Performance of IRS on malaria prevalence and incidence using pirimiphos-methyl in the context of pyrethroids resistance in Koulikoro region, Mali

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Abstract

Background: Koulikoro Health District is one of three districts of Mali where the indoor residual spray (IRS) has been implemented from 2008 to 2016. With widespread of resistance to pyrothroid, IRS was shifted from pyrethroid to pirimiphos-methyl in 2014 -2016. We assessed the added value of IRS to LLINs on the prevalence of parasitemia and malaria incidence among children under 10 years old.

Methods: We compare these outcomes in two health zones: one where IRS intervention was deployed (zone test, district of Koulikoro) and the neighboring health zone where no IRS was applied (control zone, district of Banamba). In both settings we carried out two cross-sectional surveys at the beginning of the rainy season (June) and the end of the rainy season (October) to assess the effect of IRS on seasonal changes in malaria parasitemia.

Results: The incidence of malaria was measured through passive case detection (PCD) from the health facilities. A 50 % increase was observed in malaria parasitemia from June to October in control villages (14.0% to 42.3%) compared to IRS villages 17.9% (9.2% vs 13.2%). The overall malaria incidence rate was 2.7 per 100 person-months in IRS area and 6.8 per 100 person-month in control areas. The Kaplan Meier survival analysis showed that children living in IRS area remain much longer free from malaria than children of the control area (P < 0.001). IRS using pirimiphos-methyl has been successful in reducing substantially the prevalence and the incidence of malaria in children under 10 years old in area of pyrethroids resistance of Koulikoro.

Conclusions: As IRS intervention was ended after 2016 campaign, further studies are needed to determine the rebound effect and monitor potential emergence of organophosphate resistance for better management of insecticide resistance

Background

Many efforts have been made in the fight against malaria during the past 15 years in sub-Saharan Africa where funding for control and elimination has increased by about 60 million between 2010 and 2015 [1]. These investments covert the different control strategies implemented by the National Malaria Control Programs (Prevention, Diagnosis, Treatment, and Surveillance) to achieve the objectives of the Global Technical Strategy 2016-2030 for Malaria control [2] As results of those
efforts, substantial reduction of the number of malaria cases worldwide have been reported, varying from 237 million in 2010 to 216 million in 2016. However, sub-Saharan Africa still accounts for 90% of the malaria burden at the global level [3,4].

Access to prevention is an essential component in the fight against malaria. Current prevention strategy is based on the correct and early management of malaria cases, Chemoprevention by Intermittent Preventive Treatment (IPT) in pregnant women and Seasonal Malaria Chemoprevention (SMC) in children from 3 to 59 months, the use of long-lasting insecticidal nets (LLINs) and Indoor Residual Spraying (IRS) [2,5,6]. Each of the last two strategies has shown significant results in reducing the burden of malaria in Africa [4,7,8]. Studies have also demonstrated the public health impact and cost-effectiveness of the combination of LLINs and IRS [9,10]. However, the rapid spread of vector resistance to insecticide is a challenge for malaria control programs.

In Mali, in addition to LLINs, IRS was applied in three districts since 2008 with the support of US President Malaria Initiative (PMI) including Koulikoro where it was applied for about ten years (2008 to 2016). The Ministry of Health (MOH) through the National Malaria Control Program (NMCP) oversees the IRS campaign activities which are performed once annually, at the beginning of the rainy season (May—June—July). During the course of the campaigns, different insecticides have been used as insecticide resistance was emerging. Since the start of the IRS campaign, no research has been conducted to assess the added value of IRS to LLINs on key malaria indicators such as incidence and prevalence among vulnerable populations for potential adjustment of the strategy. The aim of this study is to assess the effect of the added value of IRS by comparing malaria prevalence and incidence in children of 6 months to 10 years old in selected villages of Koulikoro district where IRS and LLINs are used in combination to selected villages of its neighbor district of Banamba where only LLINs are used.

Methods

Study areas

The study was conducted in the districts of Koulikoro and Banamba in Mali from June to October 2016. In both areas, the climate is typically Sahelian with a dry long season lasting from November to May.
and a short rainy season from June/July to October. The mean annual rainfall is 600–1200 mm. The monthly mean temperature during the rainy season varies between 29 and 33°C. *An. gambiae s.l.* is the predominant malaria vector (> 98%). Malaria transmission occurs mostly during the rainy season (June to October) with a mean monthly mosquito man biting rate reaching its peak in August/September and almost undetectable during the dry season (January/May).

In both districts, LLINs, Seasonal Malaria Chemoprevention (SMC) in children of 3 to 59 months, and Preventive Intermittent Therapy (IPT) with Sulfadoxine-Pyrimethamine in pregnant women are the malaria preventive measures recommended by NMCP. The only major difference was that IRS was applied in the district of Koulikoro and not in Banamba used as control district.

