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Mass Drug Administration With Dihydroartemisinin-piperaquine and Malaria Transmission Dynamics in The Gambia: A Prospective Cohort Study

Julia Mwesigwa,[1,2] Jane Achan,[1] Muna Affara,[1] Miriam Wathuo,[1] Archibald Worwui,[1] Nuredin Ibrahim Mohammed,[1] Fatoumatta Kanuteh,[1] Aurelia Prom,[1] Susan Dierickx,[3] Gian Luca di Tanna,[4] Davis Nwakanma,[1] Teun Bousema,[5] Chris Drakeley,[6] Jean Pierre Van Geertruyden,[2] and Umberto D'Alessandro[1,6]

[1]Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Banjul; [2]Department of Global Health, Faculty of Medicine and Health Sciences, University of Antwerp, and [3]Centre of Expertise on Gender, Diversity and Intersectionality, Brussels University, Belgium; [4]Risk Centre, Institut de Recerca en Economia Aplicada, Department of Econometrics, Statistics and Applied Economics, Universitat de Barcelona, Spain; [5]Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, The Netherlands; and [6]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom

(See the Editorial Commentary by Guler and Rosenthal on pages 287–9.)

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

Methods. Annual rounds of MDA with dihydroartemisinin-piperaquine (DP) were implemented were implemented in 2014 and 2015 in six village pairs before the malaria transmission season. Blood samples were collected from residents between July and December for microscopy and nested PCR. Incidence and prevalence of infection, clinical disease, and risk of malaria reinfection 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 (incidence rate [IR] = 0.2 per person year [PPY]) than in 2013 (IR = 1.1 PPY; $P < .01$); monthly infection prevalence declined in the first three months post-MDA. Clinical malaria incidence was lower in 2014 (IR = 0.1 PPY) and 2015 (IR = 0.2 PPY) than in 2013 (IR = 0.4 PPY; $P < .01$), but remained higher in eastern Gambia. Individuals infected before MDA had a 2-fold higher odds of reinfection post-MDA (adjusted odds ratio = 2.5, 95% confidence interval 1.5–4.3; $P < .01$).

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

Keywords. dihydroartemisinin-piperaquine; mass drug administration; malaria infection; clinical malaria; gametocytes.

Malaria causes approximately 216 million cases and 445 000 deaths annually, most of them in Sub-Saharan Africa. *Plasmodium 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, 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 of following a yearly MDA round with DP for 2 consecutive years, and to determine the risk of malaria reinfection 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

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Correspondence: J. Mwesigwa, Medical Research Council Unit The Gambia at LSHTM, P.O. Box 273, Banjul, The Gambia (jmwesigwa@mrc.gm).

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(January-June). In 2013, a cohort including all residents was set up in 6 pairs of villages, in 6 regions: the West Coast Region, North Bank Region, Lower River Region, Central River Region, and Upper River Region, which was divided into the north (URR-N) and south (URR-S) regions. Villages in each pair were 1–3 km apart and close to the Senegalese border (Figure 1). Residents were predominantly farmers.

Residents who provided written, informed consent were enrolled in May 2013 and included in monthly surveys during 3 transmission seasons (2013–2015 from 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). Clinical malaria cases were identified by passive detection at health facilities. Participants with histories of fever in the previous 24 hours and/or an axillary temperature greater than 37.5°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 Dihydroartemisinin-Piperaquine

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 with a body weight ≥5 kg 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. Residents who returned from travel after the MDA did not receive DP (Figure 2).

Treatment Administration

DP (Eurartesim, Sigma-Tau, Industrie Farmaceutiche Riunite, Italy) administration, according to weight-based dosing guidelines, was directly observed by 5 field research teams that were 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 the timing after treatment. AEs were graded by severity, as mild, moderate, or severe.

