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Effect of indoor residual spraying on malaria incidence, parasitemia and parasite density among children less than five years of age in northern Benin

Aurore Ogouyèmi-Hounto[1,2*], Bella Hounkpe[3], Yolande Sissinto Savi de Tove[1,2], Edgard Edah[2], Parfait Houngbegnon[2] Augustin Koukpoliyi[2], Victoire de Souza[2], Adicath Adeothy[3], Alexis Tchevoede[3] and Dorothée Kinde Gazard[1,2]

[1]Laboratory Center for Integrated Control against Malaria, Faculty of Health Sciences, University of Abomey Calavi, Cotonou, Benin.
[2]National Malaria Control Program / Ministry of Health, Cotonou, Benin.
[3]Biostatistics Division of the Integrated Pest Management Center for Malaria, Cotonou, Benin.

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The effects of indoor residual spraying (IRS) on malaria transmission have been documented. However, the impact on morbidity has not always been highlighted. The aim of this study was to evaluate the effects of IRS on malaria incidence, parasitemia and parasite density among children less than five years of age in Benin. We conducted a cohort study in sprayed and unsprayed areas during the malaria transmission season in 2017. At inclusion, finger prick blood samples were used to assess baseline parasitemia by microscopy and rapid diagnostic tests (RDT), and children were then followed up over 7 months during which thick blood smear microscopy and RDT were repeated every month. Prevalence of parasitemia at baseline was 40.70% in the sprayed, 25.3% in the unsprayed area and remains high over the entire monitoring period with the exception of month 4. We noticed a decrease in the incidence rate in the sprayed area of 8% over the period of persistence of the insecticide, while in the unsprayed area the incidence increased by 17%. This study demonstrated that IRS can effectively reduce malaria incidence in an area of high endemicity. We recommend a larger scale study to evaluate the effects of IRS on malaria morbidity after several rounds of spraying.

Key words: Effects indoor residual spraying, malaria incidence, parasitemia, parasite density, children less than 5 years, Benin.

INTRODUCTION

In sub-Saharan Africa, malaria still remains a public health problem despite progress in scaling up malaria control interventions in many countries such as case management, vector control interventions like insecticide-treated nets (ITNs) and indoor residual spraying (IRS). According to several authors, IRS associated with ITNs is most effective for endophagic and endophilic mosquito vectors, where they provide a community-wide effect;

*Corresponding author. E-mail: aurorefel@yahoo.fr.

thus persons who do not receive personal protection can still benefit from these interventions in their communities (Binka et al.,1998; Hawley et al.,2003; Killeen et al., 2007).

Multiple studies have shown the effectiveness of IRS for reducing vector densities and malaria transmission in many settings (Akogbeto et al., 2011; Mashauri et al., 2017; Coleman et al., 2017; Sy et al., 2018) and IRS is now recommended by WHO in areas of intense and perennial malaria transmission (WHO, 2006). In contrast to evidence of the effect of IRS on malaria transmission, its impact on the malaria burden has not been clearly documented. However, in recent years several studies have been interested in the effectiveness of IRS on malaria morbidity. Some studies have focused on the effects of the IRS alone, as in Malawi suggesting that one round of IRS per year might reduce malaria infection burden and anemia (Skarbinski et al., 2012).

In the same context, Steinhardt et al. (2017) found that parasite prevalence was highest in an area that was not sprayed, significantly lower in an area which had been sprayed and geometric mean parasite density followed a similar trend. Also, in South Africa, Mpumalanga Province has achieved the goal of reducing malaria morbidity and mortality by over 70%, partly as a result of scale-up of IRS interventions (Ngomane et al., 2012). The same observations were made by Wagman et al. (2018) in Mali. Other studies have focused on the combined effect of IRS and ITNs on clinical malaria (Hamel et al., 2011; Pinder et al., 2015; Katureebe et al., 2016).

