Research Square

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Performance of pirimiphos-methyl based Indoor Residual Spraying on entomological parameters of malaria transmission in the pyrethroid resistance region of Koulikoro, Mali.

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Abstract

Background: Following mosquito vector resistance to both pyrethroid and carbamates, organophosphate (pirimiphos-methyl) was used for the Indoor Residual Spray campaigns performed in 2015 to 2016 in the district of Koulikoro. In this context, we assessed the effect of IRS on malaria transmission by comparing entomological indices in two localities: Koulikoro (LLINs+IRS), and Banamba (LLINs -only) districts.

Methods: The study was conducted in two villages of each district (Koulikoro and Banamba). Pyrethrum spray catches and entry window trapping were used to collect mosquitoes on a monthly basis. WHO tube tests were carried out to assess mosquito susceptibility to insecticides. Mosquitoes were identified to species level by PCR and their infection to P. falciparum was detected by ELISA.

Results: An. coluzii was the most frequent species. Its density was rainfall dependent in the no-IRS area, and almost independent in the IRS area. The infection rate (IR) in the no-IRS area was 0.96%, while it was null in the IRS area. In the no-IRS area, the entomological inoculation rates (EIR) was 0.21 infective bites /person month with a peak in September. High resistance to pyrethroids and carbamates and susceptibility to organophosphates was observed at all sites.

Conclusion: The introduction of pirimiphos-methyl based IRS in the area resulted to a significant decrease in malaria transmission. An.gambiae s.l., the main malaria vector of the area, was resistant to pyrethroids and carbamates, and remained susceptible to the organophosphates.

Background.

Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are actively promoted as the main prevention tools for malaria control and elimination [1]. The recent wide deployment of these two control tools is considered to be responsible for the substantial reduction of the incidence and deaths related to the disease in Africa [2, 3] but they are generally not sufficient to eliminate transmission [4]

Malaria affects about 40% of the population in Mali [5]. The health services registered 2,345,481 cases of malaria including 750,973 severe cases in 2018 (Ref). Children under 5 years are the most affected by the disease with 33.70% of cases, followed by pregnant women (4.77%). The number of recorded deaths was 1001, with a case fatality rate of 1.33 ‰[6].

The national strategy for malaria control in Mali is based on four main interventions: i) Early diagnosis and treatment by ACTs, ii.) Seasonal Malaria Chemoprevention (SMC) in children aged 3 to 59 months (SMC), iii) Preventive Intermittent Treatment (IPTp) with sulfadoxine-pyrimethamin (SP) in pregnant women and, iv) Vector control. Vector control relies heavily on LLINs at country level and IRS in selected districts. With the emergence and expansion of the resistance of *Anopheles gambiae sensu lato* (*An. gambiae s.l.*) to insecticides the fragile progress made in malaria control can be compromised [7]. The wide and long term uses of pyrethroid insecticides in LLINs and in the agricultural sector seem to be one of the main causes of the increasing resistance of malaria vector to these products [8, 9].

As part of the strengthening of vector control strategies in the district of Koulikoro, IRS was initiated by the National Malaria Control Program (NMCP) with the support of the US President's Malaria Initiative (PMI) since 2008. Pyrethroids (deltamethrin and lambda-cyhalothrin) were the first insecticides used in the IRS for the first 4 years [10] . Following resistance to these insecticides, they were replaced by carbamates (Bendiocarb) in 2011. Because of its short short lifespan on mud made walls, the bendiocarb (Carbamate) was also replaced by pirimiphos-methyl (Organophosphate) in 2015. A mass distribution of LLINs was implemented in 2014 to achieve universal coverage of all populations at risk. Notwithstanding the deployment of all these strategies by the NMCP and its partners, no study was done so far to assess the effect of IRS campaigns on malaria transmission as measured by entomological inoculation rate in this context of vectors resistance to insecticides. In this study, we assessed the effect of IRS on malaria transmission by comparing entomological indices in two localities of the district of Koulikoro, where IRS was implemented for about 9 consecutive years, to two other similar villages of its neighbored district of Banamba, where IRS had never been implemented.