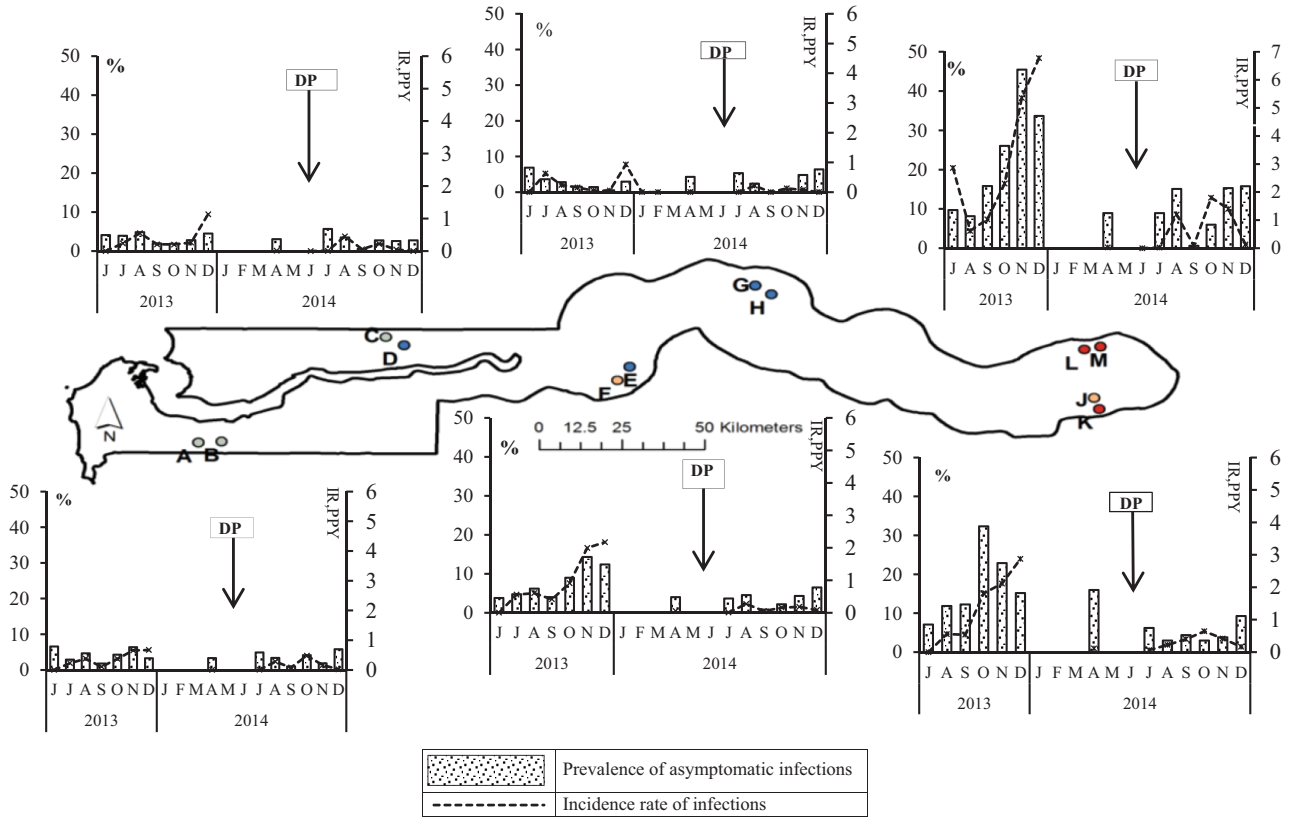

Figure 1. Study sites and monthly malaria prevalence and incidence of infection by region, before (2013) and after (2014) 1 annual MDA round. Abbreviations: DP, dihydroartemisinin-piperaquine; IR, incidence rate; MDA, mass drug administration; PPY, per person, per year.