On the other hand, Mumbengegwi et al. (2018) in the Zambezi region in Namibia, found that there was no significant correlation between IRS coverage and malaria incidence, while in Uganda discontinuation of IRS was associated with a rapid increase in malaria morbidity to pre-IRS levels (Raouf et al., 2017), reflecting an effect of IRS on malaria burden. Thus, each country implementing IRS will have to be interested in its impact on malaria morbidity. In Benin, since 2008, The US President's Malaria Initiative (PMI) began supporting IRS starting with five highly endemic regions in southern Benin (Ouéme) from 2008 to 2011 and further expanding to five more regions in northern Benin (Atacora) from 2008 to 2016.

The current program continued in 2017 to cover 2 regions in Atacora. Spray areas are selected on the basis of malaria incidence or prevalence. As in other countries, the effects of IRS on transmission have been proven in Benin (Akogbeto et al., 2011; Aikpon et al., 2014; Akogbeto et al., 2015) but there has been no assessment of the impact of IRS on the burden of malaria using epidemiological data. Thus, after several years of IRS in Benin, it was considered important to assess malaria incidence in the sprayed areas. Moreover, to evaluate the added value of IRS, it was important to compare this incidence with an area with no IRS. The purpose of this study was to measure the effects of IRS on malaria incidence but also on parasitemia and parasite density, in children aged 0 to 59 months.

MATERIALS AND METHODS

Study site, sample and data collection

The study was conducted in Benin in two health areas (named DCO) within 3 communes (Djougou - Copargo – Ouaké) in the Donga Department, which is the IRS area, and with 2 communes (Bèmbèrèkè-Sinendé, BS) in the Borgou Department, the no IRS area (Figure 1). The insecticide used was Pirimiphos Methyl CS, with a persistence of 4 months. The two areas are located in northern Benin, and have the same, climatic, socio-cultural and economic characteristics. Two villages were randomly selected per commune in DCO and three villages per commune in BS, which makes a total of twelve villages involved in the study. The control villages had no contact with the sprayed areas. The north of Benin has year-round malaria transmission with a seasonal peak from June to December, during the main rainy season. *Anopheles gambiae* complex is the primary malaria vector. The two study sites received LLINs through a mass distribution campaign in 2014 and 2017. The malaria infection burden is high in the study areas (unpublished data of the Ministry of Health). According to the last malaria indicator survey (MIS) conducted in 2015, malaria prevalence was 54.8% in the Department of Donga and 57.1% in the Department of Borgou; the highest incidences were observed in the Departments of Borgou (25.8%) and Donga (29.5%), while the national average is 15.5%.(unpublished data of Ministry of Health).

In the study sites, a general census of households with children under five took place in each of the twelve identified clusters. After the census phase, a simple random draw without remission was conducted to identify the households to be included in the cohort per cluster. Thirty-four households were surveyed in each commune. By the fixed and closed cohort technique, the sample is constituted from the beginning of the study simultaneously in all the clusters. Included in the study were children from 0 to 42 months of selected households meeting the following criteria: i) residence for at least one month in the study area, ii) parental informed consent. Not included were i) children with hemoglobin below 7 g/dl, ii) permanent movement out of the study site, iii) inability to comply with the study schedule and procedures. Children hospitalized for more than one month and children lost to follow-up or who died during the follow up were excluded from the study. Only one child was selected per household and the included children were followed for up to 7 months.

This closed cohort study was conducted between May and November of 2017 to coincide with the peak malaria transmission season. In each commune, after verbal consent from parents/guardians, children included provided finger prick blood samples for baseline malaria detection by microscopy (thick drop and thin smear) and hemoglobin measurement by Hemocue to identify children whose hemoglobin level was less than 7 g/dl. In addition, SD Bioline Pf HRP2 rapid diagnostic tests were performed on all children to guide treatment of positive children during the survey. A questionnaire was administered to capture information on the demographics of households, the use of malaria prevention methods like LLIN, and existence of larval breeding in the house or in the immediate environment of the child. Every month, in each cluster, children attended the health center and a blood smear with a rapid diagnostic test for malaria (RDT) were made.