The study villages were selected along the border of the two districts where there is a similarity in term of the landscape, agricultural practices and population. Koula (7.65W, 13.12N) and Karadiè (7.60W, 13.24N) were selected 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).

**Population and Study design**

A non-randomized design was used to select two villages in the intervention district (Koulikoro) and two villages in the control district (Banamba). In each selected village, the research team conducted a census of the population. A unique identifier was assigned to each individual. All children aged 6 months to 10 years were invited to participate in the study. After a screening for eligibility, they were included if they agreed to comply with study follow up procedures and if their parents or legal guardians gave a written informed consent. Exclusion criteria were being non-residents of one of the 4 study sites and the refusal of parents or guardians to give their consent. We included 950 children from LLINs+IRS area (Koula and Karadiè) and 621 children from the area of LLINs-only (N’Galamadibi and Kolondialan). After signing the consent form, all the enrolled participants were subjected to two cross-sectional surveys: one at the beginning (before IRS implementation) and one at the end of the rainy season. In collaboration with the National Malaria Control Program (NMCP), new LLINs were distributed to all participants in both areas just after the first cross-sectional survey. During each survey, demographic data, clinical information, hemoglobin level measurement, blood spot on filter
paper and blood smear were performed from each subject. Parents/guardians of all children were questioned on the ownership and use of LLINs the night before. In addition to the cross-sectional, passive case detection was set up in each study site in collaboration with the local health staff. Presumed malaria cases (fever) from all participants were tested using a rapid diagnostic test (RDT). Positive cases were treated according to the national policy.

**Microscopy:**

The thick and thin blood films were stained with 10% Giemsa and examined under the ×100 oil immersion objective lens of a light microscope. The number of asexual parasites was counted against 200 leucocytes.

**Data analysis:**

The parasite prevalence was estimated as the number of positive by microscopy over the number of examined. Malaria case was defined as febrile cases with axillary temperature ≥ 37.5°C and positive to rapid diagnostic test (RDT). Data was collected on case report forms (CRFs) and/or by electronic data capture system and transferred to Microsoft Excel v. 2016. The analysis was performed in R-studio 1.1.41 and Prism v.7 Software. The Pearson $\chi^2$ test was used to compare the proportions and the Student’s test to compare the averages. The associations between risk factors and parasite carriage were calculated by univariate and multivariate logistic regression models with forward stepwise and interaction selection terms between certain variables in order to know the respective weight of each of these factors on parasitemia.

**Ethical considerations:**

The protocol of this project has been approved by the Ethics Committee of FMPOS/USTTB under the letter N°2014/51/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 Harmonization 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.
Results

**Table 1**: Malaria parasite rate, reported fever, LLINs usage and anemia prevalence in children of 6 months to 10 years in areas of LLINs+IRS and LLINs-only in June and October 2016

| Malaria indices | June 2016 |          | October 2016 |          |
|-----------------|-----------|-----------|--------------|----------|
|                 | LLINs+IRS (N=950) Freq (%) | LLINs-only (N=621) Freq (%) | χ²    | P- value | LLINs+IRS (N=950) Freq (%) | LLINs-only (N=621) Freq (%) | χ²    | P- value |
| Parasitemia     | 87 (9.15) | 87 (14.0) | 0.0027*      | 121 (13.2) | 253 (42.25) | 0.0027* |
| Gametocyte index| 24 (2.53) | 14 (2.25) | 0.7316       | 29 (3.17) | 68 (11.45) | 0.000*** |
| Fever           | 122 (12.84) | 52 (8.37) | 0.0058       | 196 (21.42) | 275 (53.70) | 0.000*** |
| LLINs           | 871 (91.68) | 130 (20.93) | 0.000***     | 886 (96.83) | 530 (89.23) | 0.000*** |
| Anemia          | 306 (32.21) | 329 (52.97) | 2.38e-16*    | 409 (44.70) | 364 (61.28) | 0.000*** |

The mean age of the study population was 5.6 ± 2.8 years and the sex ratio 1.1 for the male. As shown in Table 1, in June representing the start of the rainy season, malaria parasitemia was significantly lower (P = 0.0027) in LLINs+IRS area (9.2%, n = 950) compared to the area of LLINs-only (14.0%, n = 621). For the gametocyte index, there was no difference between the two areas.

Surprisingly prevalence of malaria fever cases was higher (P = 0.0058) in LLIs+IRS area 12.8%, n = 122) than in the area of LLINs-only (8.4%, n = 52). LLINs usage was very high (P < 0.001) in LLINs+IRS area (91.7%, n = 871) compared to the area of LLINs-only (20.9%, n = 130). More anemia cases (P<0.001) were observed in area of LLINs-only (53.0%, n = 323) than in LLINs+IRS area (32.2%, n = 306).

