Mass drug administration with dihydroartemisinin-piperaquine and malaria transmission dynamics in The Gambia - a prospective cohort study

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Summary

Annual MDA with DP over two years reduced malaria infection and clinical disease incidence; the decrease in clinical malaria was not sustained in eastern Gambia. Multiple MDA rounds over large areas may result in larger and sustained reduction in transmission.

Abstract

Background

Mass drug administration (MDA) may further reduce malaria transmission in low transmission areas. The impact of MDA on dynamics of malaria transmission was determined in a prospective cohort study.

Methods

Annual rounds of MDA with dihydroartemisinin-piperaquine (DP) were implemented over two years (2014 and 2015) in six village pairs before the malaria transmission season. Monthly blood samples were collected from all residents between July and December for microscopy and nested PCR. The incidence and prevalence of infection and clinical disease, and the risk of malaria re-infection post-MDA were determined.

Results

Coverage of three DP doses was 68.2% (2014) and 65.6% (2015), compliance was greater than 80%. Incidence of infection was significantly lower in 2014 (IR=0.2 PPY) than in 2013 (IR=1.1 PPY) (P<0.01); monthly infection prevalence declined in the first three months post-MDA. Clinical malaria incidence was significantly lower in 2014 (IR=0.1 PPY) and 2015 (IR=0.2 PPY) than in 2013 (IR=0.4 PPY) (P<0.01) but remained higher in eastern Gambia. Individuals infected before MDA had a 2-fold higher odds of re-infection post-MDA (AOR=2.5, 95% CI: 1.5-4.3, P<0.01).

Conclusions

MDA reduced malaria infection and clinical disease during the first months of each transmission season. The reduction was maintained in low transmission areas, but not in eastern Gambia. One MDA round could be followed by focal MDA targeting individuals found infected during the dry season. Repeated MDA rounds, some of them during the dry season over a much larger geographical area, may result in a more marked and sustained decrease of malaria transmission.

Key words

Dihydroartemisinin-piperaquine, mass drug administration, malaria infection, clinical malaria, gametocytes

Introduction

Malaria causes approximately 216 million cases and 445,000 deaths annually, most of them in Sub-Saharan Africa (SSA). *Plasmodium (P) falciparum* is the main species [1], with the other species representing less than 5% of infections in Western Africa [2, 3]. Malaria has decreased over the last decades worldwide, including in The Gambia [4], where its transmission has become heterogeneous, with infection prevalence of 10-40% in the east and <5% in the west [5-8].

The World Health Organization (WHO) recommends mass drug administration (MDA), which is a full course of an antimalarial treatment to the whole population [9, 10], for areas approaching malaria elimination [9, 11]. Successful campaigns, besides treatment efficacy, depend on high coverage and good compliance [12]. MDA with an artemisinin-based combination treatment (ACT) reduces transmission by clearing asexual infections and early stage gametocytes in asymptomatic infected individuals [11]. Dihydroartemisinin-piperaquine (DP) is used for MDA because of its simple dosing schedule, its long post-treatment prophylaxis period [13-15], and good safety profile [16]. Recent reviews on DP safety [17] did not confirm earlier reports of increases and prolongation of the QTc interval within 48 hours [14, 18].

The objectives of this study were to describe the malaria transmission dynamics following one yearly MDA round with DP for two consecutive years, and to determine the risk of malaria re-infection after each MDA round.

Methods

Study sites and follow up

Malaria transmission in The Gambia is seasonal (July-December), with little transmission during the dry season (January-June). In 2013, a cohort including all residents was set up in six pairs of villages in five regions; West Coast Region (WCR), North Bank Region (NBR), Lower River Region (LRR), Central River Region (CRR), Upper River Region divided in the north (URR-N) and south (URR-

S). Villages in each pair were 1-3km apart and close to the Senegalese border (Figure 2). Residents were predominantly farmers.

Residents who provided written informed consent were enrolled in May 2013 and included in monthly surveys during three transmission seasons (2013-2015; June-December). An additional survey was done during the dry season in both 2014 and 2015. Information on malaria symptoms, treatment, and risk factors was collected as well as a finger-prick blood sample for haemoglobin measurement, thick blood smears and dried blood spots (Whatman 3 Corporation, Florham Park, NJ, USA). Clinical malaria cases were identified by passive detection at health facilities. Participants with history of fever in the previous 24 hours and/or axillary temperature greater than 37.5^{o}C had a rapid diagnostic test (Paracheck Pf, Orchid Biomedical System, India) and positives were treated with artemether-lumefantrine. Mean monthly rainfall data were collected from regional meteorology stations.