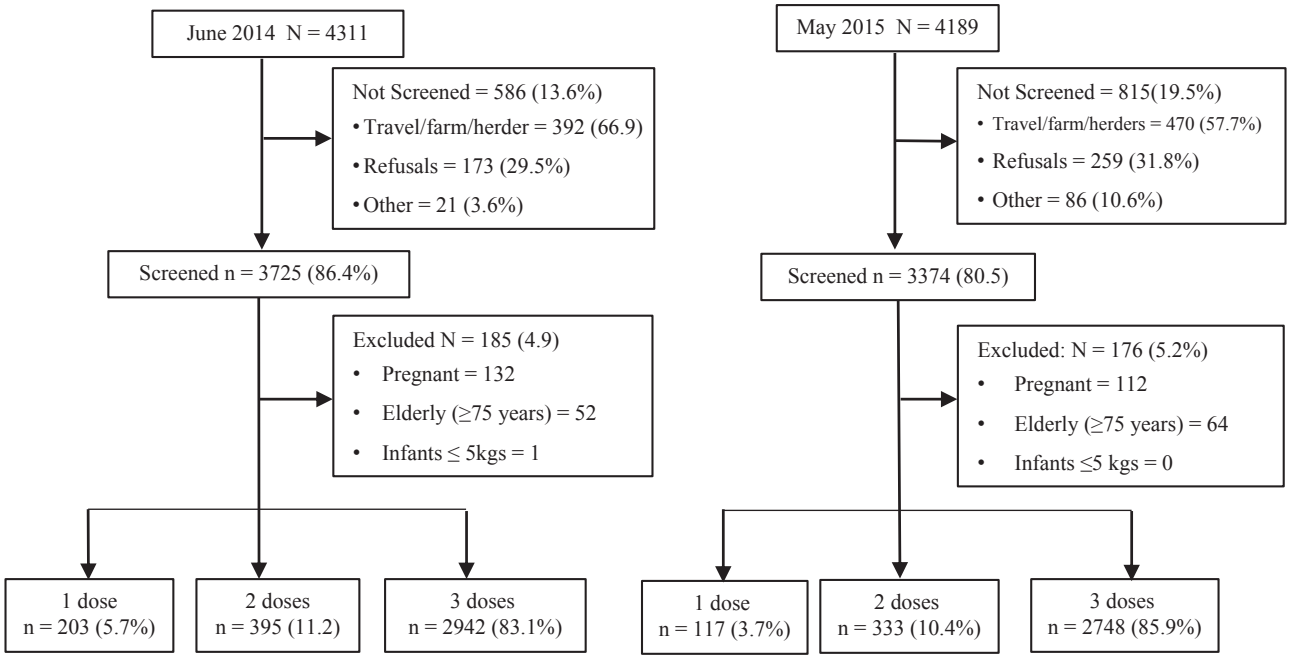

Figure 2. Study flow diagram.

Molecular Diagnostics and Parasitology

P. falciparum was detected by nested polymerase chain reaction (PCR) from the blood-spot samples collected in the 2014 monthly surveys. Briefly, DNA was extracted using an automated QIAxtractor robot (Qiagen) and 4 µl was 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 visualization 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 2 independent microscopists, and discrepancies were settled by a third reader. Parasite density was estimated by the number of parasites per 200 white blood cells, assuming 8000 white blood cells per µL. Blood smears were considered negative after reading 100 high-power fields.

Consent

Verbal approval was obtained at village sensitization meetings in May–April of 2013–2015 and 2 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 written assent. The study was approved by the Gambia Government/Medical Research Council Ethics Committee (SCC 1318). The approval to import DP was obtained from the Gambian Medicine Control Agency.

Data Management

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

Study Outcomes

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

Statistical Analysis

The incidence rates of infection and clinical malaria were calculated as the number of infections or clinical cases, divided by the total person-time at risk (per person, per year). The prevalence of asymptomatic infection was calculated as the number of infections, divided by the number of individuals with no history of fever. DP coverage was calculated as the number of treated individuals who received 3 DP doses, divided by the village population. Compliance was calculated as the proportion of eligible individuals who had full treatment. Gametocyte

prevalence was calculated as the number of individuals with gametocytes, divided by the total number of infected individuals, as determined by microscopy.

The risk ratio of infections and incidence rate ratio of clinical malaria, before and after MDA, were estimated by comparing the prevalences and incidences in April 2014 and in July–December 2014, as well as in the 2013 transmission season and in the 2014 and 2015 transmission seasons. DP efficacy was determined in 2014 for the treated individuals that were 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. The protective efficacy for clinical malaria was determined for 2014 and 2015 post-MDA using a mixed-effects logistic regression model, and accounting for clustering at the regional level. Multivariable models were adjusted for age, gender, long lasting insecticide treated net (LLIN) use, sleeping outdoors, and travel history. Analyses were performed using Stata version 13.0 [21].

