AFRICAN JOURNAL OF PARASITOLOGY, MYCOLOGY AND ENTOMOLOGY
Official journal of the African Society of Parasitology

Malaria determinants among adults of Dielmo, a Senegal malaria endemic village, before the introduction of long-lasting-insecticide-treated bed-nets: an 18-year longitudinal study

Amélé Nyedzie Wotodjo [1,*], Souleymane Doucoure [1], Nafissatou Diagne [1], Adama Tall [2], Jean-François Trape [3] and Cheikh Sokhna [1,4]

[1] EMR MINES, Campus International IRD-UCAD de Hann, Dakar BP 1386, Senegal; souleymane.doucoure@ird.fr (S.D.); diagnenafissatou51@gmail.com (N.D.); Cheikh.Sokhna@ird.fr (C.S.)
[2] Institut Pasteur de Dakar, 36 Avenue Pasteur, Dakar BP 220, Senegal; docteuradamatall@gmail.com
[3] Institut de Recherche pour le Développement, MIVEGEC, Dakar BP 1386, Senegal; jean-francois.trape@ird.fr
[4] Aix Marseille Université, IRD, MINES, 13013 Marseille, France
* Corresponding author: amele-nyedzie.wotodjo@ird.fr; Tel.: (+221)-33-849-35-39

Submitted: 11 May 2024, accepted: 30 July 2024, published: 20 August 2024

Abstract: Background: Limited data on malaria morbidity among African adults exposed since birth to intense malaria transmission are available. This study aimed to investigate malaria morbidity determinants among adults living in Dielmo village, Senegal, where a longitudinal epidemiological study was carried out over an 18-year period before the introduction of insecticide-treated nets. **Methods:** Between July 1990 and June 2008, a longitudinal study was carried out in Dielmo, a Senegalese village, among adults aged at least 15 years to evaluate determinants of *P. falciparum* clinical malaria attacks. Malaria diagnosis was confirmed by thick blood smear. Data were analyzed using a random-effect negative binomial regression. **Results:** Of a total of 12,253 person-trimester observations, 768 *P. falciparum* uncomplicated clinical malaria attacks and a series of biological and epidemiological parameters were analyzed. Being aged 30 years or more, the combination therapy treatment period, and being born in the village of Dielmo were significantly associated with a lower risk of clinical malaria, while the third trimester of the year (rainy season) and the condition of pregnancy were significantly associated with an increased risk of clinical malaria. None of the biological parameters investigated were associated with the occurrence of malaria attacks. **Conclusion:** This study provides longitudinal data on malaria among adults exposed to intense perennial transmission. It shows that the incidence of the disease among adults first decreased rapidly and then progressively with age during the different treatment policy periods, with pregnancy as the only individual major factor of increased risk of clinical malaria among those investigated in our study.

Keywords: malaria; adults; pregnancy; Dielmo; Senegal

How to cite: Wotodjo, A.N.; Doucoure, S.; Diagne, N.; Tall, A.; Trape, J.-F.; Sokhna, C. Malaria determinants among adults of Dielmo, a Senegal malaria endemic village, before the introduction of long-lasting-insecticide-treated bed-nets: an 18-year longitudinal study. *Afr. J. Parasitol. Mycol. Entomol.*, 2024, 2(1): 10; doi:10.35995/ajpme02010010.

1. Introduction

Although detailed studies on malaria among West African adults carried out in the 1950s [1] and 1960s [2] demonstrated that clinical malaria could occur in adults exposed since birth to high levels of malaria transmission, research on malaria in Africa in the following decades focused on children and pregnant women since the malaria burden was essentially concentrated in these populations [3]. As a result, limited epidemiological data are available on malaria among adults from West African rural communities and its determinants.

Since 1990, a longitudinal study has been carried out in Dielmo, a malaria endemic village of Senegal [4]. The inhabitants of Dielmo were monitored daily for fever. Our database, which contains much historical information about malaria episodes that occurred in this population as well as parasitological, biological, and demographic data, allowed a retrospective analysis. This study aimed to investigate the determinant factors of clinical malaria in adults from the beginning of the Dielmo project in July 1990 until June 2008 when long-lasting-insecticide-treated nets were introduced in this village and other villages of the area.

2. Methods

2.1. Village of Dielmo

The study site, Dielmo, and the procedures of parasitological, entomological, and epidemiological surveillance were described elsewhere [4,5]. In brief, Dielmo is a Senegalese village where malaria is endemic. The village is situated in a Sudanian savanna region of central Senegal at 280 km southeast of Dakar. The presence of the Nema river allows the breeding sites of *Anopheles* throughout the year [4]. Malaria transmission is intense and perennial with 255.1 and 232.3 infected bites per person per year in 1991 and 2007, respectively [6]. Most inhabitants of Dielmo are farmers.

2.2. Participants and procedure

Between July 1990 and June 2008, a longitudinal study was carried out in Dielmo, among adults aged 15 years and over, to evaluate determinants of *P. falciparum* clinical malaria attacks. Passive and active surveillance efforts, including monitoring of the presence of inhabitants of Dielmo, were conducted daily. To assess malaria incidence, thick blood smears were performed for all cases of fever detected at the health center of the project or at the morning visit performed at home by our team. Thick smears were examined on 200 oil-immersion fields for malaria parasites. The parasite leukocyte ratio was measured for *P. falciparum*. Episodes of fever were attributed to malaria when the parasite density of *P. falciparum* was higher than an age-dependent threshold [7]. During the study period, malaria attacks were treated from July 1990 to December 1994 with oral

quinine; from January 1995 to October 2003 with chloroquine; from November 2003 to May 2006 with Amodiaquine plus Sulphadoxine-pyrimethamine (SP), and from June 2006 to June 2008 with Amodiaquine plus Artesunate, an artemisinin-based combination therapy (ACT). However, for adults who were permanently resident in Dielmo, clinical malaria attacks lasted only a few hours [8]; thus, in most case, only symptomatic treatment was given to reduce selection for drug-resistance in malaria parasites [5].

At the beginning of the project, blood was collected from inhabitants in order to perform ABO group tests and rhesus- and hemoglobin-type tests. Information about sex, age, period of treatment, being resident of Dielmo, being born in Dielmo, attending French school, attending Koranic School, literacy (attending French or Koranic school), and pregnancy were available for each individual included in the project in 4D software version 2004.5.