Laboratory procedures

Thick and thin smear were made at the sampling site in each region

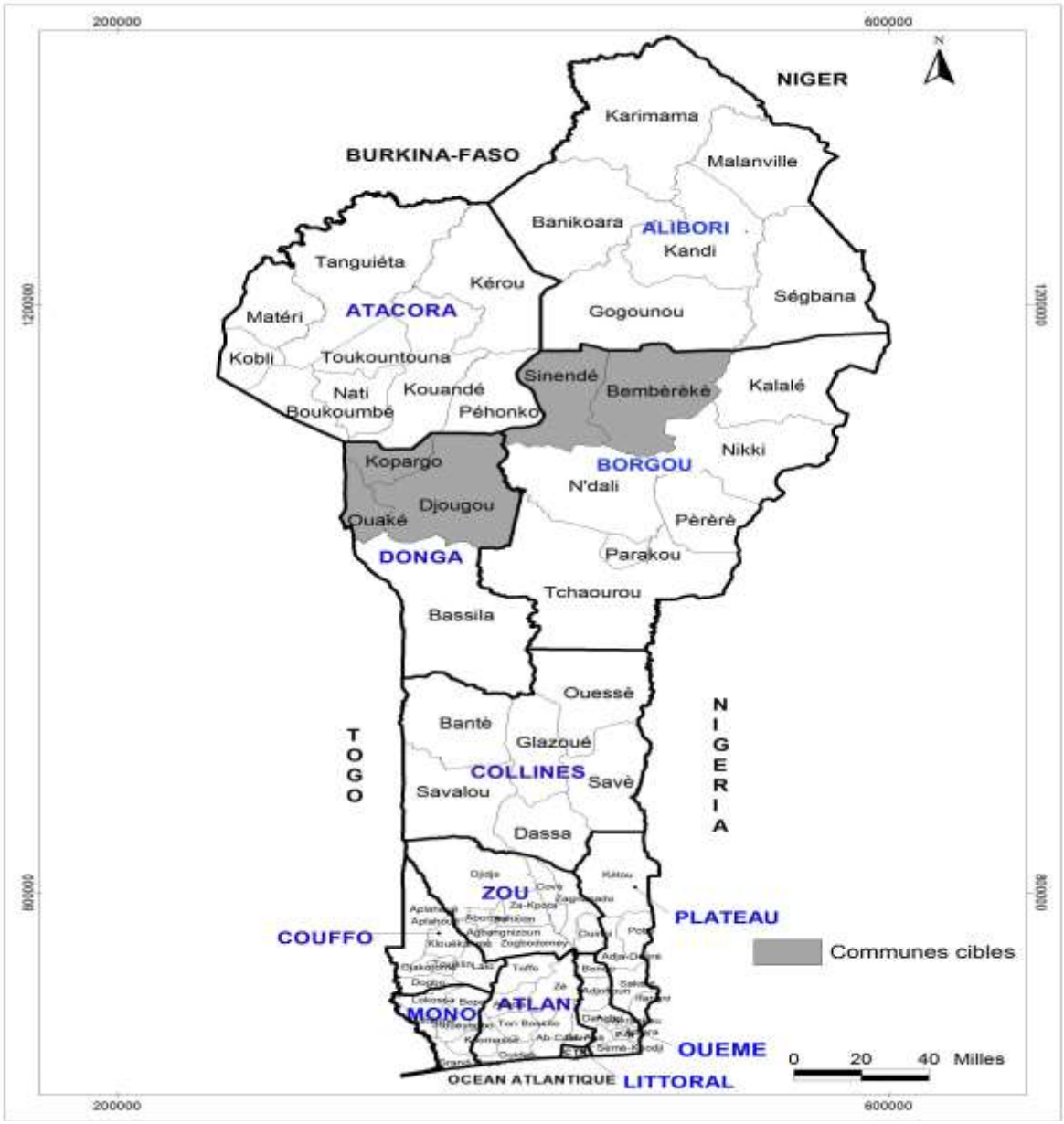

Figure 1. Map of Benin showing study areas.