Materials And Methods.

Study areas: This study was conducted in the villages of Karadié (7.60W, 13.24N) and Koula (7.65W, 13.12N) in the district of Koulikoro and Kolondialan (7.51W, 13.49N) and N'Galamadibi (7.48W, 13.48N) in the district of Banamba (Figure 1). The climate in both districts is a typical Sudano -sahelian savannah with two seasons: a long dry season (November to May) and a wet season (June to October) with a mean annual rainfall of 900–1200 mm. The monthly mean temperature during the rainy season varies from 29 to 33ºC. *An. gambiae s.l.* is the predominant malaria vector (> 98%). Malaria transmission occurs mostly during the rainy season (June to October) with the mean monthly mosquito human biting rate reaching its peak in August and September.

LLINs, SMC for Children of 3 to 59 months old, and IPT with SP for pregnant women are control interventions implemented in both districts. Besides this, PMI has supported nine IRS campaigns in the districts of Koulikoro (2008 to 2016), while it has never been implemented in the district of Banamba. Just before of this study a universal LLNs distribution was done in each site with support of the NMCP. Agriculture, livestock and trade are the main economic activities.

Mosquito vector sampling. In each selected village, vector populations were sampled monthly from June to November 2016 by Pyrethrum Spray Catch (PSC) and Entry Windows Traps (EWT).

Pyrethrum spray catches (PSC). In each study village, 30 sentinel houses were randomly selected from a list of total households. The sampling was constrained with the type of housing (e.g. thatch roof vs metal roof). Indoor-resting mosquitoes were collected by PSC which consisted of spraying pyrethrum in the selected houses from 8:00 to 11:00 in the morning. Two teams of 2 entomologists (a total of 4) were operating in parallel and sampling 10-15 houses per day.

Entry window trapping (EWT). This method consisted of mounting on windows, traps which collected the mosquitoes entering the rooms (Figure 2). Ten traps were mounted in ten randomly selected rooms. The catches were done during three successive nights per month. One of the local guides of the different villages was responsible for closing the traps very early in the morning (around 6:00 am) to prevent the trapped mosquitoes to escape with a small curtain sewn on the opening of the traps. The trapped mosquitoes were removed from the traps using a mouth aspirator, held in carton cups, and the number recorded on a data sheet.

Insecticide susceptibility bioassay (WHO, 2016). *Anopheles gambiae s.l.* larvae were collected in different types of breeding habitats in and around each study site and reared to adults at the insectary at Bamako. At emergence, adult mosquitoes of 2-5 day-old females were exposed to impregnated filter papers with deltamethrin [0.05%], bendiocarb [0.1%] and pirimiphos-methyl [0.25%]. Approximately 20-25 mosquitoes per tube with 2-6 replicates were exposed to impregnated filter papers at the diagnostic concentrations for 1 hour and then transferred to a clean holding tube supplied with 10% sugar. Mortalities post exposures were determined after 24 hours according to WHO standard operating procedures[11]. All the tests were carried out at 27 ± 1°C and a relative humidity of 70-80%.

Sample processing. Collected mosquitoes were identified to species level using Polymerase Chain Reaction (PCR) technique [12]. The infection rate and human blood index (HBI) were established using the Enzyme Linked Immuno-Sorbent Assay (ELISA) techniques following the protocols of Burkot et al[13] and Beier et al [14], respectively.

Statistical analysis. The data were entered in Excel and analyzed in SPSS version 22, STATA version 10, and GraphPad Prism 7. The following entomological parameters were calculated: vector density per room, human biting rate (HBR), infection rate (IR), entomological inoculation rate (EIR), human blood index HBI) and parity rate (PR). The density of malaria vector was calculated as the average number of indoor resting mosquitoes per room; the HBR as the average number of mosquito bites (fed + half gravid) over rooms sleepers per time unit; the IR corresponds to the percentage of anopheles of a given species carrying sporozoites; the HBI as the proportion of females mosquito having human blood in their guts; the PR was calculated as the percentage of parous females relative to the total number of mosquitoes dissected (parous + nulliparous); and the EIR was calculated as the total number of infectious bites per human per time unit. The Pearson correlation test was used to determine the correlation between density and rainfall. The Chi-square test was used to compare the HBR, HBI, and PR.