In October, representing the end of the rainy season and the peak of transmission, malaria parasitemia remains significantly lower (P < 0.001) in LLINs+IRS area (13.2%, n = 950) compared to the area of LLINs-only (42.3%, n = 621). However, in both areas, there was an increase in the parasite rate from June to October. This increase was 17.9% (9.2% vs 13.2%) in LLINs+IRS area, and up to 50.3% (14.0% vs 42.3%) in the area of LLINs-only. In opposite to June, where there was no difference in the gametocyte index between the two areas, gametocyte index was significantly higher (P < 0.001) in the area of LLINs-only (11.5%) compared to the LLINs+IRS area (3.2%) in October. The same pattern was observed with the fever. LLNs usage increased in both areas in October compared to June. However, it remained lower in the area of LLINs-only (89.2%, n = 530) compared to the area of LINs+IRS (96.8%, n = 886).

Figure 2 showed the variation of the asexual parasite rate by age group in the two areas. In June
there was no significant difference in parasite rate between the two age groups of the same area as well as between the two areas. In October, the parasite rate was significantly higher (P = 0.0007; P = 0.0003) in children of 5–10 years than in those < 5 years in the same area as well as in between areas (P<0.0001).

**Table 2**: Simple logistic regression between parasitemia and area, age group, fever and LLINs usage, anemia among children of 0-10 years old during the peak of transmission (October 2016)

| Parasitemia | Crude OR (95% CI) | P-value |
|-------------|------------------|---------|
| **Areas**   |                  |         |
| LLINs+IRS   | 1                |         |
| LLINs-only  | 4.9 (3.7-6.2)    | < 0.001*** |
| **LLINs**   |                  |         |
| No          |                  |         |
| Yes         | 0.6 (0.8-1.01)   | 0.05031 |
| **Age**     |                  |         |
| < 5 years   | 1                |         |
| > 5 years   | 1.6 (1.3-2.1)    | < 0.001*** |
| **Fever**   |                  |         |
| No          | 1                |         |
| Yes         | 4.6 (3.3-6.4)    | < 0.001*** |
| **Anemia**  |                  |         |
| No          | 1                |         |
| Yes         | 1.4 (1.1-1.8)    | 0.002** |
| **Fever sinc week** | 1       |         |
| Yes         | 2 (1.6-2.6)      | < 0.001*** |

Table 2 presents the results of the univariate logistic regression analysis performed on the data of the cross-sectional survey in October 2016 in the two study areas. It was more likely to carry malaria parasite: in area with LLINs only compared to area with LLINs+IRS (OR = 4.2, 95%CI = 3.7—6.2) and in older children (> 5 years) compared to younger (OR = 1.6, 95%CI = 1.3–2.1). Having fever, anemia, and antecedent of fever in the previous two weeks were all positively associated with parasite carriage (Table 2). Children owing LLINs were at borderline of protection (OR = 0.6, 95%CI = 0.8–0.01; P = 0.0503) compared to those who didn’t.

Figure 3 shows results of the final stepwise multivariate regression model. Interactions between explanatory variables were assessed by including proper cross-product terms in the regression models. The likelihood ratio test was used compare model with and without the inter-action term to estimate the significance of the interaction. In this model LLINs was excluded from and we noticed an increase in the risk of parasite carriage and the study areas (OR adjusted = 5.6, p<0.0001). Children > 5 years old were twice likely (OR adjusted = 2.3, P <0.0001) to carry parasite compared to < 5 years old. The risk of infection associated with fever decreased (OR adjusted = 2), but was still significant (p = 0.028). Association between anemia and two weeks antecedent fever was not
significant.

The overall incidence rate in children of 1–10 years was 2.7 for 100 person-month in LLLIs+IRS area and 6.8 for 100 person-month in the area of LLINs-Only. However, during the first two months (July-August) and after the end of the rainy season (December–February), there was not a significant difference in malaria incidence between the two areas as shown in figure 4. It was from September to November that malaria incidence was significantly lower in LLINs+IRS area compared to the area of LLINs-only. As in malaria parasitemia, the peak of malaria incidence was observed in October in both areas but was much lower in the IRS area than the area without IRS.

The Kaplan Meier survival curve applied to the number of malaria episodes in children of 1–10 years old in each study area showed that children living in IRS area were more likely to be free of malaria (P < 0.001) than in the area without IRS (Figure 5).