The presence or absence in the village of each enrolled individual was monitored daily. Adults were considered to be resident of Dielmo if they had spent at least 75% of time in the area since their inclusion in the project. They were considered to be quarterly resident if they had spent at least 75% of time in the quarter at Dielmo. All adults aged 15 years old and over who were inhabitants of Dielmo were included in this study. The malaria clinical attack incidence rate was calculated as the ratio of the number of clinical malaria attacks recorded, divided by the number of person-days of follow-up during a given period. The mean yearly incidence rates were derived from the daily incidence rates based on 365.25 days per year.

To assess malaria prevalence each year, cross-sectional surveys were conducted quarterly, with two surveys during the dry season and two in the rainy season. Thick smears were performed in all individuals enrolled in the Dielmo project who were present in the village during the survey.

To assess the malaria transmission, the entomological inoculation rate (EIR) was calculated based on mosquito collection by human landing catch (HLC). Every month, two households were used to trap mosquitoes over three consecutive nights by HLC. These two households, 200 m apart, have been mosquito collection sites since the beginning of the Dielmo project in 1990 and remained unchanged throughout the course of the study. In each collection site, the HLC method was performed inside and outside the houses to assess malaria transmission. The Dielmo health center provided medical surveillance for all collectors, as for the other members of the community. The EIR per number of infective bites/person/night was then assessed from the monthly values for human bite rates (i.e., the number of landing mosquitoes per person) and the proportion of infected mosquitoes.

Written informed consent was obtained from all participants. The study was approved by the Ministry of Health of Senegal and the assembly of the Dielmo population.

2.3. Care of pregnant women

In July 2003, the intermittent preventive treatment (IPT) for pregnant women was implemented officially at the national level in Senegal. The implementation of this treatment was effective in the Néma-Nding health post near Dielmo and coincided with the implementation of combination therapy in Dielmo. Pregnant women were sensitized to take part to the IPT program by a midwife living in Dielmo who was recruited for the project.

2.4. Outcome and independent variables definition

Our analysis is based on person-trimester observations: adults who had at least one clinical malaria attack during the quarter were compared to those who did not have clinical malaria in the same quarter. Malaria cases were counted separately for the same individual if they occurred fifteen days apart or more. Our outcome variable was the number of malaria attacks per adult per quarter.

Explanatory variables such as the type of hemoglobin, ABO blood group, rhesus group, sex, age group (15–29; 30–44; 45–59; and 60 years old and over), period of treatment, being quarterly or permanently resident in Dielmo, being born in Dielmo, attending French school, attending Koranic

school, literacy (attending French and or Koranic school), quarter of the year, and pregnancy were analyzed separately for an association with the occurrence of malaria clinical risk. Then, variables with $p < 0.2$ in bivariate analysis were integrated in a random-effect negative binomial regression model to take into account the interdependence of successive observations in the same individuals. Step-wise elimination of variables was performed based on the AIC (Akaike information criterion) in the model. To evaluate the effect of the IPT program, we separately analyzed women observations during the study period, before and after the IPT implementation. Analyses were performed using Stata Software, version 11.0 (College Station, TX, USA). The significance level was fixed at $p < 0.05$.

3. Results

3.1. Description of participants and clinical malaria attacks

A total of 12,253 persons-trimester observations of 405 adults aged at least 15 years were analyzed, with 768 (6.3%) clinical malaria cases and 11,485 observations of no clinical malaria cases. The mean number of malaria attacks per adult per quarter during oral quinine or chloroquine periods was 0.09 [0.08–0.09] (maximum = four attacks per adult per quarter), while during the combination treatment period (Amodiaquine plus SP or Amodiaquine plus Artesunate periods), the mean number of malaria attacks was 0.04 [0.03–0.05] (maximum = two attacks per adult per quarter). All triple and quadruple attacks during a quarter among the same person occurred before the implementation of combination therapy. The sex ratio among the person-trimester observations was 0.99 (6094/6159). Only 10.6% of the observations (n = 1296) were related to adults who had attended French school and 55.1% of the observations (n = 6747) were from those who had attended Koranic school. Adults who were born in Dielmo represented 74.0% of the observations (n = 9065). Among the observations recorded, 74.3% (n = 9109) were from Dielmo adults who were permanently resident during the whole study period, showing a relatively stable population. The O group was the most represented over the observations with 40.8% (n = 5003), followed by the A group (28.6%), the B group (23.2%), and the AB group (4.7%). The HBs and HBc hemoglobin types represented, respectively, 9.4% (n = 1149) and 1.0% (n = 117), whereas the HBa type represented 88.3% (10,818) of the observations. Regarding the age group, 45.3% of the observations (n = 5550) concerned adults aged 15–29 years and 26.4% (n = 3238) were from adults aged 30–44 years. Adults aged 45-59 years represented 16.4% (n = 2008) of the observations whereas those aged at least 60 years represented 11.9% (n = 1457) of the observations. Almost all quarters of the years had approximately the same number of observations (first quarter: 25.6%; second quarter: 25.4%; third quarter: 24.2%; and fourth quarter: 24.8%). Table 1 describes individual characteristics among the whole study population and according to the presence of clinical malaria attacks. There were 622 observations among pregnant women with 94 clinical malaria attacks.

3.2. Incidence of clinical malaria attacks during the study period

According to the treatment periods, the incidence density of clinical malaria attacks varied significantly during the study period, with the highest levels during the chloroquine and oral quinine treatment periods, with 0.42 and 0.38 attacks per person per year, respectively, and the lowest levels during Amodiaquine plus SP and ACTs treatment periods, with 0.19 and 0.21 attacks per person year, respectively. According to age group, the incidence density was 0.53, 0.32, 0.22, and 0.15 attacks per person per year among adults aged 15–29, 30–44, 45–59, and 60 years old, respectively, during the treatment period of oral quinine, whereas it was 0.21, 0.29, 0.11, and 0.08 attacks per person per year among adults aged 15–29, 30–44, 45–59, and 60 years old, respectively, during the Amodiaquine plus SP treatment period. Figure 1 shows malaria incidence among the age groups according to the treatment period. For each treatment period, it decreased with age, except for the Amodiaquine plus SP treatment period.

