Jpn. J. Infect. Dis., 75, 288-295, 2022

Original Article

Effects of Indoor Environmental Factors and House Structures on Vaporization of Active Ingredient from Spatial Repellent Devices in Rural Houses in Malawi

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ABSTRACT: The use of a metofluthrin-impregnated spatial repellent device (MSRD) is a new and effective method for preventing mosquito blood feeding. Indoor environmental factors such as room temperature and ventilation rate are thought to be important for MSRD activity. Measurements of room temperature and vaporization of metofluthrin from MSRD in typical rural metal-roof and thatched-roof houses in southeastern Malawi were conducted. The relationship between house structure and the number of collected Anopheline mosquitoes with and without MSRD treatment was also investigated. The difference between daytime and nighttime room temperature was significantly higher in metal-roof houses than in thatched-roof houses. The vaporization of metofluthrin from the MSRD was not accelerated by the high room temperature, but by the high indoor air flow by ventilation. The number of mosquito collections was significantly higher in thatched-roof houses than in metal-roof houses. MSRD-treated thatched-roof houses have a higher probability of mosquito infestation, but the vaporization of metofluthrin is also higher because of indoor air flow, resulting in a reduction in mosquito numbers. Metal-roof houses with closed eaves reduce the probability of mosquito invasion, and a longer predicted effectiveness occurs with MSRD because of the controlled release of metofluthrin through lower indoor air flow.

INTRODUCTION

Insecticide-treated nets (ITNs) and long-lasting insecticidal nets (LLINs) are effective only when the mosquito vectors are endophagous and their blood-feeding time corresponds to the human sleeping period (1). Iwashita et al. reported that children under 15 years of age had lower rates of bed net use than those in other age groups in houses along Lake Victoria in western Kenya (2). The use of bed nets was limited to parents and their infants sleeping in the bedroom, while the rest of the family (especially children) often slept in the living room without bed nets, leading to a high malaria transmission rate among this generation (2). The effective use of bed nets is strongly influenced by the ease with which they can be installed in the house, which is especially important for children above infancy who usually sleep in rooms away from their parents where bed nets are difficult to install. Therefore, simplifying the installation of bed nets or preventing mosquito attacks by other methods could protect this generation from malaria and could reduce the overall morbidity of the community.

Metofluthrin (SumiOne®), 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl (EZ) (1RS, 3RS;1RS,3SR)-2,2-dimethyl-3-(prop-1-enyl) cyclopropanecarboxylate, belongs to a new type of pyrethroid group that has a high vapor pressure and high insecticidal and spatial repellent activity against mosquitoes (3). Metofluthrin-impregnated spatial repellent devices (MSRD) have been suggested to be effective in preventing mosquito blood feeding in several regions under different conditions (4–9). MSRD has also been reported to be highly effective in repelling pyrethroid-resistant malaria vector mosquitoes in Kenya (10) and Malawi (11). We examined the effect of the combined use of the MSRD and long-lasting insecticidal net LLIN (Olyset® Plus) on malaria prevalence and vector mosquitoes in malaria-endemic villages in south-eastern Malawi. The intervention reduced the infection rate in children as well as the number of pyrethroid-resistant vector mosquitoes invading houses. In the above study, we concluded that continued intervention using MSRD at 3-month intervals with two strips per 10 m^2 to reduce

Received August 10, 2021. Accepted October 19, 2021.
J-STAGE Advance Publication November 30, 2021.
DOI: 10.7883/yoken.JJID.2021.584
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Fig. 1. Typical brick houses in the study sites (A, metal-roof house; B, thatched-roof house), MSRD hung from ceiling in the metal-roof house (C) and in the thatched-roof house (D), and a micro data logger (Thermochron® Type G) for measuring room temperature (E).

the density of malaria mosquitoes was recommended in order to effectively control malaria (11).