Mass drug administration with DP

In 2014 and 2015, MDA with DP was implemented over 6 to 14 days in June and May, respectively, across all study villages. DP was administered to participants aged 6 months to 75 years old, body weight ≥5kg, and no known history of cardiac or renal disease. Women aged 11-45 years were offered a urine human chorionic gonadotropin pregnancy test; positive women were excluded and referred to antenatal care clinics for intermittent preventive treatment (IPTp). Residents who had travelled and returned after the MDA did not receive DP (Figure 1).

Treatment administration

DP (Eurartesim®, Sigma-Tau, Industrie Farmaceutiche Riunite, Italy) administration according to weight-based dosing guidelines was directly observed by five field research teams working with government nurses and village health workers.

Safety profile

Adverse events (AEs) were monitored passively for 28 days. Relatedness of AEs to the intervention was based on known DP side-effects and timing after treatment. AEs were graded by severity as mild, moderate or severe.

Molecular Diagnostics and Parasitology

P. falciparum was detected by nested PCR from the blood spot samples collected in 2014 monthly surveys. Briefly, DNA was extracted using an automated QIAxtractor robot (Qiagen) and 4µl used in a nested PCR [19]. All PCR products were run with the QIAxcel capillary electrophoresis system (Qiagen) using the screening cartridge and 15-1000 bp-alignment markers. Results were exported and double scored using both the QIAxcel binary scoring function and manually by visualisation of the gel images; discrepancies were scored by a third reader.

Thick smears from all the positive nested PCR samples and clinical malaria cases (n=1480) were read by two independent microscopists and discrepancies settled by a third reader. Parasite density was estimated by number of parasites per 200 WBC, assuming 8,000 WBC/µL. Blood smears were considered negative after reading 100 high power fields.

Consent

Verbal approval was obtained at village sensitization meetings in May-April 2013-2015 and two weeks prior to the MDA. Information sheets were given to all study participants. Written individual consent was obtained from literate adults; parents or guardians consented for children <12 years and children 12 <18 years provided assent. The study was approved by the Gambia Government/Medical Research Council Ethics Committee (SCC 1318). Approval to import DP was obtained from the Gambian Medicine Control Agency.

Data management

Data were captured using case report forms and verified for internal consistency by the field coordinators. Data were double entered using the SQL program version 36, verified and cleaned.

Study outcomes

The primary outcome was malaria (*P. falciparum)* infection determined by nested PCR; secondary outcomes included DP coverage and compliance, incidence of clinical malaria, prevalence of gametocytaemia, asymptomatic and sub-patent infections and AEs. Asymptomatic malaria was an infection by nested PCR in an afebrile individual with no history of fever in the previous 24 hours [20]. Clinical malaria was defined as positive microscopy or RDT with history of fever or temperature >37.5^{0}C [15]. Sub-patent infections were infections positive by nested PCR and negative by microscopy.

Statistical analysis

The incidence rates of infection and clinical malaria were the number of infections or clinical cases divided by the total person-time at risk (per-person per year, PPY). Prevalence of asymptomatic infection was the number of infections divided by the number of individuals with no history fever. DP coverage was the number of treated individuals who received three DP doses divided by the village population. Compliance was the proportion of eligible individuals who had full treatment. Gametocyte prevalence was the number of individuals with gametocytes divided by total number of infected individuals by microscopy.

Risk ratio of infections and incidence rate ratio (IRR) of clinical malaria, before and after MDA, were estimated by comparing prevalence and incidence in April 2014 with July-December 2014; and the 2013 transmission season with the 2014 and 2015 transmission seasons. DP efficacy was determined in 2014 for treated individuals sampled between days 14 to 28 and around day 42. For participants infected in the dry season (April), logistic regression models were fitted to determine the odds of infections at 4 weeks and around day 42 post-MDA. Protective efficacy for clinical malaria was determined for 2014 and 2015 post-MDA using a mixed effects logistic regression model accounting for clustering at regional level. Multivariable models were adjusted for age, gender, LLIN use, sleeping outdoors and travel history. Analyses were performed using Stata version 13.0 [21].