Table 1: Socio-demographic, biological, and other characteristics among adults according to the presence of clinical malaria attacks (n = 12,253).

		Number of Observations (n = 12,253) n (%)	Malaria Cases	
Characteristics	**Subcategory**		**No (n = 11,485) n (%)**	**Yes (n = 768) n (%)**
Socio-demographic characteristics				
Sex				
	Male	6094 (49.7)	5708 (49.7)	386 (50.3)
	Female	6159 (50.3)	5777 (50.3)	382 (49.7)
Age group				
	15–29 years old	5550 (45.3)	5129 (44.7)	421 (54.8)
	30–44 years old	3238 (26.4)	3008 (26.2)	230 (29.9)
	45–59 years old	2008 (16.4)	1927 (16.8)	81 (10.5)
	60 years old and over	1457 (11.9)	1421 (12.4)	36 (4.7)
French School				
	No	10,863 (88.7)	10255 (89.3)	608 (79.2)
	Yes	1296 (10.6)	1141 (9.9)	155 (20.2)
Koranic school				
	No	4822 (39.4)	4557 (39.7)	265 (34.5)
	Yes	6747 (55.1)	6331 (55.1)	416 (54.2)
Literacy				
	No	4735 (38.6)	4476 (39.0)	259 (33.7)
	Yes	7432 (60.7)	6927 (60.3)	505 (65.8)
Resident/quarter				
	No (<75% of time spent)	2727 (22.3)	2613 (22.8)	114 (14.8)
	Yes (⩾75% of time spent)	9526 (77.7)	8872 (77.2)	654 (85.2)
Resident all the study				
	No (<75% of time spent)	3144 (25.7)	2936 (25.6)	215 (28.0)
	Yes (⩾75% of time spent)	9109 (74.3)	8556 (74.4)	553 (72.0)
Being born in Dielmo				
	No	3162 (25.8)	2852 (24.8)	310 (40.4)
	Yes	9065 (74.0)	8609 (75.0)	456 (59.4)
Pregnancy				
	No	5537 (89.9)	5249 (90.9)	288 (75.4)
	Yes	622 (10.1)	528 (9.1)	94 (24.6)
	not concerned	6094		
Biological characteristics				
HB type				
	AA	10,818 (88.3)	10,153 (88.4)	665 (86.6)
	AS	1149 (9.4)	1074 (9.4)	75 (9.8)
	AC	117 (1.0)	114 (1.0)	3 (0.4)
ABO Group				
	O	5003 (40.8)	4668 (40.6)	335 (43.6)
	A	3505 (28.6)	3278 (28.5)	227 (29.6)
	B	2871 (23.4)	2730 (23.8)	141 (18.4)
	AB	577 (4.7)	541 (4.7)	36 (4.7)
Rhesus group				
	+	11,071 (90.4)	10,378 (90.4)	693 (90.2)
	-	885 (7.2)	839 (7.3)	46 (6.0)

Table 1: *Cont.*

Characteristics	Subcategory	Number of Observations (n = 12,253) n (%)	Malaria Cases	
			No (n = 11,485) n (%)	Yes (n = 768) n (%)
Other characteristics				
Treatment period				
	Oral quinine	2535 (20.7)	2356 (20.5)	179 (23.3)
	Chloroquine	5983 (48.8)	5539 (48.2)	444 (57.8)
	Amodiaquine + SP	1977 (16.1)	1899 (16.5)	78 (10.2)
	ACTs	1758 (14.3)	1691 (14.7)	67 (8.7)
Quarter of the year				
	First quarter of the year	3137 (25.6)	2974 (25.9)	163 (21.2)
	Second quarter of the year	3115 (25.4)	2950 (25.7)	165 (21.5)
	Third quarter of the year	2968 (24.2)	2721 (23.7)	247 (32.2)
	Fourth quarter of the year	3033 (24.8)	2840 (24.7)	193 (25.1)

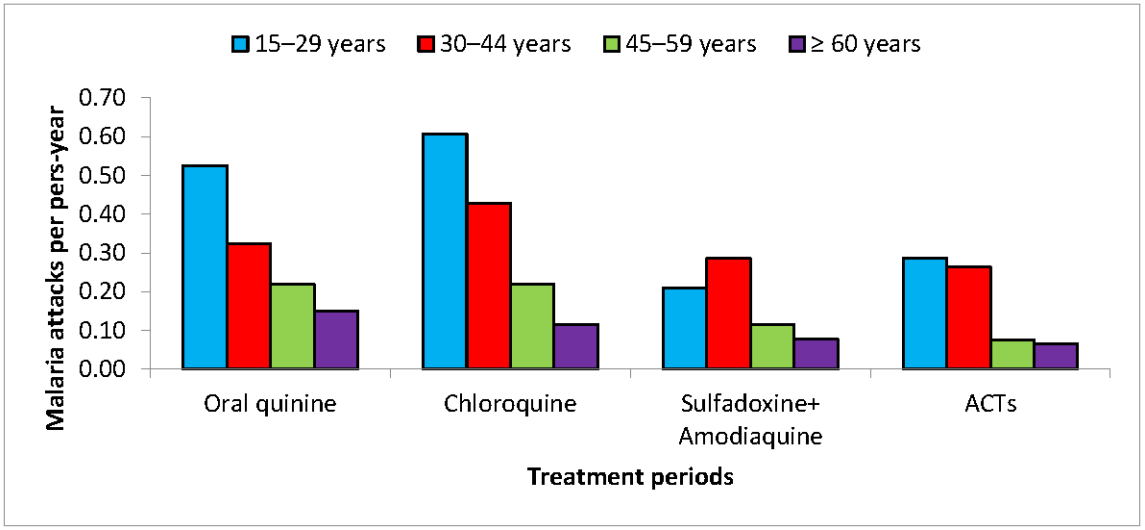

Figure 1: Malaria incidence among adults by age group according to different treatment periods in Dielmo.