The effective duration of the MSRD appears to be correlated with the vaporization over time, which can be regulated by formulation factors, such as polymer type and density, which determine the bleeding rate of an active ingredient. A high vaporization speed might lead to rapid effectiveness, but the effective duration may be reduced. In contrast, a low vaporization rate might result in long-lasting efficacy, but there could be a minimum vaporization over time under which no efficacy is expected. Indoor environmental factors, such as room temperature and ventilation rate, are thought to be important for residual activity as well as formulation factors. In the present study, we measured the room temperature in typical rural houses in southeastern Malawi. The vaporization of metofluthrin from the MSRD in the houses was also detected by chemical analysis, and its relationships with house structures and indoor environmental factors such as room temperature and air flow are discussed.

MATERIALS AND METHODS

Study area and houses: The study was performed in two adjacent villages, Chiliko and Chilore, in Likangala, in the eastern area of the Zomba district (15°23'S, 35°20'E), in the southeastern region of Malawi. The Zomba district is located in a malaria endemic area with a high prevalence of malaria (12). Malaria is one of the leading causes of death in the district (Zomba District Health Office, 2009). *Anopheles arabiensis* Patton and *Anopheles funestus* sensu stricto (s.s.) Giles are the main malaria vectors in the study area, and both possess high metabolic resistance to pyrethroids and DDT. No single point mutation in the voltage-gated sodium channel (L1014F or L1014S) was detected in *An. arabiensis* and *An. funestus* s.s. at the study site (11). Most of the houses in the study area were built of mud bricks, some fired, and the rest dried. The houses were broadly categorized into two types: metal-roofed and thatched-roofed (Fig. 1).

Selection of the houses and intervention of the MSRD: The study was performed between January and

Table 1. Number of persons dwelling, total floor area, number of MSRD treated, and type of roofs in the selected houses in Chiliko village

House no.	No. of persons		Floor area (m^2)	No. of MSRD / house	No. of MSRD / 10 m^2	Roof type
	≤ 10 years	> 10 years				
A002	1	2	28.16	8	2.84	Thatched
A004	1	2	21.84	-	-	Thatched
A006	2	4	33.39	-	-	Metal
A008	4	2	19.84	-	-	Thatched
A010	2	2	19.89	-	-	Thatched
A018-a	2	2	33.92	-	-	Thatched
A018-b	2	2	19.8	-	-	Thatched
A021	3	2	32.66	10	3.06	Metal
A022	3	3	35.38	-	-	Metal
A023	1	2	14.4	-	-	Metal
A025	2	3	38.86	-	-	Metal
A026	2	2	38.08	11	2.89	Metal
A027	2	2	15.75	3	1.90	Thatched
A030	0	2	23.22	7	3.01	Thatched
A032	0	2	20.01	6	3.00	Metal
A033	2	2	30.72	-	-	Metal
A036	1	2	30.24	8	2.65	Metal
A042	2	3	14.35	3	2.09	Thatched
A044	2	5	30	-	-	Metal
A046-1	2	2	12	4	3.33	Metal
A046-2	2	4	29.76	-	-	Metal
A047	1	5	37.52	8	2.13	Metal
A049	3	2	44.16	-	-	Metal
A052	1	3	18.32	-	-	Thatched
A053	2	3	16.47	3	1.82	Thatched
A062	0	2	37.24	11	2.95	Metal
A064	0	5	34.76	-	-	Thatched
A067	1	2	25.2	-	-	Metal
A070	2	3	38.54	8	2.08	Thatched
A072	0	2	19.8	4	2.02	Thatched
A076	0	3	15.66	-	-	Thatched
A080	1	2	29.67	6	2.02	Metal
A090	3	3	22.95	5	2.18	Thatched
A091	3	4	20.4	-	-	Thatched
A092	0	3	15.66	3	1.92	Thatched
A099	2	2	32.76	10	3.05	Thatched
A100	0	3	36.4	-	-	Metal
H41	1	2	18	-	-	Metal
H42	0	6	26.46	8	3.02	Thatched
H43	1	3	19.04	6	3.15	Thatched

MSRD, metofluthrin-impregnated spatial repellent device.