Results

A total of 4,312 and 4,189 individuals were followed in 2014 and 2015, respectively. The median age was 13 years (IQR: 5, 28). LLIN use the previous night was low in April (2014: 43.3%, 1374/3171; 2015: 51.8%, 1545/2982), but increased substantially during and after the rainy season; overall use was 87.8% (3072/3501) in 2014 and 77.9% (2940/3771) in 2015. Few residents travelled; 4.8% (946/22,795) in 2014 and 3.9% (149/3738) in 2015, with median of 22 (IQR: 12, 31) days absence (Table 1).

Screening for MDA was done for 86.4% (3725/4312) and 80.54% (3374/4189) of potential participants in 2014 and 2015, respectively; 5% of them were non-eligible mainly because of pregnancy. In 2014, 763 individuals did not participate because they were absent (66.1%, 504/763) or refused (22.7%, 173/763). In 2015, 55.6% (470/845) were away or (26.1%, 259/845) refused. Compliance to three DP doses was 83.1% (2942/3540) in 2014 and 85.93% (2748/3198) in 2015 (Figure 1). Coverage of the three doses was 68.2% (2942/4312) in 2014 and 65.6% (2748/4189) in 2015.

Monthly infection prevalence was significantly lower during the whole 2014 transmission season, after MDA, than in 2013 (2014: 5.9%, 1307/22036, 2013: 8.7%, 1796/20552, RR=0.7, P<0.01). Malaria prevalence was significantly lower in the 3 months following MDA, i.e. July (5.9%,188/3150, RR=0.8 P=0.02) August (4.7%, 160/3411, RR=0.6 P<0.0)1 and September (1.9%, 60/3252, RR=0.3 P<0.01) than in April 2014 (7.5%,213/2827) (Table 2).

In 2014 and all regions, incidence of infections was significantly lower than in 2013 (Supplementary Table 1 and Figure 2). Malaria prevalence remained significantly higher in URR-S (355/5208, 6.8%) and URR-N (244/2342, 10.4%) than in WCR (P<0.01) (Supplementary Table 2). In 2014, the largest reduction in malaria prevalence was in eastern Gambia; in November, at peak transmission, asymptomatic malaria prevalence was lower in 2014 than in 2013; it decreased by 50% or more in URR-S (65.2% reduction, 2013=13.6%, 92/679 versus 2014=4.7%, 31/658, Risk Ratio=0.05

P<0.01), URR-N (57.9%, 2013=36.4%, 122/335 versus 2014=15.3%, 53/346, Risk Ratio=0.2, P<0.01) and LRR, (49.7% reduction, 2013=8.9%, 39/436 versus 2014=4.5%, 15/333, Risk Ratio=0.5, P=0.001) .

More than half of all infections were sub-patent in 2014 [April: 55.1% (92/167); July: 50% (65/129); August: 50.4% (65/129); September 68.3%, (41/60); October 58.1% (118/203); November 56.3% (126/224); December 68% (41/60)]. Overall gametocyte carriage during the 2014 transmission season was 8.3% (46/552); and lower in August (2/70, 2.9%) than in April (8/87, 9.2%) (Supplementary Table 3). Median *P. falciparum* densities were significantly lower in the 2014 transmission season compared to 2013 in all regions but URR-N (Figure 4). One *P. malariae* infection was detected in 2014, before MDA, and seven *P. ovale* infections in 2013.

In 2014, malaria prevalence between 14-28 days and 42 days post-MDA was 5.5% (131/2432) and 4.2% (147/3534), respectively, with half infections (49.6%, 65/131) sub-patent. MDA decreased the risk of being infected but the difference between treated and untreated individuals was statistically significant only for those who had received the 3-day treatment, both in July (AOR: 0.6; 95%CI: 0.4-1.0) (P=0.04) and August (AOR: 0.5; 95% CI: 0.3-0.9, P=0.02) (Table 3).

The odds of clinical malaria in July 2014 were significantly lower among subjects who took three DP doses (AOR=0.3, 95% CI: 0.1-0.9, P=0.02) compared to untreated individuals. At 3-4 weeks post-MDA 2014, nineteen (8.92%) individuals among the 213 infected in April were still infected, 10 had received the full 3-day treatment, more than half (52.6%, 10/19) being patent infections.

Efficacy of MDA in clearing and preventing infections was assessed in 2,276 individuals who received full treatment and with known infection status in both July and August 2014. Among the 113 individuals infected in July 2014, 89.4% (101/113) had cleared the infection by August; only 82 (3.8%) among the 2,163 individuals not infected in July became infected in August.