RESULTS

A total of 4312 and 4189 individuals were followed in 2014 and 2015, respectively. The median age was 13 years (interquartile range: 5, 28). LLIN use the previous night was lower each year in April (2014: 43.3%, 1374/3171; 2015: 51.8%, 1545/2982), but increased substantially during and after the rainy seasons; the overall use was 87.8% (3072/3501) in 2014 and 77.9% (2940/3771) in 2015. Few residents traveled: 4.8% (202/4189) in 2014 and 3.9% (149/3738) in 2015, with a median of 22 (interquartile range: 12, 31) days absence (Table 1).

Screening for MDA was done for 86.4% (3725/4312) and 80.5% (3374/4189) of potential participants in 2014 and 2015, respectively; 5% of them were non-eligible, mainly because of pregnancy (Figure 2). In 2014, 586 individuals did not participate, because they were absent (66.9%, 392/586) or refused (29.5% (173/586). In 2015, 57.7% (470/815) were away and (13.8%, 259/815) refused. Compliance to 3 DP doses was 83.1% (2942/3540) in 2014 and 85.9% (2748/3198) in 2015 (Figure 2). Coverage of the 3 doses was 68.2% (2942/4312) in 2014 and 65.6% (2748/4189) in 2015.

After MDA, the monthly infection prevalence was significantly lower during the whole 2014 transmission season, as compared to 2013 (2014: 5.9%, 1307/22 036; 2013: 8.7%, 1796/20 552; risk ratio [RR] = 0.7; $P < .01$). Malaria prevalence was significantly lower in the 3 months following MDA—that is, in July (5.9%, 188/3150; RR = 0.8; P = .02), August (4.7%, 160/3411; RR = 0.6; $P < .01$), and September (1.9%, 60/3252; RR = 0.3; $P < .01$)—than in April 2014 (7.5%, 213/2827; Table 2).

In 2014, across all regions, the incidences of infection were significantly lower than in 2013 (Supplementary Table 1 and Figure 1). Malaria prevalence remained significantly higher in the URR-S (355/5208, 6.8%) and URR-N (244/2342, 10.4%) than in the West Coast Region ($P < .01$; Supplementary Table 2). In 2014, the largest reduction in malaria prevalence was in eastern Gambia. In November, the time of peak transmission, asymptomatic malaria prevalence was lower in 2014 than in 2013; it decreased by 50% or more in the URR-S (65.2% reduction; 2013 = 13.6%, 92/679, versus 2014 = 4.7%, 31/658; RR = 0.05; $P < .01$), URR-N (57.9%; 2013 = 36.4%, 122/335 versus 2014 = 15.3%, 53/346, RR = 0.2; $P < .01$), and Lower River Region (49.7% reduction; 2013 = 8.9%, 39/436 versus 2014 = 4.5%, 15/333; RR = 0.5; $P = .001$).

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)
Long lasting insecticide-treated net use previous night		
April	1374/3171 (43.3)	1545/2982 (51.8)
June[a]	-	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)	26/27 770 (1.3)
December	52/3170 (1.6)	39/2796 (1.4)
House structure (n = 2233)		2111 (75.3)
Traditional house	1182 (52.9)	
Modern house	1051 (47.1)	

[a]No survey was conducted in June 2014 before the mass drug administration campaign.

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). The overall gametocyte carriage during the 2014 transmission season was 8.3% (46/552), and was 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, as compared to the 2013 season, in all regions but the URR-N (Figure 3). Before MDA, 1 *P. malariae* infection was detected in 2014 and 7 *P. ovale* infections were detected in 2013.