Discussion

In this study, we compared malaria prevalence and incidence in two areas of integrated malaria control strategies to evaluate the effect of the added value of IRS. Data were collected in both areas through two cross-sectional surveys and 8 months of passive case detection in the health clinics. The results of the cross-sectional surveys at both the start and end of malaria transmission season showed that malaria parasitemia was significantly lower in the area with LLINs+IRS compared to the area with LLINs-only. Since the two areas are comparable in terms of malaria epidemiology and interventions, this difference can be attributed to the added value of the IRS in the area of LLINs+IRS. Indeed, it is of common knowledge that each of the LLINs [9,11,12] and IRS [13–15] significantly reduce malaria burden when deployed separately. Thus, their integration is expected and supported by many studies [14,16–19] to make more reduction in malaria burden compared to their respective single impact. Despite the IRS, there was an increase in malaria parasitemia from the start to the end of the rainy season as expected in seasonal malaria transmission areas where transmission intensity rich it peak at the end of the rainy season[20]. However, the increase in the area of LLINs+IRS was much lower (17.9%) than in the area without IRS (50.3%), supporting our previous observation. The nine years of IRS campaign have certainly contributed to reduce and even to suppress the peak of the
transmission in the area of LLINs+IRS, which was apparent in the area without IRS. We also noted that there was not a difference in gametocyte index between the two areas at the start, while at the end of the rainy season, this index was significantly higher in the area of LLINs-only (11.5%) compared to the area of LLINsIRS (3.2%). This observation partially explains the lowest prevalence of malaria parasitemia in IRS area because gametocyte index is the potential source of infection for mosquito, hence malaria transmission [20,21]. The results of the logistic regression analysis allowed us to see the real risk related to malaria infection in the area without IRS while highlighting certain risk factors overestimated such as fever or confounding factors such as anemia that could also be caused by other conditions.

Regardless of the study area, malaria parasitemia was higher in the age group of 5 -10 years than in the > 5 years (Table 2). This unexpected observation was also reported by Touré and al. (2016) who reported that children of 6-9 years old were at least twice more likely to carry parasites than children < 5 years old [22]. Explanation to his observation was the expansion and focus of current control interventions (LLINs, SMC, IPT etc..) on children < 5 years. Walldorf and al. (2015) also reported that school-age children and adults less exposed to antimalarial interventions were representing a reservoir of malaria infection in replacement of children < 5 years [23].

As with the parasitemia, malaria incidence in children of 1-10 years old was significantly lower in the LLINs+IRS area compared to the area of LINs-only. The traditional transmission peak was observed in both areas, but it was much lower in the LLINs+IRS area than in the area without IRS (Figure 3). Indeed, while the insecticide can last in LLINs over about 3 years, for IRS it last over a maximum of 6 months. Thus, the IRS campaign is applied once a year with the objective to cover the peak of the transmission. As shown on the Kaplan Meier survival curve (Figure 4), children living in IRS area were less likely to develop malaria clinical case than in the area without LLINs-only. This is in line with others studies in which significant reduction in malaria incidence was reported when scaling-up IRS in combination with other interventions [24]. However, the period of coverage and protection of the residual effects of IRS was limited in the time suggesting that this strategy may need to be improved by using other class of insecticides lasting longer or by increasing the frequency of its application in
the year [25],...

The difference observed for prevalence anemia in the area with and without LLINs + IRS, between age group and the participant with and without fever, was a good indirect indicator of result the strategies used. Because the malaria is consider like the principal cause of anemia in the endemic areas[26–28].

Conclusions
Both malaria parasitemia and incidence in children of 1-10 years old were lower in area where IRS was implemented compared to control area. The children living in IRS area were most likely to survive longer to develop malaria than those living in area where it was not.

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)

Declarations
Ethics approval and consent to participate:
The protocol of this project has been approved by the Ethics Committee of the Faculty of Medicine, Pharmacy and Odonto stomatology of the University of Sciences, Techniques and Technologies of Bamako (USTTB). 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 analysed 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

FK: has worked on the research hypothesis and collecting the data analyze and manuscript writing.

MK: has worked on collecting the data and manuscript writing.

BT: has worked on collecting the data and manuscript writing.

SD: contribute to analyzed and interpreted data

SB: worked on collecting the data

SD: worked on collecting the data

NF: Correct and approved the latest version before submission.

SD: Correct and approved the latest version before submission.

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Figures

Figure 1

Map of the districts of Koulikoro and Banamba showing the selected villages
Figure 2

Malaria parasitemia in children of 6 months to 10 years by age group in areas of LLINs+IRS and LLINs-only in June and October 2016
Figure 3

Results of the stepwise multivariate logistic regression model between independent explanatory variables and parasitemia during October 2016 survey in the two study areas.
Figure 4

Monthly incidence of malaria (TDR+, Temperature > 37ºC) in children of 6 months to 10 years old in the areas of LLINs+IRS (continue line) and LLINs-only (dash line) from July 2016 to February 2017.
Figure 5

Kaplan-Meier survival curve of children of 1-10 years old living in the study areas after 8 months of follow-up.