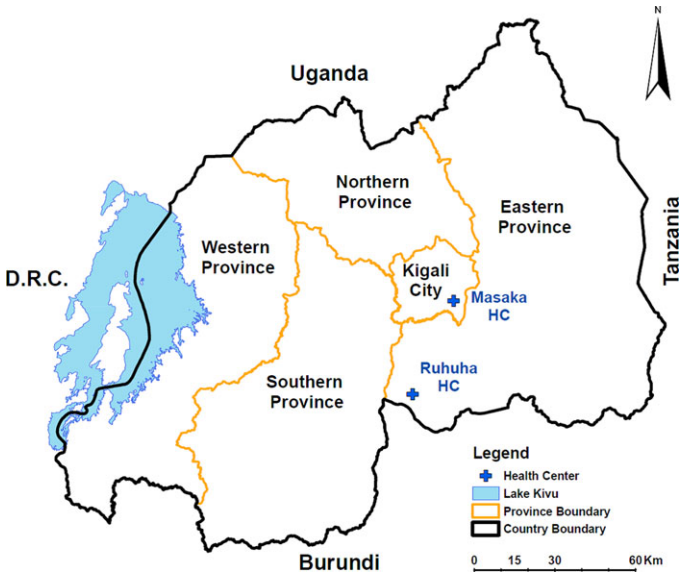

Figure 1. Map of Rwanda with the Masaka and Ruhuha study site locations.

spots were collected from participants prior to treatment (day 0) and on the day of parasite recurrence beginning on day 7 for polymerase chain reaction (PCR) genotyping to differentiate recrudescence from new infection.

Treatment outcomes

The primary treatment outcomes were PCR-unadjusted and PCR-adjusted adequate clinical and parasitological response (ACPR)[21] at 28 and 42 days follow-up. Early treatment failure (ETF), late parasitological failure (LPF), late clinical failure (LCF) and ACPR were classified in accordance with the WHO protocol.[21] A participant was considered as experiencing ACPR if he/she was not classified as experiencing ETF, LPR or LCF. Parasite clearance on day 2 and day 3 were calculated and compared across the two drugs. Treatment outcomes for each drug were compared across the two study sites.

Laboratory techniques

Trained microscopy technicians quantified asexual parasites on thick smears (per 8000 white blood cells) and thin smears were used for species identification. A minimum of 100 fields were read before slides were deemed parasite negative. Each slide was assessed independently by two microscopy technicians at each health centre and a geometric mean parasite density was calculated.

Dried filter paper blood spots from patients on day 0 and from patients with parasite recurrence on day 7 and onwards were punched, placed in a 96-well plate, lysed overnight in a saponin solution and DNA was extracted with the InstaGene Matrix resin (Bio-Rad, Hercules, CA, USA) as described previously by Canier et al.[23] DNA samples from day 0 and from the day of parasite recurrence were analysed for genotyping of msp1, msp2 (merozoite surface proteins 1 and 2) and glurp (glutamate-rich protein) loci. Recurring parasites were classified as recrudescence if parasites were the same strain as those on day 0 or as a new infection if they were of different strains compared with the day 0 parasites.

Data analysis

Two clerks double-entered data into Microsoft Access (Microsoft, Redmond, WA, USA) at the two study sites. Analyses were conducted using the WHO Microsoft Excel software for data management and analysis[24] as well as Stata version 14.2 (StataCorp, College Station, TX, USA).[25] Kaplan–Meier survival curves were created to display the cumulative probability of ACPR up to day 42 after treatment initiation. Log-rank tests were employed to compare the ACPR proportions for the two ACTs. A per-protocol analysis was conducted excluding patients with new infections during the follow-up period to calculate the proportion of the ACPR in the PCR-adjusted data set. Data were excluded from the PCR-adjusted analyses if the genotyping results were unclassifiable or identified a new infection. The efficacies of the two drugs were also compared across study sites. Chi-square or Fisher's exact tests were employed to analyse categorical data. Independent samples t tests were used to analyse continuous data. Statistical significance for all tests was set at α=0.05.