Individuals infected in the dry season (2014) had a 2-fold higher odds of being infected in July (AOR=2.5, 95% CI: 1.5-4.3, P<0.01), August (AOR=2.8, 95% CI: 1.6-5.1, P=0.001) and throughout the transmission season (AOR=2.5, 95% CI: 1.7-3.6, P<0.01) (Supplementary Table 4).

The odds of clinical malaria were significantly lower in 2014 (AOR=0.4, 95% CI: 0.3-0.6, P<0.01) and 2015: AOR=0.6, 95% CI: 0.5-0.7, P<0.01) in fully treated than in untreated individuals (Table 4). Incidence of clinical malaria was significantly lower in all regions after the first and second MDA than in 2013. (Supplementary Table 5) Incidence of clinical malaria was similar after the first and second MDA round, except in URR-S and URR-N where incidence was significantly higher in 2015 than in 2014 (Figure 3 and Supplementary Table 5). In URR, rainfalls lasted longer (May-December) in 2015 than in 2013 and 2014 (Figure 3).

Dihydroartemesinin-piperaquine safety

Within the 28 days post-MDA, 302 and 269 AEs were reported in 2014 and 2015, respectively, with similar proportions of symptoms in both years. The most common AEs were headache (2014 =18.9%, 57/302: 2015=18.2%, 49/269), fever (2014=12.6%, 38/302: 2015=11.5%, 31/269), malaise (2014=11.9%, 36/302: 2015=12.6%, 34/269), and vomiting (2014=11.3%, 34/302: 2015=10.0%, 27/269). AEs were either mild or moderate in severity and were all probably related to DP except for fever and chills. (Supplementary Table 6) No serious adverse events were detected.

Discussion

We assessed the impact of an annual round of MDA with DP, an ACT with a long post-treatment prophylactic period, on malaria transmission dynamics over two consecutive years and in areas of differing transmission intensity in The Gambia. [8].

Prevalence and incidence of infection in 2014 were significantly lower than in 2013 but remained significantly higher in eastern Gambia compared to other regions. Monthly prevalence, after a significant decrease in the first 3 months post-MDA, returned to similar pre-MDA levels. Clinical malaria decreased in both intervention years but remained significantly higher in eastern Gambia, increasing in the second year compared to the first, confirming the higher transmission intensity in this region. [8, 22]. One annual MDA round over two consecutive years resulted in a temporal decline of malaria infections and clinical disease, with a temporal shift and decrease in the peak

prevalence and incidence of infection and clinical disease. In The Gambia, MDA with sulfadoxine-pyrimethamine and a single artesunate dose resulted in a lower incidence of clinical malaria for two months following MDA [10]. Two MDA rounds in Zambia showed lower prevalence for at least six months in the low transmission sites [11]. In Myanmar, MDA with DP and a single low dose of primaquine significantly reduced *P. falciparum* prevalence three months after MDA in intervention villages compared to controls [19]. Therefore, although WHO currently recommends MDA where transmission is low, such recommendations could be extended to moderate transmission areas given the substantial but time-limited decrease in prevalence and incidence we observed. Multiple MDA rounds could result in a larger and more sustained reduction [23], particularly if appropriately timed; for example a round during the dry season could decrease the human reservoir before transmission begins. In addition, DP could be combined with invermectin, that would reduce mosquito survival [24].

One annual MDA round was unable to maintain the observed malaria decline throughout the transmission season. Nevertheless, incidence of clinical malaria in the western and central regions remained low across the two intervention years while in eastern Gambia we observed an increase during the second year, probably due to environmental factors such as the longer duration of rainfall that resulted in higher mosquito density and survival. Therefore, in low transmission areas such as western and central Gambia, one appropriately-timed annual MDA round could reduce the clinical case burden on the health care system and maintain this effect over time if implemented regularly. Cost-benefit comparisons between this approach and clinical case management are needed to confirm this potential value. As the intervention was implemented in two villages in each region, transmission may have been maintained by population movements [25-27]. Increasing the size of the intervention area, extending the duration of campaigns and ensuring individuals who missed MDA are prioritised in additional rounds would achieve a larger effect [23]. Since transmission

intensity varied substantially by year and there were no control villages, it is not possible to quantify the MDA's additional (to standard control interventions) impact on malaria transmission.