In 2014, the malaria prevalence between 14–28 days and 42 days post-MDA was 5.5% (131/2432) and 4.2% (147/3534),

Table 2. Malaria Prevalence by Month and Year; Risk Ratio 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)	.2	0.8 (0.7–0.9)	.02
August	6.2 (195/3133)	4.7 (160/3411)	0.8 (0.6–0.9)	.01	0.6 (0.5–0.8)	<.01
September	5.1 (146/2867)	1.8 (60/3252)	0.4 (0.3–0.5)	<.01	0.24 (0.2–0.3)	<.01
October	11.2 (347/3113)	6.7 (210/3156)	0.6 (0.5–0.7)	<.01	0.9 (0.7–1.1)	.2
November	14.4 (503/3492)	7.6 (247/3240)	0.6 (0.5–0.7)	<.01	1.0 (0.9–1.2)	.9
December	11.2 (350/3127)	7.6 (229/3000)	0.7 (0.6–0.8)	<.01	1.0 (0.8–1.2)	.9
Total	8.7 (1796/20 552)	5.9 (1307/22 036)	0.7 (0.65–0.8)	<.01		

Abbreviations: CI, confidence interval; NA, not available; RR, risk ratio.

respectively, with half of the 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 (adjusted odds ratio [AOR] 0.6, 95% confidence interval [CI] 0.4–1.0; P = .04) and August (AOR 0.5, 95% CI 0.3–0.9; P = .02; Table 3).

The odds of clinical malaria in July 2014 were significantly lower among subjects who took 3 DP doses (AOR 0.3, 95% CI 0.1–0.9; P = .02), as compared to untreated individuals. At 3–4 weeks post-MDA 2014, 19 (8.92%) individuals among the 213 infected in April were still infected: 10 had received the full 3-day treatment, such that more than half (52.6%, 10/19) were patent infections.

The efficacy of MDA in clearing and preventing infections was assessed in 2276 individuals who received full treatment and had a 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 2163 individuals not infected in July became infected in August.

Individuals infected in the dry season (2014) had 2-fold higher odds of being infected in July (AOR 2.5, 95% CI