May 2015, which is the rainy season in the study area (http://www.worldweatheronline.com/Zomba-weather-averages/Zomba/MW.aspx). Nineteen metal-roof houses and 21 thatched-roof houses in Chiliko village were selected for the study (Table 1). The MSRD (polyethylene net materials of 8 × 15 cm impregnated with metofluthrin 10% w/w per plastic strip; Sumitomo Chemical Co., Ltd., Tokyo, Japan) was hung in the rooms of the 20 houses at two different dose regimens, approximately 2 strips per 10 m^2 for 9 houses, and 3 strips per 10 m^2 for the other 11 houses (Fig. 1A to 1D). The house residents were informed of the study, and written consent was obtained beforehand. The MSRD intervention was conducted on January 22 and 23, 2015.

Measurement of room temperature: The room temperature of the 40 houses was recorded at 2-h intervals with a micro data logger (Thermochron® Type G; KN Laboratories Inc., Osaka, Japan). The data loggers were hung from ceilings at the same height as the MSRD (Fig. 1E).

Analysis of the amount of metofluthrin in the MSRD: Four months after the hanging of the MSRD (on May 18, 2015), all strips were collected and the remaining quantities of metofluthrin in the MSRDs were analyzed using gas chromatography.

Selection of houses and collection of anopheline

Table 2. Number of persons dwelling, total floor area, and type of roofs in the houses in Chiliko and Chilore villages

House no.	Village	No. of persons		Floor area (m^2)	MSRD (strips /10 m^2)	Roof type
		≤ 10 years	> 10 years			
A236	Chiliko	0	2	15.64	-	Thatched
A251	Chiliko	2	5	14.52	-	Thatched
A255	Chiliko	2	3	17	-	Thatched
A266	Chiliko	2	2	15	-	Thatched
A269	Chiliko	2	2	14.4	-	Thatched
A270	Chiliko	1	3	36.57	-	Metal
A271	Chiliko	1	2	20.4	-	Thatched
A279	Chiliko	0	5	42.35	-	Metal
A282	Chiliko	0	2	13.32	-	Thatched
B581	Chiliko	0	1	14.62	-	Thatched
B582	Chiliko	0	4	33.39	-	Metal
B584	Chiliko	2	2	34.16	-	Metal
B594	Chiliko	3	1	18.7	-	Thatched
B595	Chiliko	2	5	30	-	Metal
B600	Chiliko	1	4	14	-	Thatched
B601	Chiliko	1	2	15.4	-	Thatched
B604	Chiliko	1	2	18.5	-	Thatched
B622	Chiliko	2	3	38.86	-	Metal
B628	Chiliko	3	1	9	-	Metal
B635	Chiliko	0	1	10.92	-	Thatched
A293	Chilore	2	5	35	2	Metal
A299	Chilore	2	2	23.22	2	Metal
A305	Chilore	2	3	21.15	2	Thatched
A310	Chilore	0	2	17.68	2	Thatched
A320	Chilore	1	3	16.32	2	Thatched
A341	Chilore	2	4	33.28	2	Thatched
A349	Chilore	4	4	36.96	2	Metal
A350	Chilore	2	2	15.84	2	Thatched
A351	Chilore	0	2	17.86	2	Thatched
A364	Chilore	0	3	39.96	2	Thatched
A365	Chilore	1	3	18.55	2	Thatched
A367	Chilore	1	3	39.9	2	Thatched
B643	Chilore	2	3	33.12	2	Metal
B646	Chilore	3	4	2.8	2	Thatched
B648	Chilore	2	4	27.5	2	Thatched
B650	Chilore	1	4	28.2	2	Metal
C001	Chilore	NA	NA	NA	2	Thatched
C002	Chilore	NA	NA	NA	2	Metal
C003	Chilore	NA	NA	NA	2	Thatched

MSRD, metofluthrin-impregnated spatial repellent device; NA, not available.