and sent to Cotonou. They were stained using Giemsa and double-read by expert microscopists at the Parasitology Reference Laboratory of Centre National Hospitalier et Universitaire Hubert Koutoucou Maga of Cotonou to determine malaria parasitemia. Discordant results were resolved by a third microscopist. Blood smears were considered negative if no parasites were found after counting 200 fields. Parasitemia was defined as the presence of asexual *P. falciparum* parasites on a thick blood film. Hemoglobin concentration was measured by using the Hemocue Hb Analyze. Children who tested positive for malaria using the RDT on site were treated with artemether-lumefantrine, the nationally recommended treatment for uncomplicated malaria in Benin. Children with hemoglobin results less than 7 g/dl were not included in the study but referred to a health facility for management.

Data analysis

The collected data are entered into the Epi Data. The key outcomes of parasitemia, malaria incidence, and parasite density were presented with graphs to appreciate the level of each study area during the follow up period and between the sprayed and no-sprayed areas. Qualitative variables were described in terms of number and percentage. For quantitative variables, averages and standard deviations were calculated. Proportional comparisons were between the sprayed and no-sprayed areas made using the Chi-square test. Thereafter, the Relative Risk (RR) was calculated and Chi-square test was used to test the strength of the association between exposure (Exposure = no IRS; no Exposure =IRS) and parasitemia. Finally, we used logistic mixed regression in

Table 1. characteristics of children at baseline.

Parameter	DCO		BS		Total		p
	n	%	n	%	n	%	
Sex							
Female	93	47	84	49	177	48	
Male	105	53	88	51	193	52	
Availability of LLIN in the household (N=350)							p<0.001
Yes	122	78.2	182	93.8	304	86.9	
No	34	21.8	12	6.2	46	13.1	
Availability of LLIN for the study child (N=347)							p=0.391
Yes	115	74.2	150	78.1	265	76.4	
No	40	25.8	42	21.9	82	23.6	
Use of LLIN the previous night by the child (N=335)							p=0.020
Yes	117	81.3	172	90.1	289	86.3	
No	27	18.8	19	10.0	46	13.7	
Existence of larval breeding in the house or in the immediate environment of the child (N=343)							p=0.12
Yes	19	12.2	34	18.2	53	15.5	
No	137	87.8	153	81.8	290	84.5	
Parasitemia							p=0.002
Positive	50	25.3	70	40.7			
Negative	148	74.5	102	59.3			

the first time to assess if there is a significant difference in the evolution of parasitemia in each study area and in the second time to appreciate if there is difference between the two areas in the evolution of parasitemia. All analyses were conducted using the Stata software and $P < 0.05$ being considered statistically significant.

Study limitations

For organizational and logistic reasons, no samples were collected before spraying, which was carried out from May 3 to May 30, 2017. Follow-up of children was from May to November 2017. Inclusion samples taken at the end of May were collected during spraying. Data collection to assess parsitaemia was only possible during and after spraying; therefore, it was not possible to compare data before and after spraying.

Ethics statement

The National Committee for Ethics in Health Research of Benin (Comité National d'Ethique pour la Recherche en Santé; Ministere de la Sante) gave ethical approval for the study. The objectives and schedules of the study were first explained to community leaders and to all eligible households in local languages. Consent was obtained from the chief of each cluster and traditional authorities. Approval of parents or legal guardians was taken.

RESULTS

Of 408 children screened for enrolment in the cohort, 38 were excluded due to hemoglobin levels below 7 g/dl. The sample size from the beginning of the study according to the inclusion criteria was therefore 370 children in the closed cohort. Losses to follow-up occurred either because of deaths, migration or absence of the mother.