Mosquito mortality rates were calculated by dividing the number of survivor mosquitoes by the number exposed to the insecticide.

- Mortality in the range of 98–100% indicates susceptibility of the mosquitoes.
- A mortality of less than 98% is suggestive of the existence of resistance and further investigation is needed.
- Mortality of less than 90% indicates a confirmed resistance.

Results.

Mosquito species composition

A total of 2258 female specimens of *An. gambiae s.l.* were collected over the study period, 1988 by PSC and 270 mosquitoes by EWT. *An. gambiae s.l.* was the only malaria vector collected in both areas.

Molecular species composition of *An. gambiae s.l.*

An, gambiae s.l. consisted of three species: *An. coluzzii*, *An. arabiensis* and *An. gambiae s.s. An. coluzzii* was by far the most frequent species in both the IRS (96%, n = 97) and the no-IRS (95%, n = 430) areas (Figure 3).

Density of *Anopheles gambiae s.l.* per room

An. gambiae s.l. density increased with rainfall in the no-IRS area, while it remained low regardless of the variations in rainfall in the IRS area (**Figure 4)**. The highest density was observed in July and August in the no-IRS area. In the IRS area, two small peaks were observed: one in July (just before the IRS implementation), and one in September (two months after the IRS). There was a strong correlation between rainfall and *An. gambiae s.l.* density, with 1-month lag, and rainfall in both the IRS (R = 0.888, P = 0.018) and the no-IRS (R = 0.806, P = 0.053) areas.

Parity rate of *Anopheles gambiae s.l*.

The parity rate were estimated form samples collected by EWTs. The average parity rates were 96.42% (N= 56) and 98.36% (N= 122) in the IRS and no-IRS areas, respectively. There was no statistical significant difference (P>0.05) between the parity rates in the two zones.

Human biting rate of *Anopheles gambiae s.l.*

Using PSC, the overall mean monthly human biting rates (MHBRs) of *An. gambiae s.l.* were higher in the no-IRS area (20.41 bites/person/month) than in the IRS area (3.03 bites/person/month). In the IRS area, the peak of the MHBR (7.47 bites/person/month) was observed in September (> 2 months after IRS). In the no-IRS area it was observed in August (66 bites/persons/month). In both areas, the lowest MHBR was observed in June (Figure 5).

Infection rate and Entomological inoculation rates (EIR) in *An. gambiae s.l*.

The infection rate was obtained from pool sample of PSC and EWTs. The mean *P. falciparum* infection rate of *An. gambiae s.l.* over the study period in the no-IRS area was 1% (n = 1670). In the IRS area, the number of *An. gambiae s.l.* specimens collected and tested (n = 253) by ELISA did not allow us to detect an infection (Figure 6). In the no-IRS area, the overall mean EIR was 0.21 infective bites/person/month peaking in September with 0.75 infective bites per person per month (Figure 6).

Human blood index

The HBI (PSC) shows that the mosquitoes were highly anthropophilic in both areas. The average HBI in the IRS area was 74.27% (n=171) and 86.90% (n=1199) in the no-IRS area. However, monthly variations in this rate were observed in both areas. The highest HBIs were recorded in October in the IRS area (98%) and in August in the no-IRS area (89%). The HBI was higher in the no-IRS area compared to those in the IRS area (χ^2 = 19.84; P < 0.001).

Resistance of *An. gambiae s.l.* to insecticides

Bioassays tests were carried out on adult females emerged from larvae collected in the different field sites (F_0). Results showed high resistance to the deltamethrin in the four study sites (Figure 6) with mortality rates of 15%, 20%, 24.5% and 41% respectively in Karadié (N= 100), N'Galamadibi (N= 150), Kolondialan (N= 150) and Koula (N= 200). *An. gambiae s.l*. was resistant to the bendiocarb (Figure 6) in all study sites with mortality rates of 56%, 73%, 79%, 69% respectively in Koula (N=150), Karadié (N=100), N'Galamadibi (N=200) and Kolondialan (N=200). Susceptibility to pirimiphos-methyl was observed in all study sites.