mosquitoes: The study was performed between December 2015 and May 2016. Seven metal-roof and 13 thatched-roof houses in Chiliko village and six metal-roof and 13 thatched-roof houses in Chilore village were selected for the study (Table 2). Prior to the MSRD intervention, Olyset® Plus (permethrin 2% and PBO 1% w/w; Sumitomo Chemical Co., Ltd.) was delivered to the above 39 houses after removing the old bed nets to make uniform the indoor mosquito repelling measure except for MSRD among the houses. Two interventions of MSRD (2 strips /10 m^2) were implemented for the houses in Chilore village in January and April 2016, whereas no intervention of the MSRD was done in Chiliko village. The second intervention of MSRD in Chilore village was performed after removal of all MSRDs placed in the 1st intervention. The house residents were informed of the experiment, and written consent was obtained before conducting the study. Pyrethrum spray collections (13) were performed in the morning (07:00–10:00) by three to four staff members. Collections were performed on December 3–4, 2015, before the intervention of MSRD, and on February 12, March 8–9, April 8–13, and May 9–11, 2016, after the intervention of MSRD.

Identification of mosquitoes: The collected mosquitoes were identified as *Anopheles gambiae* sensu lato (s.l.) and *An. funestus* s.l., microscopically based on identification keys (14). DNA from the mosquito samples was extracted using the RedExtract-N-Amp^{TM} Tissue PCR kit (Sigma-Aldrich Japan, Tokyo, Japan) according to the manufacturer's instructions, and the multiplex PCR method (15,16) was used for species identification.

Data analysis: The average daytime (06:00–18:00), nighttime (20:00–04:00), and overall room temperature were calculated for four months for each house. The Wilcoxon rank sum test and one-way analysis of variance for the room temperature and the number of mosquito collections, and linear regression analysis between the average temperature and the average amount of remaining metofluthrin in the MSRD were performed using JMP Pro 15.0.0 (SAS Institute Japan Inc. Tokyo, Japan).

Ethics: The study protocol was reviewed and approved by the University of Malawi, Chancellor College Research and Ethics Committee, and the Ethical Committee of the Institute of Tropical Medicine, Nagasaki University (Approve No. 140605123-2).

RESULTS

Relationship between room temperature and the vaporization of metofluthrin from the MSRD: Changes in the room temperature in the metal-roof houses and thatched-roof houses are shown in Fig. 2A and 2B. Average room temperatures calculated for each house during the day (Dt, 06:00–18:00) and night (Nt, 20:00–04:00) in the metal-roof houses were 28.7°C (standard deviation [SD], 0.93) and 25.5°C (SD, 0.67), while those in the thatched-roof houses were 26.0°C (SD, 0.61) and 25.1°C (SD, 0.82), respectively (Fig. 2C). The Dt was significantly higher than the Nt in both the metal-roof houses (χ^2 = 27.8, df = 1, P < 0.0001) and thatched-roof houses (χ^2 = 12.2, df = 1, P = 0.0005). Although the differences in the room temperature between the metal-roof houses and thatched-roof houses were significant for both Dt (χ^2 = 28.2, df = 1, P < 0.0001) and Nt (χ^2 = 4.21, df = 1, P = 0.040), the deviation between them (Dt vs. Nt) was significantly larger in the metal-roof houses than in the roofed houses (χ^2 = 26.2, df = 1, P < 0.0001).

Chemical analysis of the amount of metofluthrin remaining in the MSRD was performed for the 20 MSRD-treated houses (8 metal-roof and 12 thatched-roof houses) (Fig 3A). A total of 124 MSRDs (62 MSRDs each for the metal- and thatched-roof houses) were analyzed. The average remaining percentage (w/w) of metofluthrin in the metal-roof houses and thatched-roof houses were 3.81% (SD = 2.1) and 1.68% (SD = 0.98), respectively. The actual percentage of measured metofluthrin in the MSRD before the intervention was 10.6% (w/w). The remaining amount was significantly higher in the metal-roof houses than in the thatched-roof houses (χ^2 = 33.8, df = 1, P < 0.0001). Fig. 3B shows the relationships between the average room temperature and the average amount of metofluthrin remaining in the MSRD per house four months after treatment. No correlation was observed between the remaining amount and average room temperature in the thatched-roof dwellings (R^2 = 0.0002). The correlation was also low in the metal-roof houses, while it showed a slight positive slope (R^2 = 0.2097), indicating that the higher the room temperature, the lower the vaporization of metofluthrin.

