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PROTECTIVE EFFICACY OF LAMBDA-CYHALOTHRIN TREATED NETS IN *ANOPHELES GAMBIAE* PYRETHROID RESISTANCE AREAS OF CÔTE D'IVOIRE

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Abstract. The efficacy of nets treated with lambda-cyhalothrin, a pyrethroid insecticide, on malaria infection and disease was assessed for the first time at the community level in *Anopheles gambiae* pyrethroid resistance areas. The study was carried out in northern Côte d'Ivoire, which is an area of *kdr* resistance. Four pairs of villages were selected and matched according to demographic, sociological, and ecological criteria. Among each pair, a village was randomly allocated to receive mosquito nets. More than 80% of beds were covered with nets treated with lambda-cyhalothrin and retreated after 6 months. In each village, 54 children aged 0–59 months were randomly selected and clinically monitored for 8 periods of 7 days throughout the year. Results showed that the efficacy of treated nets was maintained with a reduction of the prevalence of asymptomatic malaria infection by 12% and an estimated protective efficacy against malaria disease of 56%.

INTRODUCTION

Many studies have shown the efficacy of insecticide-treated bed nets in reducing malaria transmission and morbidity and all-cause child mortality.[1] The only insecticides used for the impregnation of bed nets are pyrethroid insecticides, such as lambda-cyhalothrin, deltamethrin, or permethrin.

In the sub-Sudan savannah region of Côte d'Ivoire, intensive cotton cultivation has involved large-scale insecticide spraying for several years. It is strongly suspected that this has been a source of selection for DDT and pyrethroid resistance on mosquito populations including those of *Anopheles gambiae*, which breed in the lowlands where insecticide residues concentrate after being washed down by the rains. This has led to the selection of a resistance mechanism called knock down resistance (*kdr*) with a high frequency of *kdr* allele.[2] In the course of phase II trials for the WHO Pesticide Evaluation Scheme on evaluation of insecticides, tests carried out in experimental huts on the efficacy of nets treated with permethrin and deltamethrin showed that these nets reduced the rates of hut entry, increased rates of hut exit, and caused some mortality in the local populations of *An. gambiae* despite their resistance to pyrethroids.[3] In addition, a trial in the village of Kafiné in Côte d'Ivoire, where *An. gambiae* is very resistant to pyrethroids, showed that Olyset nets into which permethrin is industrially incorporated conferred personal protection against malaria attacks.[4]

The current trial was carried out in the sub-Sudan savannah zone of Côte d'Ivoire where the association of malaria risk with different systems of rice cultivation has been previously measured.[5] The main malaria vectors of this area were *An. gambiae* s.s. and *Anopheles funestus,* but *An. gambiae* was predominant in villages close to rice fields (Dossou-Yovo J, unpublished data). *An. gambiae* was strongly resistant to pyrethroids with a *kdr* allelic frequency of around 90%. *An. funestus* was still susceptible to these insecticides (Koffi AA, unpublished data). The current study aimed to evaluate the epidemiologic impact of nets treated with lambda-cyhalothrin in a region with intense transmission due to *An. gambiae* highly resistant to pyrethroids. A comparison was made between eight villages, four provided with treated nets and the other four without any nets. The malaria burden on children less than 5 years old has been studied in terms of prevalence and density of malaria infection, of clinical malaria attacks, and level of anemia. The entomological impact of the treated nets was evaluated simultaneously in the same villages (Dossou-Yovo J, unpublished data).

MATERIALS AND METHODS

Site and sampling. A longitudinal study was conducted in the Department of Korhogo, in the North of Côte d'Ivoire, from July 1999 to June 2000. The required numbers of communities and children for epidemiologic evaluation of the intervention were estimated to detect a 50% protective efficacy with a power of 80%, a significance level of 5%, a design effect of 0.25, an average of 2.6 clinical malaria attacks per child-year in the reference group,[5] and 20% of the children lost to follow-up.[6] Thus, the required number of communities was calculated to be 4 villages for the intervention group and 4 villages for the control group, and the required number of children was 54 subjects per village followed during 56 days distributed over 8 periods of 7 consecutive days scheduled at 6 week intervals throughout the year. Among the 12 villages where malaria transmission and morbidity were previously measured, 4 pairs of villages were selected and matched according to the lowland rice cultivation system, the social and behavioral characteristics and the size of village (Table 1). Among each pair of matched villages, one was randomly allocated to receive impregnated mosquito nets, and the other remained as control. After updating the census of each village, including children born since 1997, samples of children aged 0–59 months were selected from randomly sampled compounds as in an earlier study.[5] Each head of family, or the guardian of the child, gave informed consent. The Ministry of Public Health of Côte d'Ivoire granted ethical approval for this study. During the monitoring periods, children of villages, whether participating in the study, were treated free of charge by the medical team.