MDA coverage was relatively high and comparable to previous studies; 85% in The Gambia [28], >95% in Tanzania [29], 72%-88% in Zambia [30], and 28%-61% in Myanmar [31]. Villages where coverage was below 70% had high proportions of people traveling or refusing despite meetings and mobilization campaigns, highlighting the main challenges for MDA implementation [32, 33]. Compliance was high as doses were directly observed but it may be lower in programmatic conditions [34].

In both intervention years, full DP treatment significantly reduced the risk of clinical malaria throughout the transmission season. This is due to the excellent DP efficacy and long post-treatment prophylaxis related to the long elimination half-life of piperaquine (20 days in children and 22 days in adults) [9, 12-14, 16, 35]. Incomplete treatment was not protective, probably due to the shortened post-treatment prophylaxis [36]. It is not possible to determine whether infections observed at days 28-42 were residual or new infections as no genotyping was done. About half of them were detectable only by molecular methods. Low-density infection is common following ACT treatment, 31.8% of children treated with an ACT had residual parasitaemia detected by quantitative (q) PCR at day 3 post-treatment [37] while 25% of patients treated with an ACT had parasitaemia at day 14 detected by qRT-PCR [38]. Therefore, a substantial proportion of infections detected after MDA may be residual and not new infections.

Individuals infected in April 2014, had a significantly higher risk of infection during the transmission season. Such risk is probably due to higher exposure, e.g. close proximity to breeding sites or an environment favoring exposure to the vector, and not to residual parasitaemia or gametocytaemia as the latter would decrease after two months [39, 40]. This suggests that risk of infection and clinical disease is extremely focal as already shown in The Gambia [8], Senegal [41],

and Kenya [42]. Besides treating the whole population, households with infected individuals at the beginning of the transmission season could be targetted with focal MDA [30].

The RDT for the diagnosis of clinical malaria, the Paracheck Pf, did not perform well at low parasite densities (200/µl) during the last WHO evaluation round [50]. This RDT was used only to diagnose clinical malaria cases which have higher parasite densities. Therefore, considering that Paracheck Pf had a high panel detection score at parasite densities of 2,000/µl, it is unlikely clinical malaria cases would have gone undiagnosed.

Conclusions

Annual MDA with DP reduced prevalence and incidence of infection and clinical disease in the first months of each transmission season. In western and central Gambia, where transmission is low, clinical malaria incidence was reduced over two years, despite an apparent higher transmission during the second year. One MDA round could be followed by MDA targeting households with individuals identified as infected during the dry season. Repeated MDA rounds, some of them during the dry season and over a much larger geographical area, may result in a more marked and sustained decrease of malaria transmission.

Author contribution

UD is the grant recipient, reviewed the draft manuscripts and approved the final version

JM coordinated the implementation of the study, conducted data analysis, wrote the draft manuscript and final version

JA reviewed the drafts and final version

MW and NM provided statistical support and AW was the data manager each contributing to this article and approving the final version

FK and AP conducted the sample analyses of the samples and contributed to this article

MA, SD, GLT, JPVG DN, TB and CD contributed to this article and approved the final version

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Conflict of Interest

The authors declare they do not have any conflict of interest with the study.

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Figure legends

Figure 1: Study flow diagram

Figure 2: Study sites and monthly malaria prevalence and incidence of infection by region before (2013) and after (2014) one annual MDA round

Figure legend

	Prevalence of asymptomatic infection
	Incidence rate of infection

Figure 3: Monthly incidence of clinical malaria by region before (2013) and after (2014) one annual MDA round

Figure legend

	Incidence rate of clinical malaria
	Rainfall (mm)

Figure 4: Monthly prevalence and density of *P. falciparum* infections before and after one MDA round