3.3. Factors associated with the risk of having malaria clinical attacks

In the bivariate analyses, malaria decreased significantly among the age group 30 years and over when compared with adults aged 15-29 years (OR 95% CI= 0.70 [0.56–0.87], p = 0.002; OR 95% CI = 0.42 [0.29–0.595], p < 0.001; and OR 95% CI = 0.25 [0.15–0.41], p < 0.001 for age groups 30–44 years, 45–59 years, and 60 years and over, respectively). Similarly, the treatment periods based on chloroquine and on bi-therapy compared with the treatment based on oral quinine (OR 95% CI = 0.78 [0.65–0.94], p = 0.008; 0.35 [0.26–0.46], p < 0.001; and 0.31 [0.23–0.42], p < 0.001, respectively, for chloroquine, Amodiaquine plus SP, and ACTs) and being born in Dielmo (OR 95% CI = 0.37 [0.27–0.50]; p < 0.001) were associated significantly with a decreased risk of clinical malaria. A contrario, being quarterly resident of Dielmo (OR 95% CI =2.41 [1.95–2.97], p < 0.001) was significantly associated with increased malaria risk. Similarly, attending French school (OR 95%

CI = 2.42 [1.62–3.63], $p < 0.001$) and the third and fourth trimester of the year (OR 95% CI = 1.64 [1.36–1.99], $p < 0.001$ and OR 95% CI = 1.25 [1.02–1.53], $p = 0.03$) were significantly associated with an increased risk of malaria attacks. The variables such as the type of hemoglobin, sex, rhesus group, being resident throughout the study, attending Koranic school, and blood group were not significantly associated with the occurrence of clinical malaria attacks. Table 2 shows the results of bivariate and multivariate analysis.

Table 2: Random-effect negative binomial regression models exploring factors associated with clinical malaria cases among adults (n = 12,253).

		Univariate Analysis		Multivariate Analysis	
Characteristics	**Subcategory**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
Socio-demographic characteristics					
Sex					
	Male	1			
	Female	0.92 (0.67–1.26)	0.59		
Age group					
	15–29 years old	1		1	
	30–44 years old	0.70 (0.56–0.87)	0.002	0.78 (0.62–0.98)	0.033
	45–59 years old	0.42 (0.29–0.59)	<0.001	0.51 (0.36–0.74)	<0.001
	60 years old and over	0.25 (0.15–0.41)	<0.001	0.34 (0.20–0.58)	<0.001
French School					
	No	1		1	
	Yes	2.42 (1.62–3.63)	<0.001	1.47 (0.94–2.30)	0.09
Koranic school					
	No	1			
	Yes	1.14 (0.83–1.58)	0.419		
Literacy					
	No	1			
	Yes	1.30 (0.94–1.80)	0.118		
Resident/quarter					
	No (<75% of time spent)	1		1	
	Yes (⩾75% of time spent)	2.41 (1.95–2.97)	<0.001	2.67 (2.13–3.34)	<0.001
Resident all the study					
	No (<75% of time spent)	1			
	Yes (⩾75% of time spent)	1.12 (0.80–1.57)	0.52		
Being born in Dielmo					
	No	1		1	
	Yes	0.37 (0.27–0.50)	<0.001	0.43 (0.30–0.61)	<0.001
Biological characteristics					
HB type					
	AA	1			
	AS	1.11 (0.66–1.86)	0.705		
	AC	0.28 (0.04–1.74)	0.170		
ABO Group					
	O	1		1	
	A	1.09 (0.74–1.60)	0.656	1.19 (0.83–1.70)	0.341
	B	0.74 (0.48–1.12)	0.149	0.79 (0.54–1.18)	0.248
	AB	0.89 (0.43–1.83)	0.741	1.10 (0.56–2.17)	0.786
Rhesus group					
	+	1			
	-	0.64 (0.35–1.19)	0.162		

Table 2: *Cont.*

Characteristics	Subcategory	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Other characteristics					
Treatment period					
	Oral quinine	1		1	
	Chloroquine	0.78 (0.65–0.94)	0.008	0.90 (0.75–1.09)	0.295
	Amodiaquine + SP	0.35 (0.26–0.46)	<0.001	0.42 (0.31–0.56)	<0.001
	ACTs	0.31 (0.23–0.42)	<0.001	0.42 (0.30–0.57)	<0.001
Quarter of the year					
	First quarter of the year	1		1	
	Second quarter of the year	1.00 (0.82–1.24)	0.968	0.97 (0.79–1.19)	0.761
	Third quarter of the year	1.64 (1.36–1.99)	<0.001	1.52 (1.26–1.84)	<0.001
	Fourth quarter of the year	1.25 (1.02–1.53)	0.03	1.18 (0.97–1.44)	0.104

In the final multivariate model, adjusted on all covariates, the age group ⩾ 30 years old remained protective against malaria (OR 95% CI = 0.78 [0.62–0.98], $p = 0.033$ for age group 30–44 years; OR 95% CI = 0.51 [0.36–0.74], $p < 0.001$ for age group 45–59 years; and OR 95% CI = 0.34 [0.20–0.58], $p < 0.001$ for age group 60 years and over). Similarly, treatments based on bi-therapy were protective against malaria (OR 95% CI = 0.42 [0.31–0.56], $p < 0.001$ and 0.42 [0.30–0.57], $p < 0.001$ for Amodiaquine plus SP and ACTs treatment periods, respectively). Being born in Dielmo remained protective against malaria (OR 95% CI = 0.43 [0.30–0.61]). The third quarter of the year (OR 95% CI = 1.52 [1.26–1.84], $p < 0.001$) and being quarterly resident (OR 95% CI = 2.67 [2.13–3.34], $p < 0.001$) significantly increased malaria risk.

3.4. Factors associated with the occurrence of malaria clinical attacks among women

In bivariate analyses, pregnancy was significantly associated with an increased risk of having clinical malaria (OR 95% CI = 2.28 [1.78–2.91]; $p < 0.001$). The third quarter of the year (OR 95% CI = 1.59 [1.22–2.08], $p = 0.001$) and being quarterly resident (OR 95% CI = 2.48 [1.75–3.51], $p < 0.001$) remained malaria risk factors as for the whole study population. Women aged 30 years and more were protected against malaria compared with those aged 15–29 years (OR 95% CI = 0.72 [0.53–0.98], $p = 0.035$ for age group 30–44 years; OR 95% CI = 0.44 [0.28–0.71], $p = 0.001$ for age group 45–59 years; and OR 95% CI = 0.24 [0.13–0.46], $p < 0.001$ for those aged 60 years and over). The variable being born in Dielmo was also protective against malaria (OR 95% CI = 0.35 [0.23–0.54], $p = 0.001$). The IPT period was associated with a decreased in malaria cases (OR 95%CI = 0.46 [0.36–0.60], $p < 0.001$).