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TABLE 1
Pairs of villages with their characteristics

With ITN / Without ITN	Pairs of villages: Gbahouakaha / Nongotchenekaha	Binguebougou / Fapaha	Ounadiekaha / Folofonkaha	Kaforo / Nambekaha
Agrosystem				
Double cropping rice/year	+			+
Single cropping rice/year		+		
No rice cultivation			+	
Senufo subethnical group	Tiembara	Tiembara	Tagbana	Tiembara
Size of village (*N* inhabitants)	605 / 667	1305 / 1496	720 / 726	447 / 563

ITN, insecticide-treated net.

Treatment of mosquito nets. Before impregnation, a comprehensive census was done in each village to identify every bed and sleeping mat in every house to be covered by an insecticide-treated net (ITN). At the start of the trial in June 1999, every mosquito net was treated, in the village, with lambda-cyhalothrin formulated as a capsule suspension (15 mg a.i./m^2) and marked with both wash-resistant and washable markers to check for washing or movement of nets to different houses from those for which they were intended. Mosquito nets were dipped again after 6 months in December 1999. In each village, the correct use of ITNs was regularly checked by two village health workers trained for this trial. The four villages without mosquito nets received ITNs after the trial. All bed nets were given free of charge.

Data collection. Active case detection (ACD) for malaria episodes was done during 8 periods of 7 days at 6 weekly intervals. Each day during these surveys a nurse, assisted by two health workers from the village trained for this study, visited the households of each child of the sample, and a physician supervised the field work. The presence or absence and state of health of each of the children were thus recorded daily on a specially prepared sheet (one sheet per household). The nurse examined and recorded data on every detected case of sickness at home. A thick blood film was taken from every sick child. Children were treated according to the clinical diagnosis made by the nurse. When a malaria attack was suspected, the patient was treated with chloroquine at 25 mg/kg body weight for 3 days according to the recommendations of the National Program for Malaria Control. Cross-sectional surveys (CSS) were carried out on every asymptomatic child (confirmed by an axillary temperature < 37.5°C) included in the study. During each survey, a blood sample was taken on the sixth day to confirm that those classified as asymptomatic were free of malaria infection in the days before the blood sample was taken. In November 1999 (end of the rainy season), capillary blood was also taken from each asymptomatic child, 0–2 years old, to measure packed cell volume.

Laboratory examination. Thick smears were Giemsa stained in the field and examined at the Institut Pierre Richet in Bouaké to identify *Plasmodium* species. Asexual stages of *Plasmodium falciparum* were counted in the blood volume occupied by 200 leukocytes, and parasite density was calculated by assuming 8,000 leukocytes/μL of blood. Thick smears from each village were read by the same experienced technician, under the supervision of a parasitologist. The technicians were also compared on the same set of blood samples. Their rate of parasite detection and parasite density estimates did not differ significantly. Cross-check quality control was regularly done on a randomly selected sample representing 10% of all thick smears.

Data analysis. Demographic, clinical, parasitological, and attendance data were double entered independently in an Access database (version 7, 1995). Data were analyzed using Epilnfo (version 6, 1995), STATA® statistical package (StataCorp. 2001) and Egret (version 2, 1999) software programs. For each person, only one blood sample per monitoring period was considered for the analysis. When a pathological condition was detected, the blood sample taken during the clinical episode was retained for analysis. When many blood samples were available in an asymptomatic period, one of them was randomly selected for the analysis. The association between the parasite density and the occurrence of clinical episodes was tested using a random-effect logistic regression model, taking clinical status (pathological episode versus asymptomatic state) as the dependent variable, and parasite density and age as the independent variables. In this type of model, a random intercept variable is allowed to vary with subjects, and this random subject-specific intercept allows one to take into account the interdependence of the observations made on the same person. The independent variables and their interaction terms were tested and kept in the model when their effects were significant likelihood ratio statistic, $P < 0.05$). For each pathological period, the probability that it was caused by malaria was estimated by the attributable fraction calculated from the odd ratios associated with the estimated parasite density in the logistic model.[7] The pathological episodes were clinically defined by a high axillary temperature (≥ 37.5°C), a body hot to the touch, sweats, shivers, headaches, nausea or vomiting,[8] or by a history of fever during the 48 hours preceding the first day of ACD or, for infants, anorexia or any pathological condition described by the mother.[9] For individuals and given periods, the number of malaria attacks was estimated by the sum of probabilities that pathological episodes were due to malaria, depending on the parasite density. Malaria incidence density was calculated by the ratio of pathological episodes attributable to malaria divided by the child-days under survey during the monitoring periods. Clinical malaria incidence data were gathered by villages, surveys, and age groups (0–23, 24–59 months). The effect of the intervention was tested using the likelihood ratio statistic in a Poisson regression model taking into account the effect of the design (matching), survey, and age, with the estimated number of malaria attacks as dependent variable and the cumulative number of monitoring days as exposure variable. A goodness-of-fit test was used to check the adequacy of the model. Protective Efficacy was calculated as PE = (1 − Adjusted incidence density ratio) × 100.[10] The confidence interval for the clinical protective efficacy was calculated from the confidence interval of the adjusted incidence density ratio. Parasitological data were analyzed separately in terms of prevalence and density of *P. falciparum* asexual blood forms. A generalized estimating equation (GEE) approach was used for statistical analysis of repeated measures,[11] which can be used with normal distributions and discrete data. To take into account the interdependence of observations made on the same person, an exchangeable correlation structure was used in which the correlation be-