Figure legend

	P. falciparum prevalence
	P. falciparum densities

Table 1: Study subjects characteristics

Characteristic	2014 n (%)	2015 n (%)
Gender		
Male	1966 (46.1)	1932 (46.1)
Female	2296 (53.9)	2256 (53.9)
Age category		
≤ 5 years	1091 (25.6)	1054 (25.2)
6-15 years	1336 (31.4)	1433 (34.2)
≥ 16 years	1830 (42.9)	1702 (40.6)
LLIN use previous night		
April	1374/3171 (43.3)	1545/2982 (51.8)
June*	-	2201/3106 (70.9)
July	2222/3318 (66.9)	2011/2984 (67.4)
August	3184/3542 (89.9)	2599.3024 (85.9)
September	3122/3281 (95.2)	2769/2938 (94.3)
October	3146/3310 (95.1)	2808/2950 (95.2)
November	3003/3163 (94.9)	2532/2800 (90.4)
December	2879/3191 (90.2)	2112/2806 (75.3)
Travelled in the last month		
April	251/3161 (7.9)	218/2956 (7.4)
May		228/3079 (7.4)
July	277/3287 (8.4)	40/2966 (1.4)
August	86/3500 (2.5)	31/3008 (1.0)
September	126/3255 (3.9)	37/2921(1.3)
October	95/3279 (2.9)	69/2925 (2.4)

November	59/3133 (1.9)	26/27770 (1.3)
December	52/3170 (1.6)	39/2796 (1.4)
house structure (N=2233)		2111 (75.3)
traditional house (1)	1182 (52.9)	
modern house (0)	1051 (47.1)	

*No survey was conducted in June 2014 before the MDA campaign

Table 2: Malaria prevalence by month and year; risk ratio (RR) of infection by month

Month	2013 Prevalence (n/N)	2014 Prevalence (n/N)	RR 2013 vs 2014 by month (95% CI)	P-value	RR April 2014 vs other months 2014 (95% CI)	P-value
April	NA	7.5 (213/2827)			1	
June	5.3 (75/1409)	NA			NA	
July	5.3 (180/3411)	5.9 (188/3150)	1.1 (0.9-1.4)	0.2	0.8 (0.7- 0.9)	0.02
August	6.2 (195/3133)	4.7 (160/3411)	0.8 (0.6-0.9)	0.01	0.6 (0.5-0.8)	<0.01
September	5.1 (146/2867)	1.8 (60/3252)	0.4 (0.3- 0.5)	<0.01	0.24 (0.2 -0.3)	<0.01
October	11.2 (347/3113)	6.7 (210/3156)	0.6 (0.5-0.7)	<0.01	0.9 (0.7 -1.1)	0.2
November	14.4 (503/3492)	7.6 (247/3240)	0.6 (0.5-0.7)	<0.01	1.0 (0.9 -1.2)	0.9
December	11.2 (350/3127)	7.6 (229/3000)	0.7 (0.6-0.8)	<0.01	1.0 (0.8-1.2)	0.9
Total	8.7 (1796/20552)	5.9 (1307/22036)	0.7 (0.65-0.8)	<0.01		

NA : not available

Table 3: Risk factors of malaria infection 14-28 days (July 2014) and 42 days (August 2014) after MDA

	Day 14-28		Day 42	
	AOR (95%CI)	**P-value**	**AOR (95%CI)**	**P-value**
MDA DP				
No treatment	1		1	
1-2 doses	0.7 (0.4-1.3)	0.3	0.6 (0.3-1.2)	0.1
Three doses	0.6 (0.4-1.0)	0.04	0.5 (0.3-0.9)	0.02
Age group				
≤ 5 years	1		1	
6-17 years	1.2 (0.8-1.9)	0.4	1.2 (0.8-1.8)	0.3
≥ 18 years	0.9 (0.5-1.4)	0.5	0.9 (0.6-1.4)	0.4
LLIN use previous night				
No	1		1	
Yes	1.4 (0.9-1.9)	0.08	1.0 (0.6-1.4)	0.8
Gender				
Male			1	
Female			0.8 (0.6-1.1)	0.2
Study site				
WCR			1	
NBR			1.2 (0.6-2.3)	0.6
LRR			1.7 (0.9-3.2)	0.12
CRR			0.9 (0.4-1.9)	0.8

URR-S	1.0 (0.52-1.74)	0.9
URR-N	4.9 (2.8-9.0)	<0.01

OR: Odds Ratio; AOR: Adjusted Odds Ratio

* Variables with P value < 0.1 in the univariate analysis, (“gender” and “study sites") or were confounders (“LLIN use at night” and “age groups”) were included in multivariate analysis. Variables with P value >0.1 in univariate analysis “sleeping outside” and “travel history” were excluded in the multivariate analysis