Relationship between house structure and number of anopheline mosquitoes: A total of 221 female *An. arabiensis* and 65 female *An. funestus* s.s. were collected over the five periods from December 4, 2015, to May 9, 2016, in Chiliko village (without MSRD intervention) and the first collection (December 3, 2015, before the intervention of the MSRD) in Chilore village. The number of female *An. gambiae* s.s. was low (one for Chiliko village and two for Chilore village). The number of anopheline mosquitoes (*An. arabiensis*, *An. gambiae* s.s., and *An. funestus* s.s.) in the metal-roof and thatched-roof houses per collection in Chiliko village without MSRD intervention and Chilore village before MSRD intervention are plotted in Fig. 4A. The average number of mosquito collection in the metal-roof houses and the thatched-roof houses were 1.67 (Standard Error [SE], 0.83) and 2.99 (SE, 0.77), respectively. The number of mosquitoes collected was significantly higher in thatched roofs than in metal-roof houses (χ^2 = 6.94, df = 1, P = 0.0084). Anopheline mosquitoes in the metal-roof and thatched-roof houses in Chilore village in the three collections, from March to May 2016 (2, 3 and 4 months after the intervention of the MSRD), are plotted in Fig. 4B. The average number of mosquito collections in the metal-roof houses and thatched-roof houses were 0.95 (SE, 0.53) and 0.67 (SE, 0.17), respectively. The difference in the number of mosquito collections between metal-roof houses and thatched-roof houses was not significant (χ^2 = 0.64, df = 1, P = 0.424).

DISCUSSION

The present study showed higher daytime room temperature in metal-roof houses than in thatched-roof houses, which is likely due to the differing effects of solar radiation on the two roof materials. The difference in ventilation rates between the two roof types could also have contributed to the temperature differences, because most thatched-roof houses have open "eaves" between the roof and the wall, as shown in Fig. 1D, which are not present in the majority of metal-roof structures (Fig. 1C). All the thatched-roof houses (21 houses) investigated in the present study had open eaves, whereas this feature was present in only one house among 19 metal-roof houses. A recent study reported a large difference in the ventilation rate between houses with thatched roofs and open eaves and those with metal roofs and closed eaves (17). The openness (open area/volume of house) in African thatched-roof houses (in Tanzania) was reported to be twice as high as that in concrete houses in southern Vietnam (9).

The present results were unexpected, as the vaporization of metofluthrin from the MSRD did not increase in correlation with room temperature, but the amount of metofluthrin remaining in MSRD showed a slight positive correlation with room temperature, indicating that the higher the room temperature, the lower the vaporization of metofluthrin. This indicates