The mean age of the cohort children was 25.2±14.0 months in DCO and 25.4±13.7 months in BS. The characteristics of children at baseline are presented in Table 1. Male children were the most represented in the two zones. Households had significantly more LLIN in the no-IRS area (BS) than in the IRS area (DCO), but there was no difference between the two groups in LLIN availability for the children included in the study. The study children in the no IRS area slept more under LLIN than those in the IRS area. There was no link between the presence of larval breeding and membership of a IRS or no-IRS area.

At inclusion, the prevalence of parasitaemia was significantly higher in DCO (IRS area). During follow-up, prevalence of parasitaemia in DCO was higher than the prevalence in BS over the entire monitoring period with the exception of month 4, statistically significant in September (Figure 2), P=0;001. Inside each area the differences are statistically significant in BS in the 4th month with P = 0.001 and in the 5th month in DCO. P = 0.002. Table 2 shows the association between exposure and parasitemia and reveals that there is no statistically significant difference between the 2 areas.

At inclusion, the geometric mean parasite density was higher in BS (unsprayed area) where an extended peak

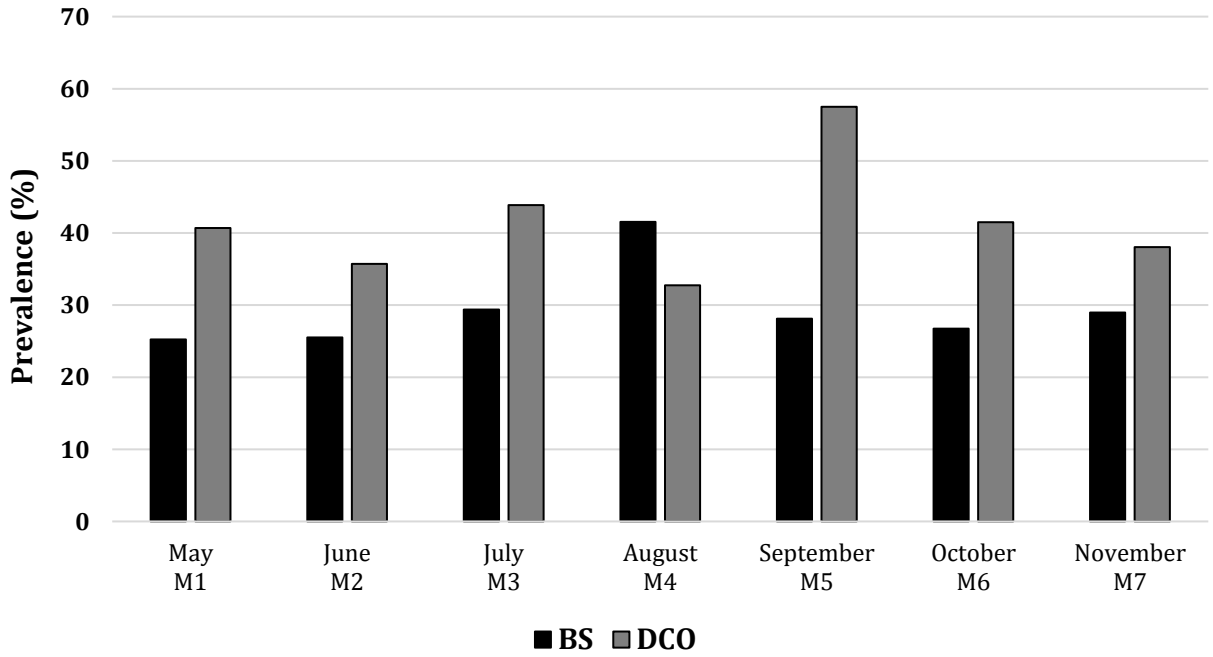

Figure 2. Parasitemia prevalence during follow up in two areas.

Table 2. Parasitemia according to exposure (IRS versus no IRS).