Results

Patient characteristics

Of the 1920 febrile children screened for potential malaria at the two study sites, 576 (30%) were deemed infected with *P. falciparum*. Of these, 550 children met the eligibility requirements for the study (Figure 2). The parent/caretaker of 14 eligible children declined to participate in the study. Subsequently, 536 children were enrolled: 267 were randomly assigned to receive AL (131 at the Masaka health centre and 136 at the Ruhuha health centre) and 269 were randomly assigned to receive DHP (137 at the Masaka health centre and 132 at the Ruhuha health centre). On day 0, two patients (both AL arm) vomited within 30 min of treatment administration and were readministered a full dose. One patient vomited 40 min after treatment on day 0 (DHP arm) and was readministered a half dose against protocol. This patient did not experience any adverse effects but was removed from the analytical data set. One additional child (Masaka health centre, DHP arm) was hospitalized on day 2 for the treatment of severe anaemia. Parasite density for this child was 96 000 at day 0, but the patient was hospitalized before attending the day 2 follow-up and was withdrawn from the study. No other participants were excluded or lost to follow-up.

Table 1 presents the baseline characteristics of participants in the study. Except for parasitaemia, the baseline profile children in the AL and DHP treatment groups were comparable. The geometric mean parasite density at day 0 was significantly lower (p=0.02) among patients in the AL arm compared with those in the DHP arm. No other statistically significant differences were present.

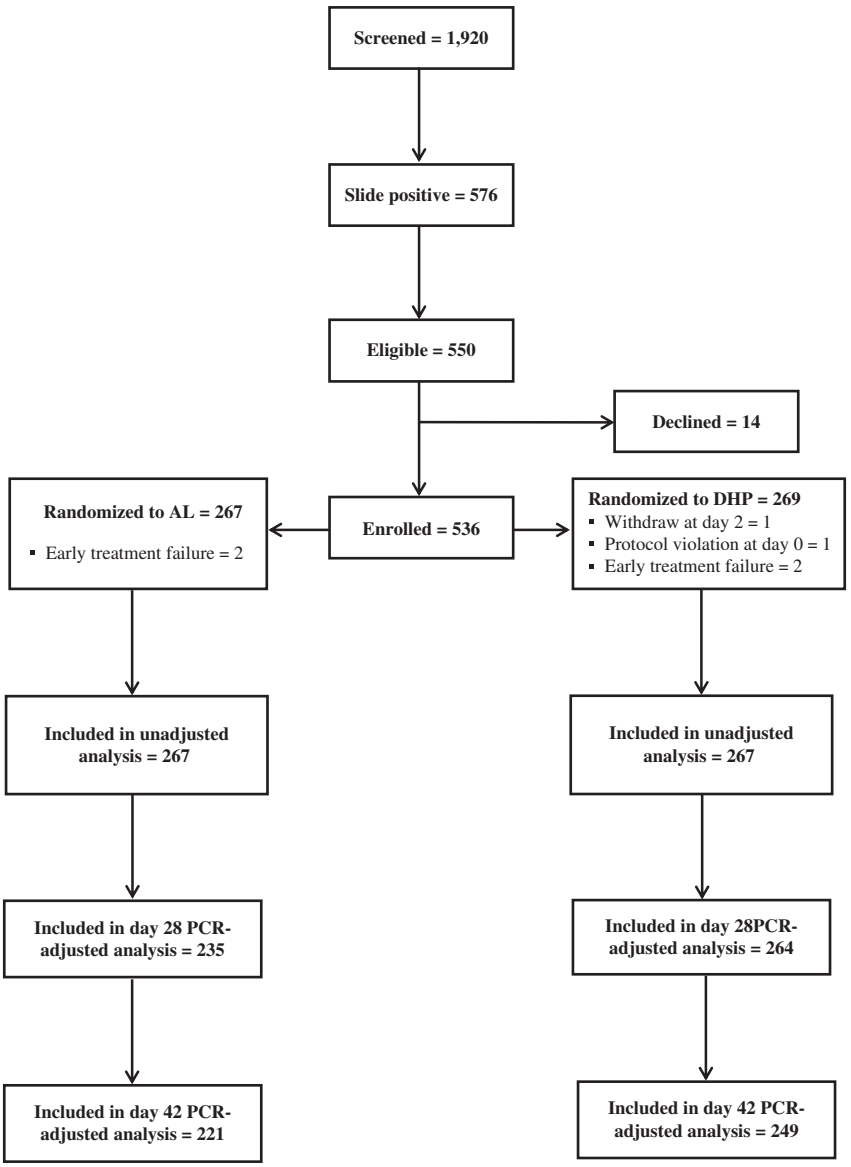

Figure 2. Trial profile.