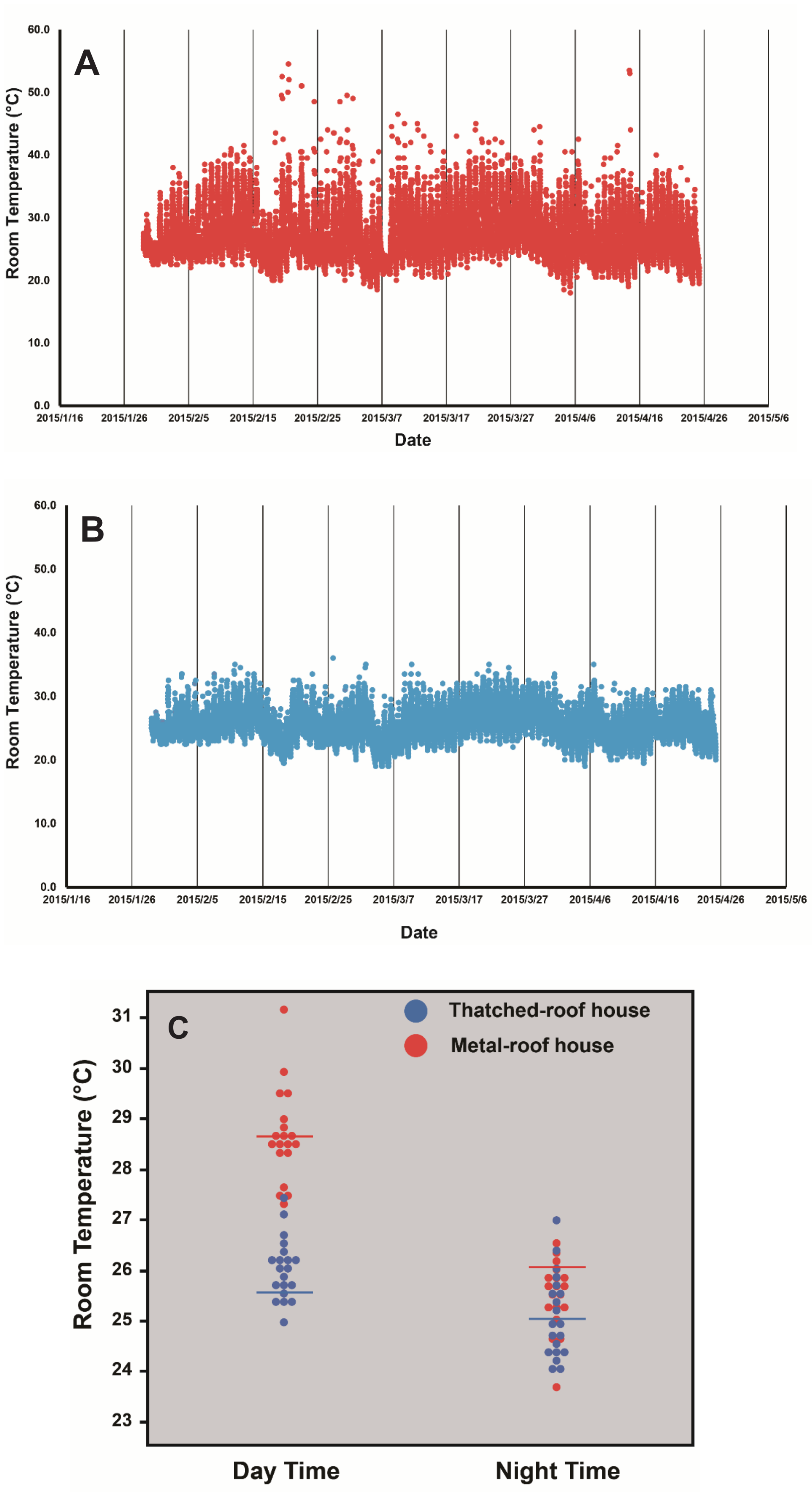

Fig. 2. Changes in the room temperature in metal-roof houses (A) and in thatched-roof houses (B) between January and April, 2015, and average day time (06:00–18:00) and night time (20:00–04:00) room temperature in metal-roof houses and thatched-roof houses (C).