Discussion.

In this study, we compared entomological indices of malaria transmission of the district of Koulikoro, where IRS was implemented for about 9 consecutive years, to the neighboring district of Banamba where IRS was never been implemented. *An. gambiae s.l*. was the only malaria vector encountered in both study areas and consisted of three species: *An. coluzzii*, *An. arabiensis* and *An. gambiae*. By far, *An. coluzzii* was the most abundant species in both areas. Similar observations have been made in several recent studies in Mali [15-18] and were explained by climatic conditions prevailing in the Sahel (temperature, humidity, etc.), where our study sites are located, and the presence of favorable larval habitats for the development of *An. gambiae s.l.* such as bricks pits, puddles, and tire tracks [19, 20].

There was a synchronous variation in *An. gambiae s.l*. density and rainfall in the no-IRS area, but not in the IRS area (Figure 3). Many studies have demonstrated the association between *An. gambiae s.l*. abundance and rainfall [21-23], especially in arid water-limited areas of Africa such as the Sahel, where the rain fed pools are heavily utilized by the dominant malaria vector species *An. coluzzii* [24]. Thus the asynchronic variation in *An. gambiae s.l*. densities, MHBRs and rainfall in the IRS area may be due to the effect of the IRS. Indeed, mosquitoes were found fully susceptible to the insecticide used in the IRS campaign of 2016, the pirimiphos-methyl, which also has an exito-repellent effect on mosquito, preventing them to enter and rest into the sprayed houses.

Our results showed high parity rates in both areas which could be a consequence of the plasticity of *An. gambiae s.l.* population allowing it to escape control interventions as reported in Senegal during an IRS campaign using pirimiphos-methyl [25].

In the IRS area, we could not detect transmission as measured by EIR because none of the tested specimens of *An. gambiae s.l.* by ELISA was infected (Figure 4), while in the no-IRS area, the transmission was typically seasonal with the peak observed at the end of the rainy season. The non-detection of transmission in the IRS area can be attributed to the effects of the insecticide (pirimiphos-methyl) used in the 2016 IRS campaign (Figure 5). This may has shorten the life expectancy of the mosquitoes population to accomplish the complete parasite development in mosquito to ensure a transmission. In addition, because of the exito-repellency effect of the pirimiphos-methyl, the PSC and the EWT, both focused on indoor resting portion of mosquitoes, may have not been appropriate. Human landing collection (HLC) could provide more power to this study, especially in the IRS area. A limitation of this study has been that the HLC method was not approved by the ethical review board of WHO. Nevertheless the PSC and EWT were consistently used across all sites.

Our results showed a high, to relatively high level of phenotypic resistance of *An. gambiae s.l.* to the pyrethroids (deltamethrin) and the carbamate (bendiocarb), and a fully susceptibility to the organophosphate (pirimiphos-methyl) at all the four study sites. This similarity in the resistance status of *An. gambiae s.l.* population in the two areas is certainly due to the short distance between them (7 Km). Indeed, mosquitoes can actively migrate up to 2-7 km [26, 27]. Moreover, malaria vectors can migrate at long-distance in the Sahel (up to 300 km) by the win as reported by a recent study in the same region of Koulikoro where this study occurred[28]. Also, previous studies have shown the same trend of resistance in *An gambiae s.l.* population, low resistance to bendiocarb in some from sentinel sites of the NMCP far away from the IRS areas [10, 20]. Local agricultural conditions can also plays a role in the spread and distribution of resistance to insecticide used for public vector control too [29-34]. We observed a difference in resistance level between the two families (carbamates and organophosphates) of insecticide. The observed difference in resistance level between the organophosphates and the carbamates could be the consequence of their difference in the level of dominance based on the specificity of the insecticides [35].

Conclusions.