Table 1. Baseline characteristics of study participants

Characteristics	AL (n=267)	DHP (n=267)	p-Value
Age (months)	97.5 (60–132)	95.1 (60–130)	0.50
Male, n (%)	129 (49.2)	132 (50.6)	0.80
Weight (kg)	24.2 (17–30)	23.0 (17–28)	0.13
Temperature (°C)	37.8 (37.0–38.5)	37.9 (37.0–38.5)	0.31
Geometric mean parasite density at day 0	14 938 (2160–17 600)	19 316 (3600–27 200)	0.02

Values are presented as median (interquartile range) unless stated otherwise.

PCR genotyping to differentiate between reinfection and recrudescence

A filter paper spot was not collected from one patient on the day of failure (LCF day 29, Ruhuha health centre, DHP arm) and consequently PCR analysis could not be conducted for this individual. The paired filter paper samples of the remaining 69 individuals (50 for AL and 19 for DHP) with parasite recurrence were submitted for genotyping. For the AL arm, 44 cases were classified as new infections (88.0%), 4 were recrudescence (8.0%) and 2 samples could not be classified (4.0%). Among the 19 samples genotyped for patients in the DHP arm, 16 were classified as new infections (84.2%), 2 as recrudescence (10.5%) and 1 could not be classified (5.3%). Data were censured at the last date of follow-up for participants with new infections or unclassified PCR results.

Treatment outcomes

Table 2 presents both the unadjusted and PCR-adjusted treatment outcomes at days 28 and 42. ETF was documented in four children, two in the AL arm (one patient with confirmed parasitaemia on day 1 with the presence of danger signs and one patient with confirmed parasitaemia on day 3 and a temperature ≥37.5°C) and two in the DHP arm (both patients with confirmed parasitaemia on day 1 with the presence of danger signs). Children who experienced ETF were subsequently treated with injectable artensunate according to the national treatment guidelines.

Prior to PCR adjustment, the proportion of children achieving ACPR at day 28 was 86.5% and 97.8% for the AL and DHP arms, respectively. The ACPR rates at day 42 were 80.5% for children in the AL arm and 91.8% for the DHP arm. The proportion of children remaining parasite free at both day 28 and day 42 was significantly higher among those treated with DHP compared with AL (p<0.01). For the PCR-adjusted data, there was no difference in ACPR rates between the AL and DHP arms at day 28 or day 42 (Table 2). On day 2, 3.4% (n=9) of children in the AL arm and 1.5% (n=4) of children in the DHP arm had parasites (p=0.17). These proportions dropped to 0.8% (n=2) for both arms on day 3 (p=0.99).

Kaplan–Meier survival analysis was employed to compare the cumulative probability of ACPR at days 28 and 42 for AL and DHP. Results of the log-rank test using the unadjusted data indicated that children treated with AL had a significantly lower probability of ACPR at both day 28 and day 42 (p<0.01) (Figure 3). The differences in the PCR-adjusted probabilities of ACPR were not statistically different between the AL and DHP arms at day 28 (p=0.69) or day 42 (p=0.48) (Figure 4).