Parameter	GE+	GE-	Total
BS (exposed)	53	130	183
DCO (No exposed)	62	101	163
Total	115	231	346

RR=0.76 ; Chi2=3.20; p-value=0.07.

between months 3 and 4 was recorded before declining from month 5. Parasite density in DCO (sprayed area) declined from inclusion levels through to month 3 followed by peaks in months 4 and 6. Parasite density in DCO was higher than in BS in months 6 and 7 (Figure 3). But, statistically, there is no difference from one month to another in the two areas (Table 3) Malaria incidence is higher in the DCO area than in the BS area over the entire study period except at month 4. Inside DCO, the incidence evolved sawtooth while in the BS area it gradually increased to month 4 before starting a decrease from month 5 (Figure 4).

DISCUSSION

The prevalence of parasitemia at baseline was significantly higher in the DCO than in the BS area. These results are consistent with those of the 2012 Demographic Health Survey (DHS) (40.1% in Donga against 25.1% in Borgou; unpublished data of Institut National de la Statistique et de Analyse Economique: INSAE) which noted a higher prevalence in Donga. This difference in prevalence between the two zones indicates a high level of transmission in Donga that could be explained by lower availability of mosquito nets in households and less use of mosquito nets by children in DCO as found in our study.

Several other factors such as construction type, and insalubrity of the environment may explain this difference in the level of transmission. In our analysis, it will be a question of comparing indicators during the follow-up in these two zones. However, this difference in prevalence at the beginning of the study must be taken into account. The prevalence remains high in both areas, showing a high transmission of malaria, which could be explained by the study period coinciding with the rainy season, a period of high transmission. Malaria parasitaemia was higher in the IRS area during the follow-up period, with the exception of August. Also in this area, we did not notice a significant decrease from one month to the next. This finding is consistent with that of Pluess et al. (2010)