This study showed that all entomological transmission parameters were lower in the IRS area compared to the no-IRS area, and transmission as measured by EIR was undetectable in the IRS area. This observation shows the added values of the IRS because mosquito population was resistant to pyrethroids which are used in LLINs (deltamethrin) but fully susceptible to organophosphates used in the 2016 IRS campaign (pirimiphos-methyl). A large randomized study is needed to better estimate the added value of the IRS in an integrated malaria control strategies and assess its cost-effectiveness.

List Of Abbreviations.

Indoor residual spraying (IRS)

Long-lasting insecticidal nets (LLINs)

Intermittent Preventive Treatment (IPT)

Seasonal Malaria Chemoprevention (SMC)

The Ministry of Health (MOH)

The National Malaria Control Program (NMCP)

Preventive Intermittent Therapy (IPT)

Case report forms (CRFs)

Rapid diagnostic test (RDT)

University of Sciences, Techniques and Technologies of Bamako (USTTB)

Human biting rate (HBR)

Infection rate (IR)

Entomological inoculation rate (EIR),

Human blood index HBI)

Parity rate (PR)

Declarations

Ethical considerations

The protocol of this project has been approved by the Ethics Committee of FMPOS/USTTB under the letter **Nº2014/51/CE/FMPOS**. The research activities related to this protocol were carried out in accordance with good clinical research practice in humans and good laboratory practice as set out in the international conventions (Helsinki Declaration; International Conference on the Harmonisation of Good Practice in Biomedical Research). All our researchers were trained in good clinical and laboratory practice during the research. In the field, the community (administrative, customary authorities) was informed of all aspects of the study.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions

MK: has worked on the research hypothesis, data collection and analysis and write the manuscript.

NS: has worked on has worked on the research hypothesis and manuscript writing.

FK: has worked on data collection and sample processing**.**

BT: has worked on data collection and sample processing**.**

BC: has worked on data collection.

SFT: Correct and approved the latest version before submission.

NS: Correct and approved the latest version before submission.

SD: worked on the research hypothesis**,** correct and approved the latest version before submission