Table 4: Risk factors of clinical malaria post-MDA by year

	2014 transmission season		2015 transmission season	
	AOR (95% CI)	P-value	AOR (95% CI)	P-value
MDA DP				
No treatment	1		1	
1-2 doses	0.7 (0.4-1.4)	0.4	0.7 (0.5-1.0)	0.05
Three doses	0.4 (0.3-0.6)	<0.01	0.59 (0.5-0.7)	<0.01
Age group				
≤5 years	1		1	
6-17 years	0.8 (0.5-1.2)	0.3	1.2 (0.9-1.6)	0.1
≥18 years	0.5 (0.3-0.8)	0.003	0.9 (0.7-1.2)	0.5
Gender				
Male	1		1	
Female	0.7 (0.5-0.9)	0.02	0.8 (0.6-0.9)	0.02
LLIN use previous night				
No	1		1	
Yes	0.5 (0.3-0.7)	<0.01	0.71 (0.5-0.9)	0.02
Travelled				
No			1	
Yes	0.7 (0.3-1.9)	0.5	1.9 (1.7-2.1)	<0.01
Month				
April	1		1	
June	0.5 (0.1-0.5)	0.6	0.4 (0.1-1.8)	0.2
July	0.1 (0.02-0.6)	0.01	0.3 (0.1-1.2)	0.1
August	0.5 (0.1-1.5)	0.2	1.3 (0.5-3.2)	0.61

September	0.8 (0.4-2.4)	0.7	4.5 (2.03-9.9)	<0.01
October	3.2 (1.3-7.9)	0.01	16.8 (7.9-35.7)	<0.01
November	12.7(5.5-9.2)	<0.01	26.2 (12.5-54.7)	<0.01
December	1.1(0.5-2.9)	0.8	5.4 (2.5-11.5)	<0.01