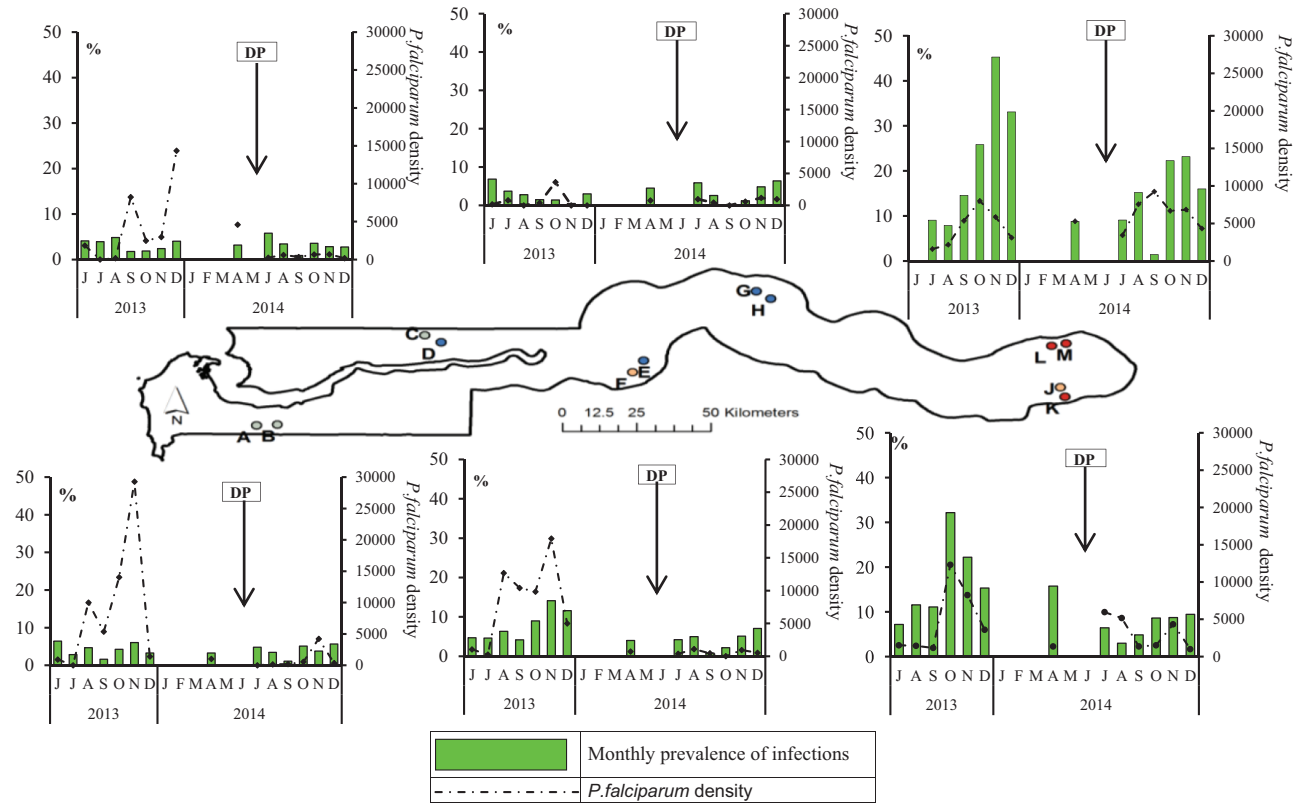

Figure 3. Monthly prevalence and density of *Plasmodium falciparum* infections, before and after 1 MDA round. Abbreviations: DP, dihydroartemisinin-piperaquine; MDA, mass drug administration.

Table 3. Risk Factors of Malaria Infection 14–28 Days (July 2014) and 42 Days (August 2014) After mass drug administration

	Day 14–28		Day 42	
	AOR (95% CI)[a]	*P* Value	AOR (95% CI)[a]	*P* Value
MDA DP				
No treatment	1		1	
1–2 doses	0.7 (0.4–1.3)	.3	0.6 (0.3–1.2)	.1
3 doses	0.6 (0.4–1.0)	.04	0.5 (0.3–0.9)	.02
Age group				
≤5 years	1		1	
6–17 years	1.2 (0.8–1.9)	.4	1.2 (0.8–1.8)	.3
≥18 years	0.9 (0.5–1.4)	.5	0.9 (0.6–1.4)	.4
Long lasting insecticide-treated net use previous night				
No	1		1	
Yes	1.4 (0.9–1.9)	.08	1.0 (0.6–1.4)	.8
Gender				
Male			1	
Female			0.8 (0.6–1.1)	.2
Study site				
WCR			1	
NBR			1.2 (0.6–2.3)	.6
LRR			1.7 (0.9–3.2)	.12
CRR			0.9 (0.4–1.9)	.8
URR-S			1.0 (0.52–1.74)	.9
URR-N			4.9 (2.8–9.0)	<.01

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; CRR, Central River Region; DP, dihydroartemisinin-piperaquine; LRR, Lower River Region; MDA, mass drug administration; NBR, North Bank Region; URR-N, Upper River Region, north; URR-S, Upper River Region, south; WCR, West Coast Region.

[a]Variables with *P* values < .1 in the univariate analysis (gender and study sites) or that were confounders (long lasting insecticide-treated net use at night and age groups) were included in the multivariate analysis. Variables with *P* values > .1 in univariate analysis (sleeping outside and travel history) were excluded in the multivariate analysis.

1.5–4.3; $P < .01$), August (AOR 2.8, 95% CI 1.6–5.1; $P = .001$), or throughout the transmission season (AOR 2.5, 95% CI 1.7–3.6; $P < .01$; Supplementary Table 4).

The odds of clinical malaria were significantly lower in 2014 (AOR 0.4, 95% CI 0.3–0.6; $P < .01$) and 2015 (AOR 0.6, 95% CI 0.5–0.7; $P < .01$) in those fully treated, as compared to untreated individuals (Table 4). The incidence of clinical malaria was significantly lower in all regions after the first and second MDA, as compared to 2013 (Supplementary Table 5). The incidence of clinical malaria was similar after the first and second MDA rounds, except in the URR-S and URR-N, where the incidence was significantly higher in 2015 than in 2014 (Figure 4 and Supplementary Table 5). In the URR-S and URR-N, the rainfalls lasted longer (May-December) in 2015 than in 2013 and 2014 (Figure 4).