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Figures

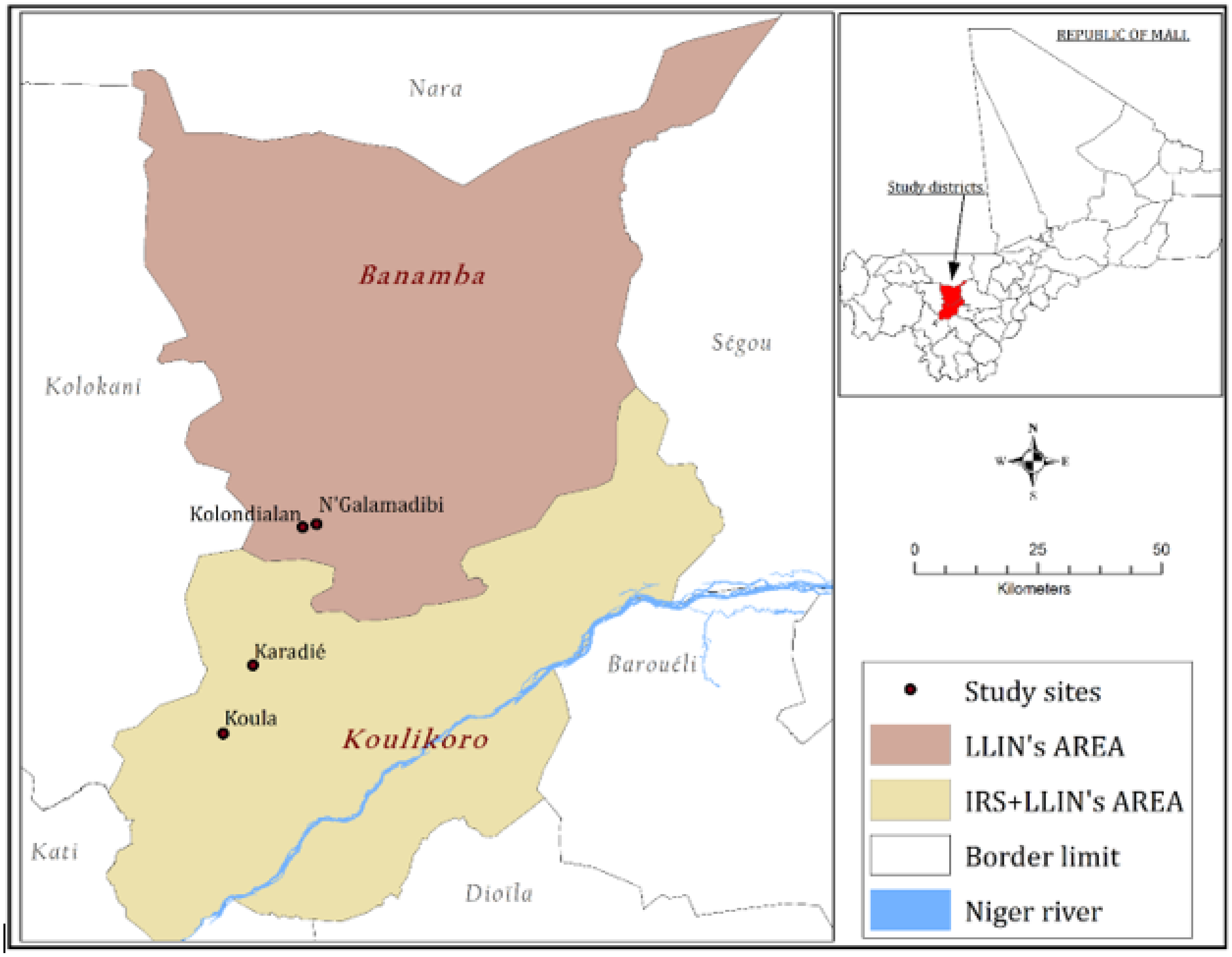

Figure 1

Map of Mali showing the different study sites

Figure 2

Field technician and local guide mounting an entry window trap

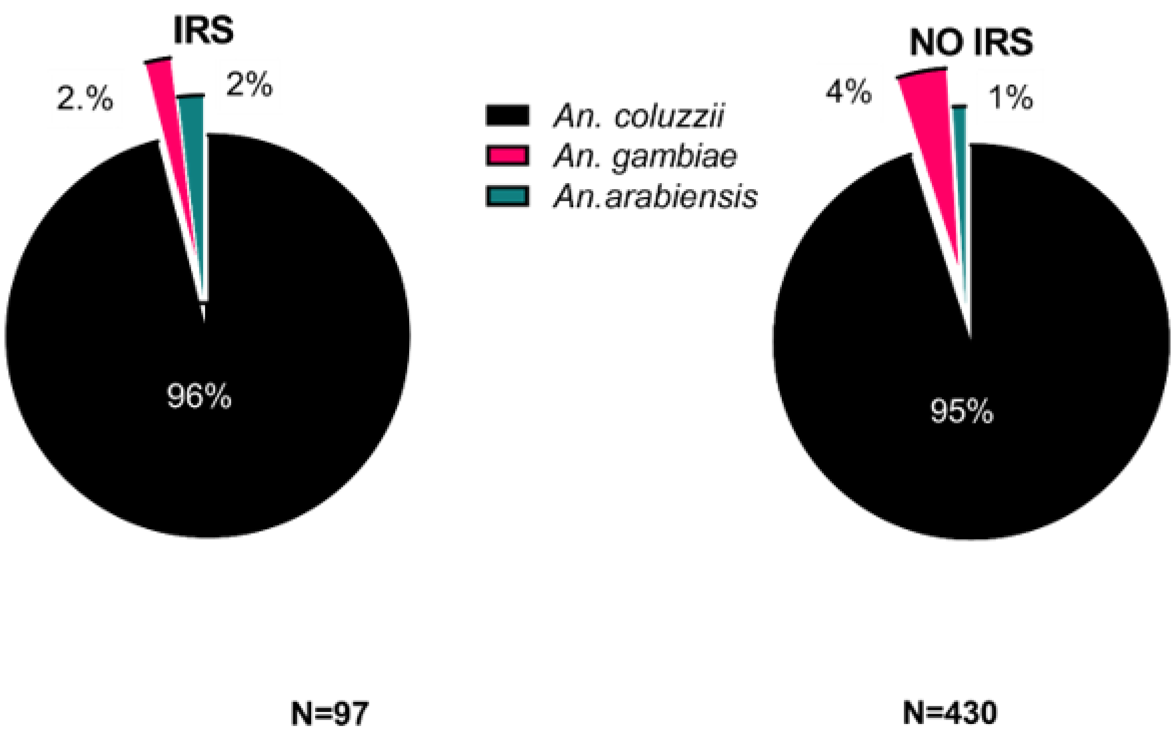

Figure 3

An. gambiae s.l. species composition in the areas of IRS and n-IRS

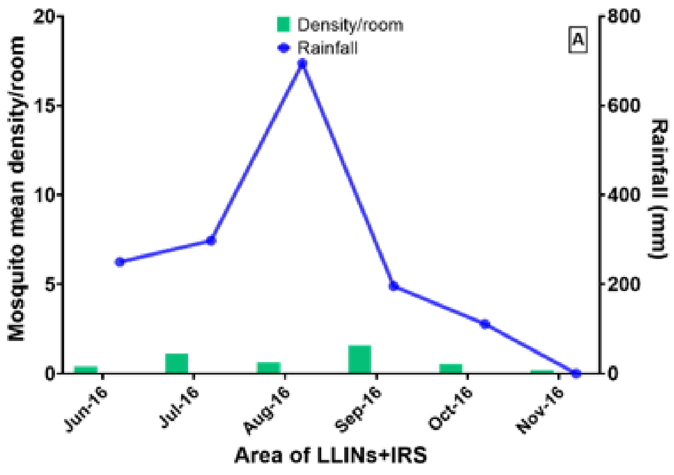