In the final multivariate analysis, IPT was not significantly associated with a decrease in malaria (OR 95% CI = 1.21 [0.66–2.23], $p = 0.543$). Pregnancy remained significantly associated with an increased risk of having malaria (OR 95% CI = 1.85 [1.46–2.34], $p < 0.001$) after adjusting with the third trimester of the year, the treatment periods, the age group, being born in Dielmo, and being quarterly resident. Table 3 shows results of bivariate and multivariate analyses among women.

3.5. Malaria prevalence and transmission

The global prevalence of malaria was 41%, 27%, 28%, and 20% during oral quinine, chloroquine, Amodiaquine plus SP, and ACTs treatment periods, respectively. According to age group, the malaria prevalence was the highest among young adults aged 15-29 years, regardless the period of treatment ($p < 0.005$). It was approximately the same in the other age group for each period of treatment

(Figure 2). No significant difference was observed in malaria prevalence during chloroquine and Amodiaquine plus SP treatment periods (p = 0.27) and during bi-therapy treatment (Amodiaquine plus SP and ACTs) (p = 0.05). Malaria transmission was the highest during the chloroquine treatment period with an EIR of 336 infected bites per person per year and the lowest during ACTs treatment period with an EIR of 150 infected bites per person per year (Figure 2).

Table 3: Random-effect negative binomial regression models exploring factors associated with clinical malaria cases among women (n = 6159).

		Univariate Analysis		Multivariate Analysis	
Characteristics	**Subcategory**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
Socio-demographic characteristics					
Age group					
	15–29 years old	1		1	
	30–44 years old	0.72 (0.53–0.98)	0.035	0.86 (0.63–1.18)	0.339
	45–59 years old	0.44 (0.28–0.71)	0.001	0.64 (0.39–1.06)	0.078
	60 years old and over	0.24 (0.13–0.46)	<0.001	0.40 (0.20–0.79)	0.008
Resident/quarter					
	No (<75% of time spent)	1		1	
	Yes (75%–100% of time spent)	2.48 (1.75–3.51)	<0.001	2.97 (2.06–4.29)	<0.001
Resident all the study					
	No (<75% of time spent)	1			
	Yes (75%–100% of time spent)	1.15 (0.71–1.86)	0.572		
Being born in Dielmo					
	No	1		1	
	Yes	0.35 (0.23–0.54)	<0.001	0.46 (0.29–0.72)	0.001
Pregnancy					
	No	1		1	
	Yes	2.28 (1.78–2.91)	<0.001	1.85 (1.46–2.34)	<0.001
Koranic school					
	No	1			
	Yes	1.13 (0.70–1.83)	0.610		
French School					
	No	1		1	
	Yes	2.24 (1.22–4.12)	0.009	1.46 (0.79–2.70)	0.232
Biological characteristics					
HB type					
	AA	1			
	AS	1.40 (0.68–2.89)	0.359		
	AC	–	1		
ABO Group					
	O	1		1	
	A	1.18 (0.69–2.03)	0.540	1.15 (0.71–1.88)	0.563
	B	0.67 (0.36–1.23)	0.194	0.67 (0.37–1.19)	0.172
	AB	0.88 (0.32–2.41)	0.806	1.17 (0.46–2.96)	0.741
Rhesus group					
	+	1			
	-	0.742(0.27–1.26)	0.512		

Table 3: *Cont.*

Characteristics	Subcategory	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Other characteristics					
Treatment period					
	Oral quinine	1		1	
	Chloroquine	0.71 (0.55–0.93)	0.011	0.74 (0.57–0.97)	0.028
	Amodiaquine + SP	0.33 (0.23–0.49)	<0.001	0.29 (0.14–0.60)	0.001
	ACTs	0.29 (0.19–0.44)	<0.001	0.28 (0.14–0.59)	0.001
IPT period					
	No	1		1	
	Yes	0.46 (0.36–0.60)	<0.001	1.21 (0.66–2.23)	0.543
Quarter of the year					
	First quarter of the year	1		1	
	Second quarter of the year	0.90 (0.67–1.21)	0.939	0.87 (0.65–1.16)	0.341
	third quarter of the year	1.59 (1.22–2.08)	0.001	1.42 (1.09–1.84)	0.01
	fourth quarter of the year	1.21 (0.92–1.60)	0.179	1.09 (0.83–1.44)	0.539