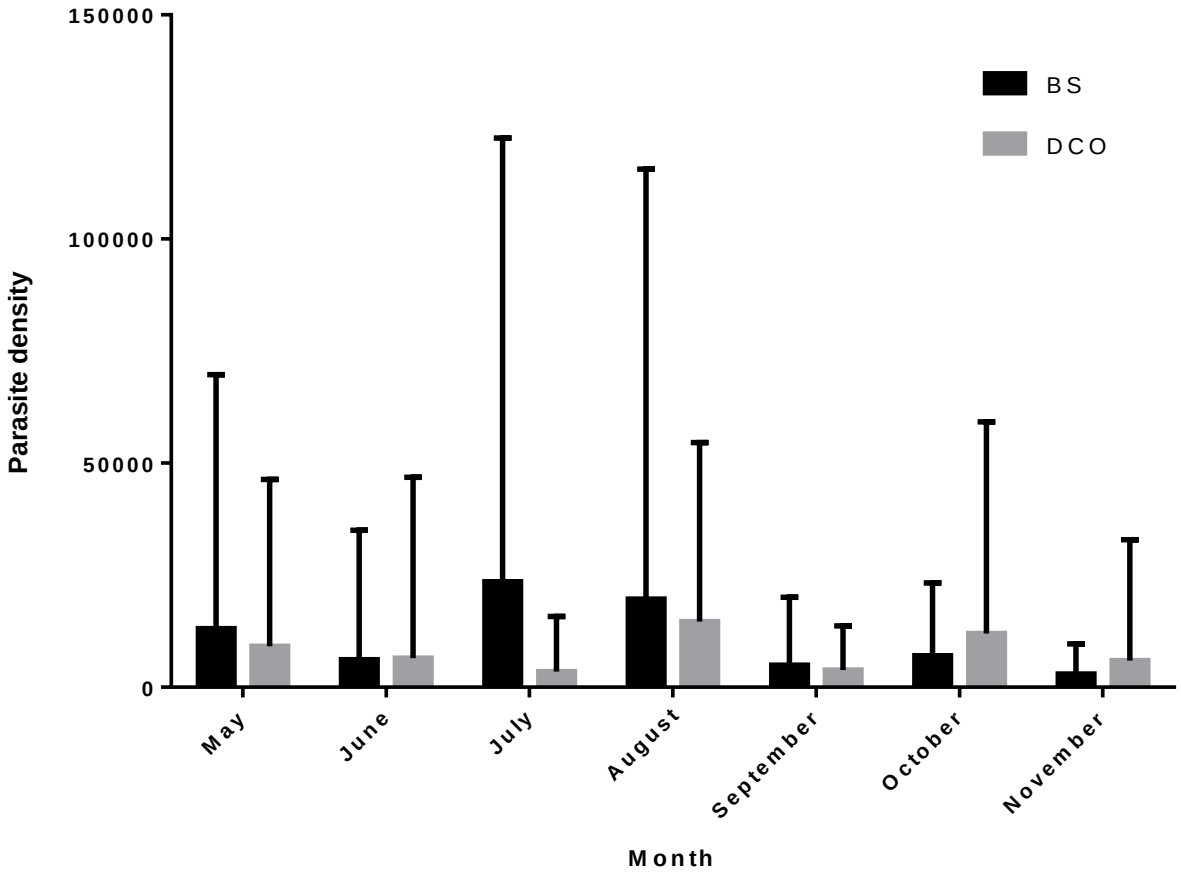

Figure 3. Evolution of parasite density during follow up in two areas.

Table 3. Evolution of parasite density during follow up in two areas.

Month	BS			DCO			p-value
	n	Mean	SD	n	Mean	SD	
May	50	13108.46	56616.06	70	9117.914	37267.26	0.64
June	50	6175.66	28848.81	60	6506.383	40302.18	0.96
July	57	23522.02	98988.87	75	3481.893	12307.55	0.08
August	81	19637.85	95965.68	55	14645.62	39913.78	0.72
September	54	4950.981	15155.53	92	3829.043	9880.212	0.59
October	50	7054.44	16237.79	66	11957.52	47225.8	0.48
November	53	2925.811	6772.029	62	5915.226	27026.51	0.43

who noted that in the IRS group, malaria prevalence was slightly lower but this was not significant.

However, the fact that the parasite density is lower at the beginning with a decrease in the two months following the spraying could reflect an effect of IRS because in the unsprayed area the average parasite density increased significantly from the 2nd to the 4th month**.** The incidence data went in the same direction as prevalence, higher in the IRS area over the entire follow-up period except in August. This result could be explained by the difference in the level of transmission observed at the start of the study with a very high prevalence of malaria infection in IRS area, despite the fact that the spraying is in progress. However, the fact that the incidence has gradually increased in the no-IRS area while it has evolved sawtooth in the IRS area might suggest that the IRS had an effect in the spray area. Indeed, the study conducted in Ethiopia (Shallo et al*.,* 2012) showed that unlike the sprayed area, malaria incidence in the villages unsprayed remained the same or