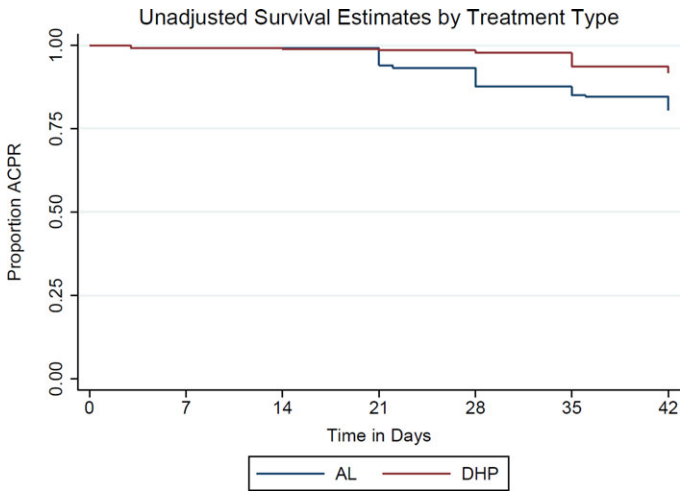

Figure 3. Kaplan–Meier survival estimates prior to PCR adjustment.

Table 2. Unadjusted and PCR-adjusted day 28 and day 42 efficacy estimates

Unadjusted	Day 28					Day 42				
	AL (n=267)		DHP (n=267)		p-Value	AL (n=267)		DHP (n=267)		p-Value
	n	%	n	%		n	%	n	%	
Early treatment failure	2	0.8	2	0.8	0.99	2	0.8	2	0.8	0.99
Late clinical failure	16	6.0	2	0.8	0.01	24	9.0	10	3.8	0.01
Late parasitological failure	18	6.7	2	0.8	0.01	26	9.7	10	3.8	0.01
Adequate clinical and parasitological response	231	86.5	261	97.8	0.01	215	80.5	246	91.8	0.01
PCR adjusted	**Day 28**					**Day 42**				
	AL (n=235)		DHP (n=264)		p-Value	AL (n=221)		DHP (n=249)		p-Value
	n	%	n	%		n	%	n	%	
Early treatment failure	2	0.9	2	0.8	0.99	2	0.9	2	0.8	0.99
Late clinical failure	2	0.9	1	0.4	0.60	3	1.4	1	0.40	0.35
Late parasitological failure	0	0	0	0	–	1	0.5	1	0.4	0.99
Adequate clinical and parasitological response	231	98.3	261	98.9	0.44	215	97.3	245	98.4	0.53

The probability of a new infection occurring among patients in the DHP arm was significantly lower than in the AL arm at both day 28 (DHP 0.74% vs AL 11.6%, p<0.01) and day 42 (DHP 6.0% vs AL 16.5%, p<0.01). Comparing efficacy results across the two study sites indicated that children treated with both AL (p=0.02) and DHP (p=0.01) in Masaka were more likely to experience parasitaemia at day 42 based on the unadjusted data compared with patients in Ruhuha (Table 3). The PCR-adjusted data indicate that the majority of these recurrences were due to new infections.

Discussion

This antimalarial resistance monitoring study demonstrated that AL remains highly efficacious in Rwanda a decade after its introduction as a first-line therapy for uncomplicated *P. falciparum* malaria, with a PCR-adjusted cure rate >98% on day 28. DHP, a potential replacement for AL, was also highly efficacious, with a PCR-adjusted cure rate of 98.9% on day 28. Similarly high efficacy rates for AL and DHP had been reported in Rwanda between 2007 and 2009,[20] suggesting that both ACTs have retained their efficacy thus far.

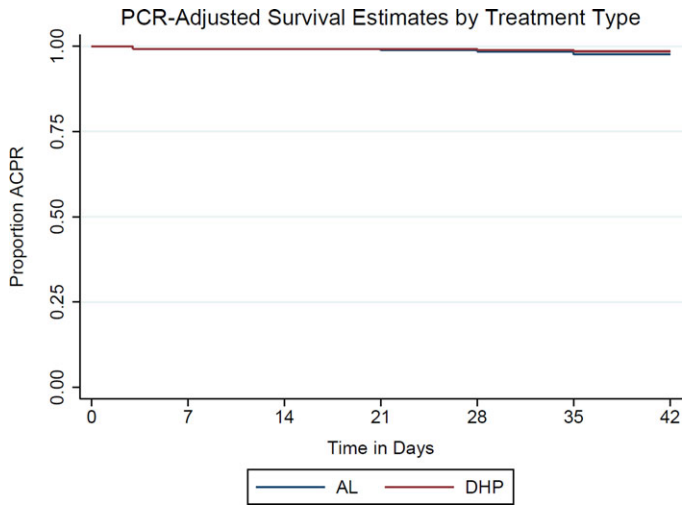

Figure 4. PCR-adjusted Kaplan–Meier survival curves.