Figure 1

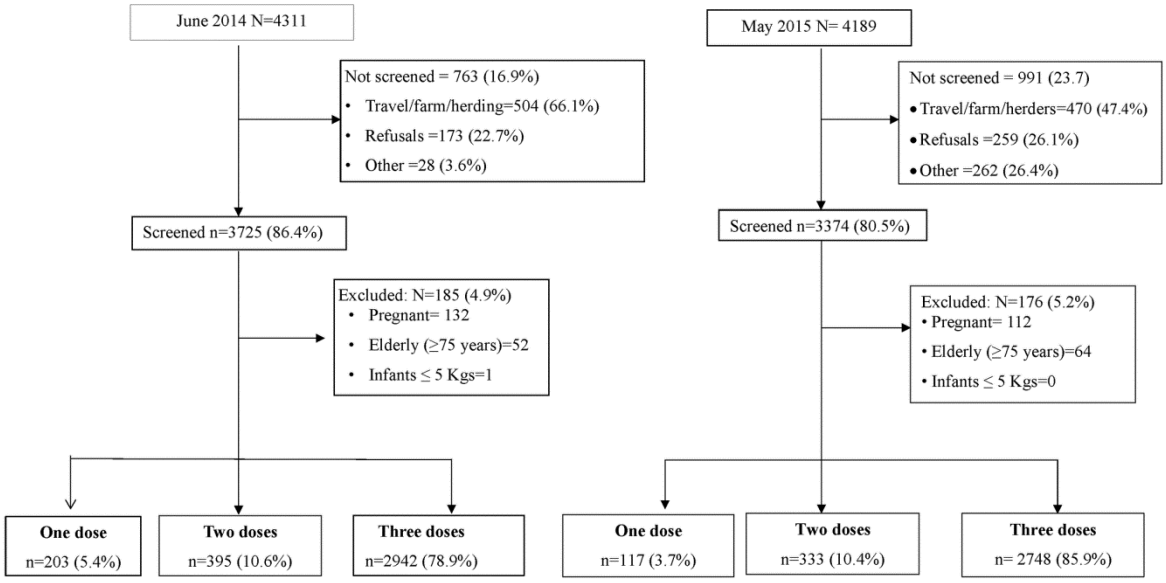

Figure 2

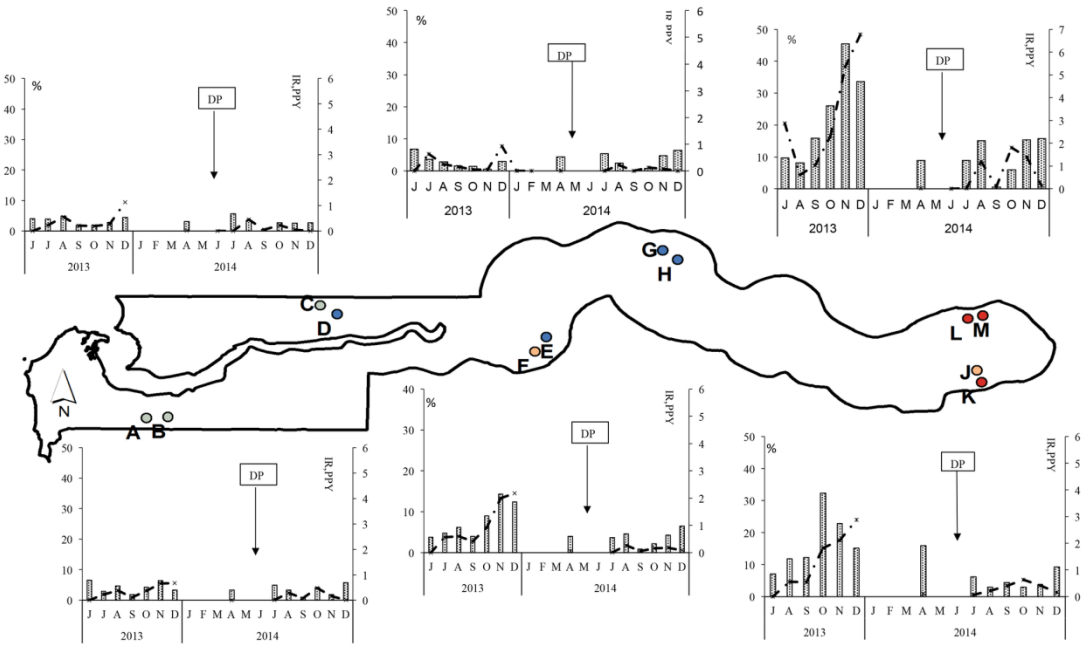

Figure 3

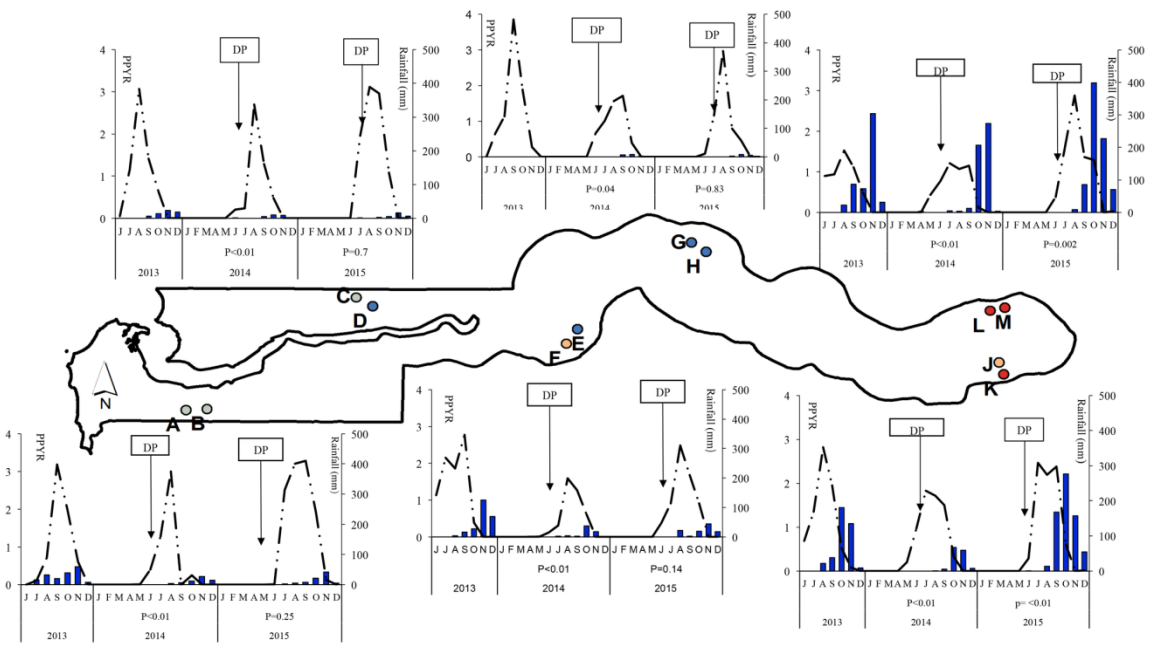

Figure 4