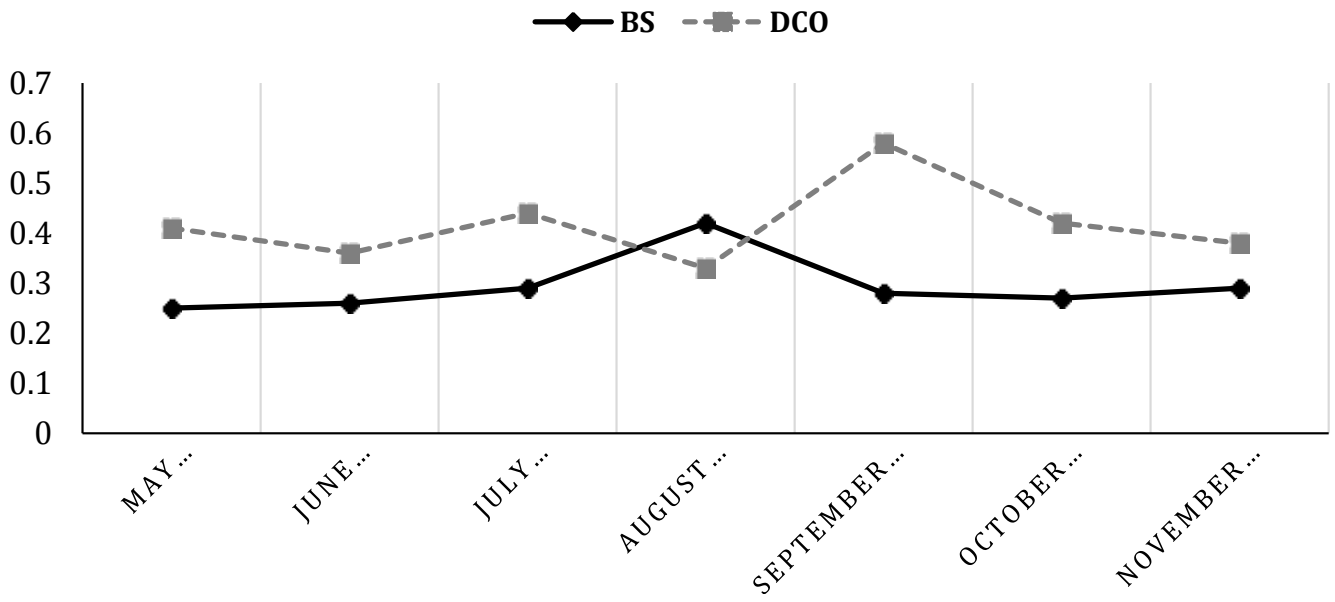

Figure 4. Malaria incidence during follow up in two areas.

increased. In this study, there was no noticeable reduction in incidence during monitoring in the IRS area which received a single spray cycle.

This is in line with the results found by Gimnig et al. (2016), that after a single spraying, there was no significant difference between the two districts regarding the prevalence of malaria infection. After two rounds of IRS, the same authors observed a significant difference between the IRS district and the no-IRS district ($p < 0.001$). The same was observed by Mashauri et al. (2013) who observed a reduction in the prevalence of malaria of 67.2% in the sprayed area after two rounds of IRS.

Kim et al. (2012) also noted a significant reduction in the prevalence of malaria infection by 62% in areas with higher initial prevalence and multiple spray cycles. The same observation was made in a study conducted in northern Uganda (Steinhardt et al., 2013). They found that the prevalence of malaria infection in children under 5 years of age was significantly lower in both IRS areas (16.7% for the area that had received six sets of IRS and 37.0% for the one that had received only three sets of IRS) than the no-IRS area (49.8%). The same observation was made in South Africa by Ngomane et al. (2012). These studies show that IRS may have an effect on malaria morbidity but this effect would be greater after several cycles of spraying, suggesting a cumulative effect of several series of IRS which must therefore be maintained and carried out continuously with several series to provide better results.

However, our study with a single spray revealed a decrease in the incidence rate of malaria infection in the IRS area of 8% between the beginning and the end of the remanence of the insecticide that would be in the 4th month (August), while at the same time in the no-IRS area the incidence increased by 17%. These results, which suggest an IRS action, are nevertheless far inferior to that of Kanyangarara et al. (2016), who found a reduction in malaria incidence of 38% following residual intradomiciliary spraying of Actellic 300CS in Zimbabwe's Mutasa district. It should be noted, however, that the effectiveness of the IRS also depends on changes in the behaviour of mosquitoes and people as well as the emergence of mosquitoes resistant to insecticides and environmental impact.

Otherwise, according to some authors there was a clear benefit of adding IRS with LLINs to reduced malaria prevalence or malaria incidence (Zhou et al., 2010; West et al., 2014; West et al., 2015; Tukei et al., 2017; Chaccour et al., 2018).

Conclusion

In this study, there was no significant difference in malaria parasitemia and malaria incidence between the sprayed area and the unsprayed area in children less than five years of age after one cycle of spray. The same observation was made during the follow-up inside the sprayed area. However, the decrease in incidence between the beginning and the 4th month of follow-up in IRS area suggests an effect of IRS. The impact of IRS on malaria burden depends particularly on a sufficient number of spray rounds per year. Further follow-up studies after several spraying cycles and taking into account human and vector behaviours could lead to better conclusions.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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