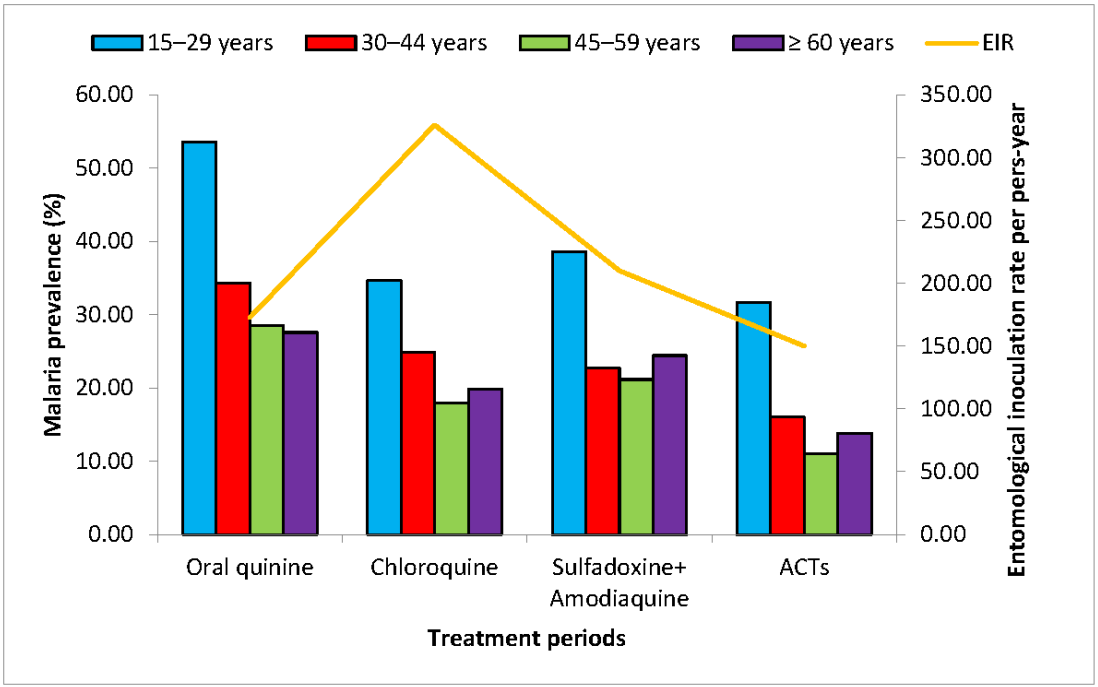

Figure 2: Malaria prevalence among adults by age group and malaria transmission according to different periods of treatment in Dielmo.

4. Discussion

Our study identified six factors that significantly affected malaria morbidity in adults of Dielmo. Age 30 years and more, bi-therapy treatment, and being born in Dielmo were protective factors against clinical malaria attacks, while the third quarter of the year (July–September, i.e., the rainy season), pregnancy,

and being quarterly resident of Dielmo significantly increased malaria risk. Regarding age, it is well known that in malaria endemic areas, age influences malaria incidence [4,9–13]. However, limited data are available about trends in the incidence of malaria attacks with age during adulthood. The trend in malaria episodes has shown that although adults are known to be more protected against malaria than children due to natural antimalarial immunity, young adults aged 15–29 years old are more vulnerable than older adults. Malaria prevalence showed the same trend, with higher asymptomatic carriage among young adults than among older adults regardless of the period of treatment. This observation is due to the acquisition of natural immunity against *Plasmodium* in malaria endemic areas, which is progressive and increases with age [11,14].

In our study, there was a significant association between place of birth and malaria incidence. Adults who were born in Dielmo suffered less attacks than others. Dielmo is a highly endemic area with perennial malaria transmission, contrary to most other areas of Senegal where transmission is lower and seasonal; this probably explains why inhabitants who were born in Dielmo acquired a better immunity against malaria than those who resided for part of their life in other areas of Senegal.

Treatments based on bi-therapy significantly decreased the risk of malaria, as seen in a previous study in Dielmo [5]. Using bi-therapy as a first-line treatment against malaria was associated with a more than half decrease in the occurrence of malaria clinical attacks. Many studies showed the efficacy of ACTs when used for malaria treatment [15–18]. Our study also showed this efficacy. In addition, the superiority of SP plus Amodiaquine compared with chloroquine or oral quinine was also highlighted in our study. Similarly to other studies [15,19,20], these results suggest that associating two drugs is more effective than using a single drug for the treatment of clinical malaria attacks.

Although transmission occurred all year round in Dielmo, the third quarter of the year was the period of higher risk of malaria. This result could be explained by the rainy season, which coincided with the third quarter where *anophelines* were the most abundant. Parasite genetic diversity was also probably higher, due to the probable occasional introduction in Dielmo of malaria parasites from areas with seasonal transmission.

There was no significant association of having attended French school during childhood with malaria risk in the multivariate analysis. In another study, higher level education was seen to be protective against malaria [21]. In the context of Dielmo, attending school usually means primary school, rarely secondary school, so they were low-literate. Some studies showed no association between education level and malaria [22,23].

In our study, blood group and hemoglobin type were not significantly associated with clinical malaria. Some studies about ABO group and hemoglobin type reported that the O group and HbAS protected against severe malaria while A, B, or AB were risk factors of severe malaria [24,25]. The O group was shown to be associated with uncomplicated malaria risk in some studies [26–29], but most studies showed no association between uncomplicated malaria and ABO groups [30–32].

Pregnancy is well known to be associated with increased malaria risk [33–36] and our study confirmed this observation. Although, pregnant women of Dielmo were enrolled in the IPT program, they had more risk of clinical malaria than other women. In Dielmo, IPT was introduced in 2003 and its coverage reached more than 80% of pregnant women (data not shown). Our results could not distinguish the effect of the IPT program, possibly because it was introduced simultaneously in Dielmo with bi-therapy treatment. When the two variables are used in the multivariate model, bi-therapy is protective against malaria whereas IPT is not significantly associated with decreasing malaria. A limitation for the assessment of the impact of IPT among pregnant women in Dielmo is the lack of information about those who have correctly observed this treatment. The efficacy of IPT to reduce malaria among pregnant women was documented in many studies [37–40].

Our results have shown that being quarterly resident of Dielmo increased malaria risk. The explanation behind this observation is that adults rarely left the village and spent little time out of Dielmo, so adults who were suffering from malaria were those who spent more time in the village. This variable was used to adjust our models.

Since only limited longitudinal data were available, our long-term study contributes to better knowledge of clinical malaria in adults exposed to intense perennial transmission.

5. Conclusion

This study provides longitudinal data on malaria among adults exposed to intense perennial transmission. It shows that the incidence of the disease among adults first decreased rapidly and then progressively with age during the different treatment policy periods, with pregnancy as the only individual major factor of increased risk of clinical malaria among those investigated in our study.

Author Contributions: C.S., J.F.T., and A.N.W. designed the study. A.N.W. analyzed the data. A.N.W. wrote the manuscript with the contribution of J.-F.T., and S.D. A.T., N.D., C.S., and J.-F.T. supervised the data collection and contributed to the monitoring of the study. All authors have read and agreed to the published version of the manuscript.

Funding: Institut de Recherche pour le Développement and the Pasteur Institute of Dakar.

Acknowledgments: We are grateful to Dielmo adults for their participation in the project. We thank all the staff of IRD and the Pasteur Institutes of Dakar who contributed to the design, healthcare, and data collection during the project.

Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Miller, M.J. Observations on the natural history of malaria in the semi-resistant West African. *Trans. R. Soc. Trop. Med. Hyg.* **1958**, *52*, 152–168. [CrossRef] [PubMed]
2. Bruce-Chwatt, L.J. A Longitudinal Survey of Natural Malaria Infection in a Group of West African Adults. *West Afr. Med. J.* **1963**, *12*, 199–217.
3. Snow, R.W.; Guerra, C.A.; Noor, A.M.; Myint, H.Y.; Hay, S.I. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* **2005**, *434*, 214–217. [CrossRef] [PubMed]
4. Trape, J.F.; Rogier, C.; Konate, L.; Diagne, N.; Bouganali, H.; Canque, B.; Legros, F.; Badji, A.; Ndiaye, G.; Ndiaye, P.; et al. The Dielmo project: A longitudinal study of natural malaria infection and the mechanisms of protective immunity in a community living in a holoendemic area of Senegal. *Am. J. Trop. Med. Hyg.* **1994**, *51*, 123–137. [CrossRef] [PubMed]
5. Trape, J.F.; Tall, A.; Sokhna, C.; Ly, A.B.; Diagne, N.; Ndiath, O.; Mazenot, C.; Richard, V.; Badiane, A.; Dieye-Ba, F.; et al. The rise and fall of malaria in a west African rural community, Dielmo, Senegal, from 1990 to 2012: A 22 year longitudinal study. *Lancet Infect. Dis.* **2014**, *14*, 476–488. [CrossRef]
6. Trape, J.F.; Tall, A.; Diagne, N.; Ndiath, O.; Ly, A.B.; Faye, J.; Dieye-Ba, F.; Roucher, C.; Bouganali, C.; Badiane, A.; et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: A longitudinal study. *Lancet Infect. Dis.* **2011**, *11*, 925–932. [CrossRef]
7. Roucher, C.; Rogier, C.; Dieye-Ba, F.; Sokhna, C.; Tall, A.; Trape, J.F. Changing malaria epidemiology and diagnostic criteria for Plasmodium falciparum clinical malaria. *PLoS ONE* **2012**, *7*, e46188. [CrossRef] [PubMed]
8. Rogier, C.; Ly, A.B.; Tall, A.; Cisse, B.; Trape, J.F. Plasmodium falciparum clinical malaria in Dielmo, a holoendemic area in Senegal: No influence of acquired immunity on initial symptomatology and severity of malaria attacks. *Am. J. Trop. Med. Hyg.* **1999**, *60*, 410–420. [CrossRef]
9. Baird, J.K. Host age as a determinant of naturally acquired immunity to Plasmodium falciparum. *Parasitol. Today* **1995**, *11*, 105–111. [CrossRef]
10. Ladeia-Andrade, S.; Ferreira, M.U.; de Carvalho, M.E.; Curado, I.; Coura, J.R. Age-dependent acquisition of protective immunity to malaria in riverine populations of the Amazon Basin of Brazil. *Am. J. Trop. Med. Hyg.* **2009**, *80*, 452–459. [CrossRef] [PubMed]

11. O'Meara, W.P.; Mwangi, T.W.; Williams, T.N.; McKenzie, F.E.; Snow, R.W.; Marsh, K. Relationship between exposure, clinical malaria, and age in an area of changing transmission intensity. *Am. J. Trop. Med. Hyg.* **2008**, *79*, 185–191. [CrossRef] [PubMed]
12. Trape, J.F.; Rogier, C. Combating malaria morbidity and mortality by reducing transmission. *Parasitol Today* **1996**, *12*, 236–240. [CrossRef]
13. Trape, J.F.; Tall, A.; Sokhna, C.; Ly, A.B.; Diagne, N.; Ndiath, O.; Mazenot, C.; Richard, V.; Badiane, A.; Dieye-Ba, F.; et al. The rise and fall of malaria in a West African rural community, Dielmo, Senegal, from 1990 to 2012: A 22 year longitudinal study. *Lancet. Infect. Dis.* **2014**, *14*, 476–488. [CrossRef]
14. Petersen, E.; Høgh, B.; Marbiah, N.T.; David, K.; Hanson, A.P. Development of immunity against Plasmodium falciparum malaria: Clinical and parasitologic immunity cannot be separated. *J. Infect. Dis.* **1991**, *164*, 949–953. [CrossRef]
15. Bhattarai, A.; Ali, A.S.; Kachur, S.P.; Martensson, A.; Abbas, A.K.; Khatib, R.; Al-Mafazy, A.W.; Ramsan, M.; Rotllant, G.; Gerstenmaier, J.F.; et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Med.* **2007**, *4*, e309. [CrossRef]
16. Hamainza, B.; Masaninga, F.; Moonga, H.; Mwenda, M.; Chanda-kapata, P.; Chalwe, V.; Chanda, E.; Kamuliwo, M.; Babaniyi, O.A. Therapeutic efficacy of artemether-lumefantrine on treatment of uncomplicated Plasmodium falciparum mono-infection in an area of high malaria transmission in Zambia. *Malar. J.* **2014**, *13*, 430. [CrossRef]
17. Teklemariam, M.; Assefa, A.; Kassa, M.; Mohammed, H.; Mamo, H. Therapeutic efficacy of artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria in a high-transmission area in northwest Ethiopia. *PLoS ONE* **2017**, *12*, e0176004. [CrossRef] [PubMed]
18. Tesfaye, M.; Assefa, A.; Hailgiorgis, H.; Gidey, B.; Mohammed, H.; Tollera, G.; Tasew, G.; Assefa, G.; Bekele, W.; Mamo, H. Therapeutic efficacy and safety of artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria treatment in Metehara, Central-east Ethiopia. *Malar. J.* **2024**, *23*, 184. [CrossRef] [PubMed]
19. Schlagenhauf, P.; Petersen, E. Antimalaria drug resistance: The mono-combi-counterfeit triangle. *Expert Rev. Anti-Infect. Ther.* **2009**, *7*, 1039–1042. [CrossRef]
20. Trape, J.F.; Sauvage, C.; Ndiaye, O.; Douillot, L.; Marra, A.; Diallo, A.; Cisse, B.; Greenwood, B.; Milligan, P.; Sokhna, C.; et al. New malaria-control policies and child mortality in senegal: Reaching millennium development goal 4. *J. Infect. Dis.* **2012**, *205*, 672–679. [CrossRef]
21. Guthmann, J.P.; Hall, A.J.; Jaffar, S.; Palacios, A.; Lines, J.; Llanos-Cuentas, A. Environmental risk factors for clinical malaria: A case-control study in the Grau region of Peru. *Trans. R. Soc. Trop. Med. Hyg.* **2001**, *95*, 577–583. [CrossRef]
22. Koram, K.A.; Bennett, S.; Adiamah, J.H.; Greenwood, B.M. Socio-economic determinants are not major risk factors for severe malaria in Gambian children. *Trans. R. Soc. Trop. Med. Hyg.* **1995**, *89*, 151–154. [CrossRef]
23. Koram, K.A.; Bennett, S.; Adiamah, J.H.; Greenwood, B.M. Socio-economic risk factors for malaria in a peri-urban area of The Gambia. *Trans. R. Soc. Trop. Med. Hyg.* **1995**, *89*, 146–150. [CrossRef] [PubMed]
24. Uneke, C.J. Plasmodium falciparum malaria and ABO blood group: Is there any relationship? *Parasitol. Res.* **2007**, *100*, 759–765. [CrossRef] [PubMed]
25. Amodu, O.K.; Olaniyan, S.A.; Adeyemo, A.A.; Troye-Blomberg, M.; Olumese, P.E.; Omotade, O.O. Association of the sickle cell trait and the ABO blood group with clinical severity of malaria in southwest Nigeria. *Acta Trop.* **2012**, *123*, 72–77. [CrossRef] [PubMed]
26. Panda, A.K.; Panda, S.K.; Sahu, A.N.; Tripathy, R.; Ravindran, B.; Das, B.K. Association of ABO blood group with severe falciparum malaria in adults: Case control study and meta-analysis. *Malar. J.* **2011**, *10*, 309. [CrossRef]
27. Pathirana, S.L.; Alles, H.K.; Bandara, S.; Phone-Kyaw, M.; Perera, M.K.; Wickremasinghe, A.R.; Mendis, K.N.; Handunnetti, S.M. ABO-blood-group types and protection against severe, Plasmodium falciparum malaria. *Ann. Trop. Med. Parasitol.* **2005**, *99*, 119–124. [CrossRef]
28. Rowe, J.A.; Handel, I.G.; Thera, M.A.; Deans, A.M.; Lyke, K.E.; Kone, A.; Diallo, D.A.; Raza, A.; Kai, O.; Marsh, K.; et al. Blood group O protects against severe Plasmodium falciparum malaria through the mechanism of reduced rosetting. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17471–17476. [CrossRef]
29. Tekeste, Z.; Petros, B. The ABO blood group and Plasmodium falciparum malaria in Awash, Metehara and Ziway areas, Ethiopia. *Malar. J.* **2010**, *9*, 280. [CrossRef]