Figure 4

Variation in An. gambiae s.l. density (green bars) and rainfall (blue line) in areas of IRS and no-IRS from June to November 2016.

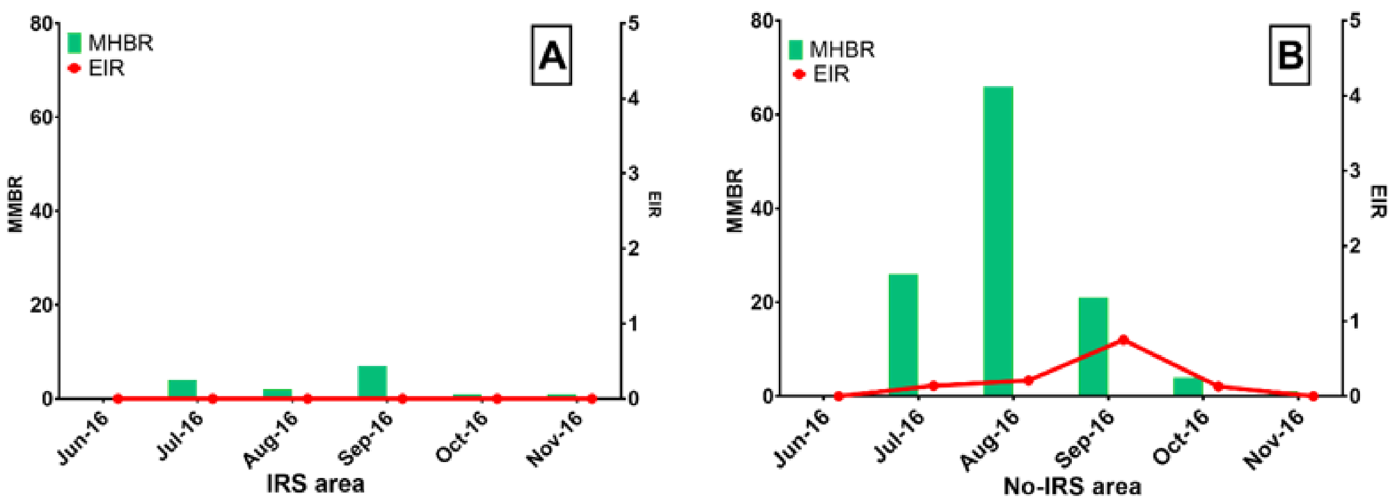

Figure 5

Monthly variation in An. gambiae s.l. man biting rates (green bars) and entomological inoculation rates (Red line) in areas of IIRS (A) and no-IRS (B) from June to November 2016.