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 2 consecutive years in areas of differing transmission intensity in The Gambia [8].

The prevalence and incidence of infection in 2014 were significantly lower than in 2013, but remained significantly higher in eastern Gambia, as compared to other regions. The 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 as compared to the first, and confirming the higher transmission

Table 4. Risk Factors of Clinical Malaria Post-Mass Drug Administration 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)	.4	0.7 (0.5–1.0)	.05
3 doses	0.4 (0.3–0.6)	<.01	0.59 (0.5–0.7)	<.01
Age group				
≤5 years	1		1	
6–17 years	0.8 (0.5–1.2)	.3	1.2 (0.9–1.6)	.1
≥18 years	0.5 (0.3–0.8)	.003	0.9 (0.7–1.2)	.5
Gender				
Male	1		1	
Female	0.7 (0.5–0.9)	.02	0.8 (0.6–0.9)	.02
Long lasting insecticide treated-net use previous night				
No	1		1	
Yes	0.5 (0.3–0.7)	<.01	0.71 (0.5–0.9)	.02
Travelled				
No			1	
Yes	0.7 (0.3–1.9)	.5	1.9 (1.7–2.1)	<.01
Month				
April	1		1	
June	0.5 (0.1–0.5)	.6	0.4 (0.1–1.8)	.2
July	0.1 (0.02–0.6)	.01	0.3 (0.1–1.2)	.1
August	0.5 (0.1–1.5)	.2	1.3 (0.5–3.2)	.61
September	0.8 (0.4–2.4)	.7	4.5 (2.03–9.9)	<.01
October	3.2 (1.3–7.9)	.01	16.8 (7.9–35.7)	<.01
November	12.7 (5.5–9.2)	<.01	26.2 (12.5–54.7)	<.01
December	1.1 (0.5–2.9)	.8	5.4 (2.5–11.5)	<.01

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; DP, dihydroartemisinin-piperaquine; MDA, mass drug administration.