30. Boel, M.E.; Rijken, M.J.; Pimanpanarak, M.; Keereecharoen, N.L.; Proux, S.; Nosten, F.; McGready, R. No association of phenotypic ABO blood group and malaria during pregnancy. *Am. J. Trop. Med. Hyg.* **2012**, *87*, 447–449. [CrossRef] [PubMed]
31. Kuadzi, J.T.; Ankra-Badu, G.; Addae, M.M. Plasmodium falciparum malaria in children at a tertiary teaching hospital: ABO blood group is a risk factor. *Pan Afr. Med. J.* **2011**, *10*, 2. [CrossRef]
32. Rout, R.; Dhangadamajhi, G.; Ghadei, M.; Mohapatra, B.N.; Kar, S.K.; Ranjit, M. Blood group phenotypes A and B are risk factors for cerebral malaria in Odisha, India. *Trans. R. Soc. Trop. Med. Hyg.* **2012**, *106*, 538–543. [CrossRef] [PubMed]
33. Desai, M.; ter Kuile, F.O.; Nosten, F.; McGready, R.; Asamoa, K.; Brabin, B.; Newman, R.D. Epidemiology and burden of malaria in pregnancy. *Lancet Infect. Dis.* **2007**, *7*, 93–104. [CrossRef]
34. Jackle, M.J.; Blumentrath, C.G.; Zoleko, R.M.; Akerey-Diop, D.; Mackanga, J.R.; Adegnika, A.A.; Lell, B.; Matsiegui, P.B.; Kremsner, P.G.; Mombo-Ngoma, G.; et al. Malaria in pregnancy in rural Gabon: A cross-sectional survey on the impact of seasonality in high-risk groups. *Malar. J.* **2013**, *12*, 412. [CrossRef]
35. Rogerson, S.J.; Mwapasa, V.; Meshnick, S.R. Malaria in pregnancy: Linking immunity and pathogenesis to prevention. *Am. J. Trop. Med. Hyg.* **2007**, *77*, 14–22. [CrossRef] [PubMed]
36. Diagne, N.; Rogier, C.; Sokhna, C.S.; Tall, A.; Fontenille, D.; Roussilhon, C.; Spiegel, A.; Trape, J.F. Increased susceptibility to malaria during the early postpartum period. *N. Engl. J. Med.* **2000**, *343*, 598–603. [CrossRef]
37. Garner, P.; Gulmezoglu, A.M. Drugs for preventing malaria in pregnant women. *Cochrane Database Syst. Rev.* **2006**, *4*, CD000169. [CrossRef]
38. Parise, M.E.; Ayisi, J.G.; Nahlen, B.L.; Schultz, L.J.; Roberts, J.M.; Misore, A.; Muga, R.; Oloo, A.J.; Steketee, R.W. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am. J. Trop. Med. Hyg.* **1998**, *59*, 813–822. [CrossRef] [PubMed]
39. Schultz, L.J.; Steketee, R.W.; Macheso, A.; Kazembe, P.; Chitsulo, L.; Wirima, J.J. The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental Plasmodium falciparum infection among pregnant women in Malawi. *Am. J. Trop. Med. Hyg.* **1994**, *51*, 515–522. [CrossRef]
40. Fokam, E.B.; Ngimuh, L.; Anchang-Kimbi, J.K.; Wanji, S. Assessment of the usage and effectiveness of intermittent preventive treatment and insecticide-treated nets on the indicators of malaria among pregnant women attending antenatal care in the Buea Health District, Cameroon. *Malar. J.* **2016**, *15*, 172. [CrossRef]