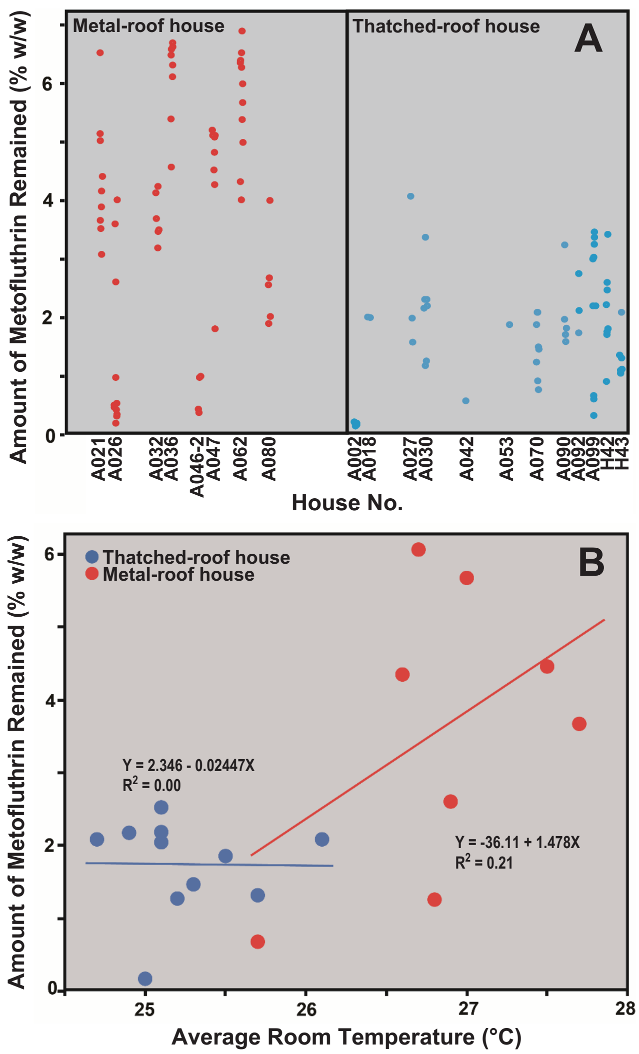

Fig. 3. Amount of remaining metofluthrin in the MSRD at 4 months after treatment in the metal-roof and thatched-roof houses (A), and relationships between the average overall room temperature and amount of remaining metofluthrin in the MSRD per house (B). The linear regression formula and correlation coefficient for each roof type are shown in the graph.

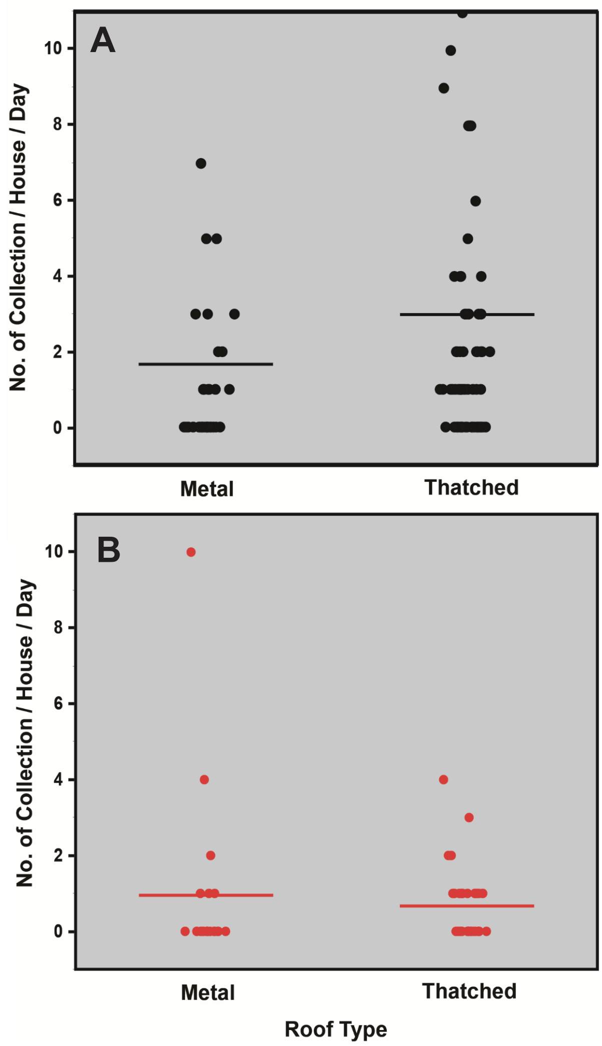

Fig. 4. Number of anopheline mosquitoes (*An. arabiensis*, *An. gambiae* s.s., and *An. funestus* s.s.) collected by 5 pyrethrum spray collections from December 4, 2015 to May 9, 2016 in the metal-roof and thatched-roof houses in Chiliko village without MSRD intervention and on December 3, 2015 in Chilore village before MSRD intervention (A), and number of mosquitoes collected in the metal-roof houses and the thatched-roof houses in Chilore village after 2, 3, and 4 months of the MSRD intervention (B).