The rate of new infections was higher in the AL arm compared with the DHP arm on both day 28 and day 42, indicating that DHP offered a greater post-treatment prophylactic effect against new infection compared with AL. This protective effect measured in the DHP arm corroborates findings from neighbouring Uganda, where a 2.5 times lower risk of new infection was observed among children treated with DHP compared with those treated with AL.[26] ACTs that provide protection against subsequent infections, such as DHP,[27] could play an important role in interventions such as mass drug administrations or seasonal malaria chemoprevention.[28] Employing such drugs strategically could help to lessen the public health impact of successive infection in children[29] and possibly older adults, who themselves experience high mortality rates if they develop severe malaria.[30,31]

The high rate of new infections observed in the current study also demonstrates the persistent risk of malaria in Rwanda. In particular, the risk of new infection was higher in Masaka compared with Ruhuha for both treatment groups. Further investigation is necessary to understand the underlying reasons for this difference, but could potentially include variations between sites in transmission intensity, vector control efforts or bed-net usage. This pervasive, nationwide risk is further demonstrated by the 11-fold increase in malaria cases documented in Rwanda between 2011and 2016.[32]

Our findings for children with uncomplicated malaria treated with AL and DHP are encouraging and are in line with other recent reports from sub-Saharan Africa.[33–35] However, the emergence of artemisinin resistance and ACT treatment failure in Southeast Asia calls for concern and underlines the need for national malaria programs to continuously monitor the efficacy of recommended ACTs.[19] A limitation worth mentioning is only two study sites were selected for the trial and, although they

Table 3. Site comparisons of unadjusted and PCR-adjusted day 28 and day 42 efficacy estimates

Efficacy	Masaka		Ruhuha		
	n	%	n	%	p-Value
AL unadjusted					
Day 28 adequate clinical and parasitological response	108/131	82.4	123/136	90.4	0.06
Day 42 adequate clinical and parasitological response	98/131	74.8	117/136	86.0	0.02
AL PCR adjusted					
Day 28 adequate clinical and parasitological response	108/111	97.3	123/124	99.1	0.35
Day 42 adequate clinical and parasitological response	98/103	95.2	117/118	99.2	0.10
DHP unadjusted					
Day 28 adequate clinical and parasitological response	131/136	96.3	130/131	99.2	0.21
Day 42 adequate clinical and parasitological response	117	86.0	128	97.7	0.01
DHP PCR adjusted					
Day 28 adequate clinical and parasitological response	131/133	98.5	130/131	99.2	0.99
Day 42 adequate clinical and parasitological response	117/120	97.5	128/129	99.2	0.35

represent areas with different urbanization classifications, these two study sites may not fully capture the efficacy pattern for the entire country.

Conclusions

AL remains highly efficacious in Rwanda a decade after its introduction as a first-line treatment for uncomplicated *P. falciparum* malaria. DHP also exhibited a high cure rate and displayed a greater post-treatment prophylactic effect against new infections. This protective quality may advocate for its use in mass drug administration and seasonal malaria chemoprevention. The very low treatment failure rate of AL suggests that the recent malaria resurgence documented throughout Rwanda is likely not due to reduced AL efficacy. However, diligent monitoring remains essential as governments seek to delay ACT resistance and ensure first-line treatments are switched if their efficacy drops below 90%.[18]

Author's contributions: AU, MW, NU, TM, CMM and CK implemented the study. AU, MJP, MPN, MW, DU, CM, EN and DH participated in analysis and interpretation of the data. AU, MJP, MPN, MW, NU, TM, DH, CK, MK, MM and AM drafted and critically revised the manuscript. All authors read and approved the final manuscript. AU and AM are guarantors of the paper.

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Competing interests: None declared.

Ethical approval: Approval for conducting this study was obtained from the Rwandan National Ethics Committee (RNEC129/RNEC/2012).

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