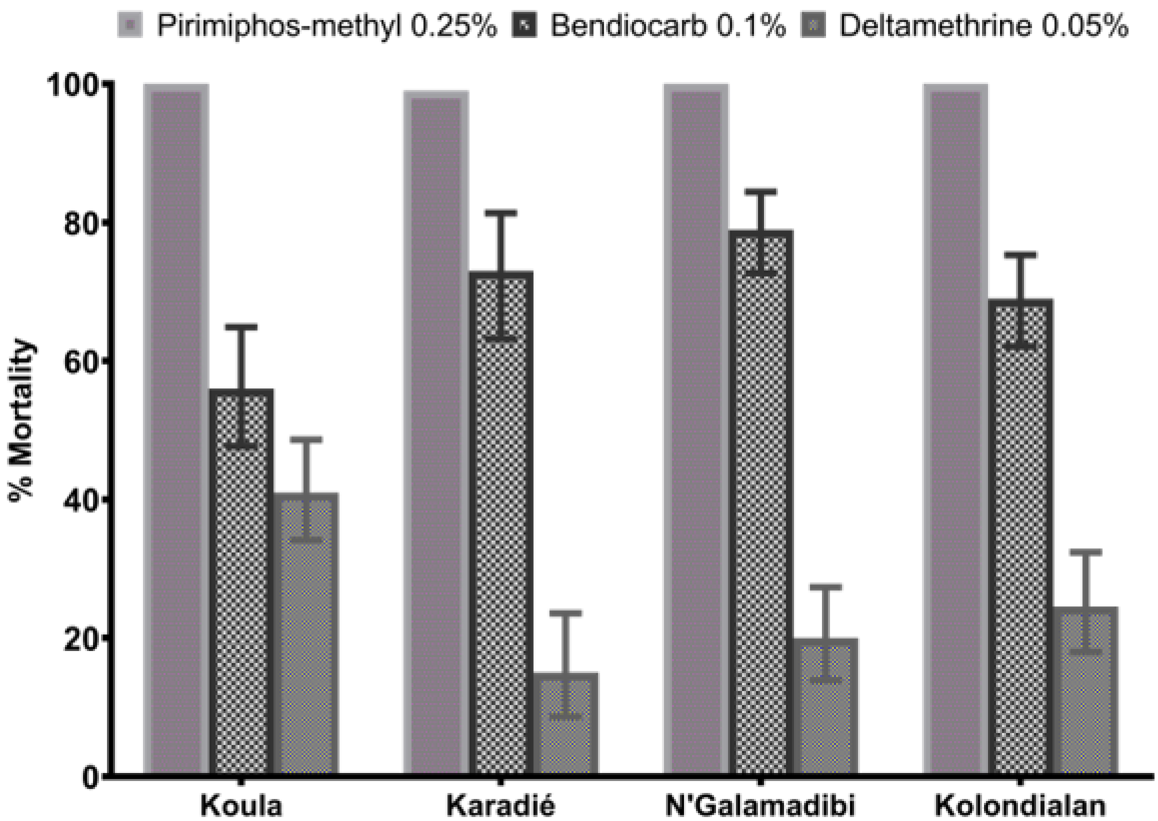

Figure 6

Observed 24 hours mortality (%) of An. gambiae s.l. following 60 mn exposition to Pyrethroids (Deltamethrin), Carbamates (Bendiocarb) and Organophosphates (Primiphos-methyl) in the selected study sites using WHO standard bioassay test.