that the major vaporization factor for metofluthrin bleed on the plastic surface of the MSRD was not temperature, but another microclimate factor, possibly the air flow by ventilation due to the difference in the structure of the houses, as explained above. The more closed the indoor condition, the lower the ventilation and the higher the room temperature. The mathematical model developed for predicting the release of metofluthrin from a cellulose-based paper revealed the dependence of vaporization as an Arrhenius function of temperature, and the mass transfer coefficient in the air was linearly dependent on the air velocity (18). The experimental data for designing the above model show that a 10°C difference in temperature caused a $< 10^{-4}$ mol difference in the vaporization of metofluthrin, whereas only a 0.2 m/sec increase in the wind velocity caused 10^{-4} mol or more vaporization, indicating that wind velocity has the greatest influence on the vaporization of metofluthrin (18). The loss of additives in low-density polyethylene (LDPE) is controlled by the desorption of the additive from the surface of LDPE and depends on the migration speed of the additive through the polymer bulk to reach the plastic surface. An increase in temperature led to an increase in the release of the additive in the LDPE film (19). However, a substantial increase in the release percentage of additive was noted in the temperature range of 35–115°C (19), and the increase in release percentage was very low in the range of 25–35°C. Therefore, the release of the additive (metofluthrin in the MSRD in the present case) on the surface of the MSRD occurring only from the increase in the temperature range (20–30°C) (Fig. 3B) was suggested to be very low in the present study. Thus, it can be concluded that most of the vaporization of metofluthrin is accelerated by the air flow caused by ventilation.

The openness of houses affects the ability of mosquitoes to invade. The eave gap between the roof and wall is thought to be the major route of entry for mosquitoes, and closing the eaves resulted in a 66%

reduction in the number of *An. gambiae* s.l. (20). The number of indoor resting anopheline mosquitoes, among which *An. arabiensis* was the most prevalent, was higher in houses with open eaves than in those with closed eaves (21). When the comparison analysis was performed only for thatched-roof houses, abundance of *An. gambiae* s.l. between the open and closed eaves was still statistically significant (22). In the present study, the number of female anopheline mosquitoes collected in thatched-roof houses was almost twice that of their metal-roof counterparts when MSRDs were not treated. The intervention of the MSRD caused a decrease in mosquito invasion both in the metal-roof and thatched-roof houses, and the difference in the number of invasions was not significant between the two roof types (Fig. 4B).

MSRD-treated thatched-roof houses have a higher probability of mosquito infestation, but the vaporization of metofluthrin is also higher due to indoor air flow, resulting in greater mortality or spatial repellency of mosquitoes. Metal-roof houses with closed eaves reduce the probability of mosquito invasion, and a longer effectiveness with the MSRD might be expected because of the controlled release of metofluthrin by lower indoor air flow. Moreover, high temperatures in metal-roof houses may shorten the life span of mosquitoes, as Lindsay et al. reported that the metal roof caused an increase in room temperature as compared to the thatched roof, causing the mosquitoes to have a short life span and negatively affecting the development of *Plasmodium* parasites (23). We have shown that the combined use of LLIN (Olyset® Plus) and MSRD with two strips per 10 m^2 at three-month intervals reduced the vector mosquito density in the present trial sites in Malawi, where more than half of the houses were rural African thatched-roof houses (11). Thatched-roof houses, which encompass the majority of houses in the rural African area, have a higher probability of mosquito infestation, but the vaporization of metofluthrin from the MSRD is also higher due to indoor air flow, resulting in a reduction in mosquito numbers. Longer durations of effectiveness could be expected in urban areas where house structures are more closed.

Acknowledgments We thank Bosco Rusuwa, Malawi University-Chancellor College, Zomba, Malawi for assisting with this study. We also thank Takashi Suzuki and Kozue Shimabukuro, Kobe-Tokiwa University, Kobe, Japan, for their assistance and technical support. This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP26305012 and funded by the joint research between Nagasaki University and Sumitomo Chemical Co. Ltd for the creation of field and semi-field bioassay systems for insecticide delivery technology.

Conflict of interest None to declare.

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