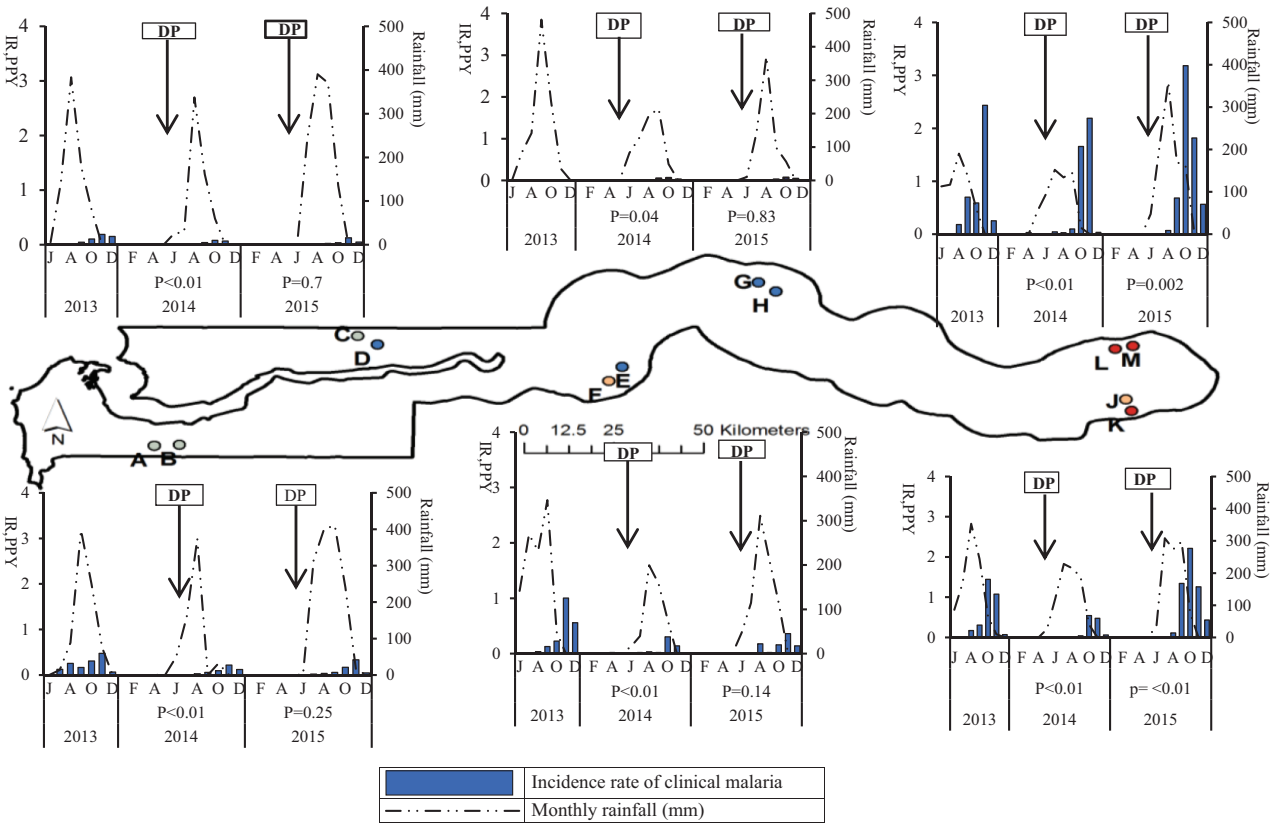

Figure 4. Monthly incidence of clinical malaria by region, before (2013) and after (2014) 1 annual MDA round. Abbreviations: DP, dihydroartemisinin-piperaquine; IR, incidence rate; MDA, mass drug administration; PPY, per person year.

intensity in this region [8, 22]. The administration of 1 annual MDA round over 2 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 2 months following MDA [10]. In Zambia, 2 MDA rounds showed a lower prevalence for at least 6 months in the low-transmission sites [11]. In Myanmar, MDA with DP and a single low dose of primaquine significantly reduced *P. falciparum* prevalence 3 months after MDA in intervention villages, as 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, which would reduce mosquito survival [24].

Here, 1 annual MDA round was unable to maintain the observed malaria decline throughout the transmission season. Nevertheless, the incidence of clinical malaria in the western and central regions remained low across the 2 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, which resulted in higher mosquito density and survival. Therefore, in low-transmission areas, such as western and central Gambia, 1 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 2 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 prioritized 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 was comparable to previous studies, which had coverage rates of 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

treatment, despite meetings and mobilization campaigns, highlighting the main challenges for MDA implementation [32, 33]. Compliance was high, as doses were directly observed, but 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]. Incomplete treatment was not protective, probably due to the shortened post-treatment prophylaxis [35]. 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, as detected by quantitative PCR, at day 3 post-treatment [36], while 25% of patients treated with an ACT had parasitaemia at day 14, as detected by quantitative real-time PCR [37]. 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—for example, 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 2 months [38, 39]. This suggests that the risk of infection and clinical disease is extremely focal, as already shown in The Gambia [8], Senegal [40], and Kenya [41]. 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 [42]. 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 2000/µl, it is unlikely that clinical malaria cases would have gone undiagnosed.

CONCLUSIONS

Annual MDA with DP reduced the 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, the clinical malaria incidence was reduced over 2 years, despite an apparent higher transmission during the second year. In future, 1 MDA round could be followed by a MDA targeting those 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. U. D. acquired funding, reviewed the draft manuscripts, and approved the final version. J. M. coordinated the implementation of the study, conducted the data analyses, and wrote the draft manuscript and final version. J. A. reviewed the drafts and final version. M. W. and N. I. M. provided statistical support, contributed to this article, and approved the final version. A. W. was the data manager, contributed to this article, and approved the final version. F. K. and A. P. conducted the sample analyses and contributed to this article. M. A., S. D., G. L. dT., J. P. V. G., D. N., T. B., and C. D. contributed to this article and approved the final version.

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