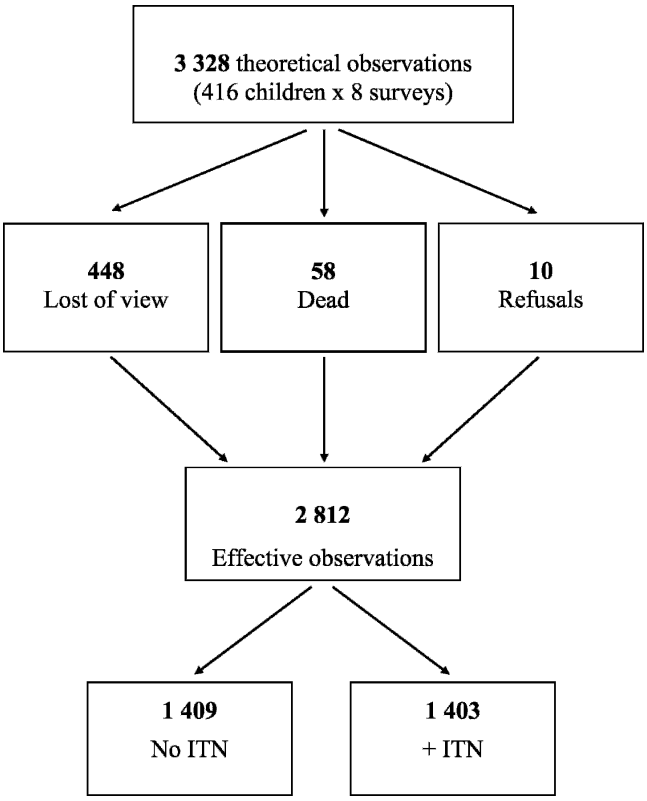

FIGURE 1. Participation in monitoring.

tween these observations made on one person at different times is assumed to be the same. The differences were tested by the Wald test and 95% confidence intervals were calculated. The prevalence of asymptomatic malaria infections was analyzed as a binomial response. The positive asymptomatic parasite density was log transformed and analyzed with a link function for a normally distributed response. The GEE approach allows some departure from the hypothesis about the distribution of the dependent variable and gives robust estimates of regression coefficients taking into account the interdependence of observations made on the same person. Comparisons between prevalences and between parasite densities and packed cell volumes were performed by chi-square test and analysis of variance taking into account the study design. Statistical tests were considered as significant when $P < 0.05$.

RESULTS

Population description. For one year, 426 children in 8 villages (216 in the 4 villages furnished with lambda-cyhalothrin–impregnated mosquito nets and 210 in the 4 untreated villages) were parasitologically and clinically monitored. Children born during the study were not included. Mean age was comparable (27 months) in the two groups. Sex ratio was well balanced: range of M/F sex ratio was 0.8 and 1.0, respectively, in the treated and control groups. Children's participation in clinical monitoring was high in both groups (Figure 1). A total of 16% were lost to follow up of which 2% had died. Each child in the control and treated groups was visited on average on 43 days (± 8) of the 56 active detection days scheduled. A total of 2,128 blood films were made with an average of 5 per child. The distribution of blood samples is shown in Figure 2. One fever episode where no thick smear was taken was excluded from the study. Each fever syndrome corresponds to one episode of illness in a child at one survey. Average coverage rate with ITNs was regularly checked and ranged from 76.7% to 84.0% in different villages.

Parasitological and hematological indexes of asymptomatic children observed by CSS. The mean annual rates of prevalence and parasite density in asymptomatic infections with *P. falciparum* observed in the baseline study in 1997[5] were comparable in the two groups of villages ($P > 0.30$). The rates of infection were about 80% and the densities averaged 143 to 199 asexual stages of *P. falciparum* per μL (Table 2). In 1999, after introduction of the ITNs, the observed rate of asymptomatic infections was higher in the untreated group than the treated one: 68.5 (95% CI, 64.9–72.1) versus 56.6%, (53.0–60.2) ($P < 0.001$). The parasite density was significantly higher in the untreated group: 69 (95% CI, 53–91) versus 29 (22–38) asexual *P. falciparum* stages per microliter ($P < 0.001$) (Table 3). The effect of the ITNs on anemia in the children aged 0 to 2 years was significantly positive in November 1999 (Table 3) with a mean hematocrit 2.0% higher in the treated group than in the control: 32.8 (95% CI, 31.9–33.7) versus 30.8%, (29.6–31.9) ($P = 0.007$).

Clinical malaria observed by ACD. We considered only one fever episode per patient per survey. In 1997, the frequency of clinical malaria attacks per child per year was comparable in the 2 groups of villages (2.3 versus 2.9, $P = 0.36$) (Table 2). In 1999, in the ITN villages, the incidence was significantly lower than in the control villages: 0.8 versus 1.8 clinical malaria attacks per child per year ($P < 0.001$). The protective efficacy of treated nets was 56% (95% CI, 25-75%). The impact was comparable in the two age classes

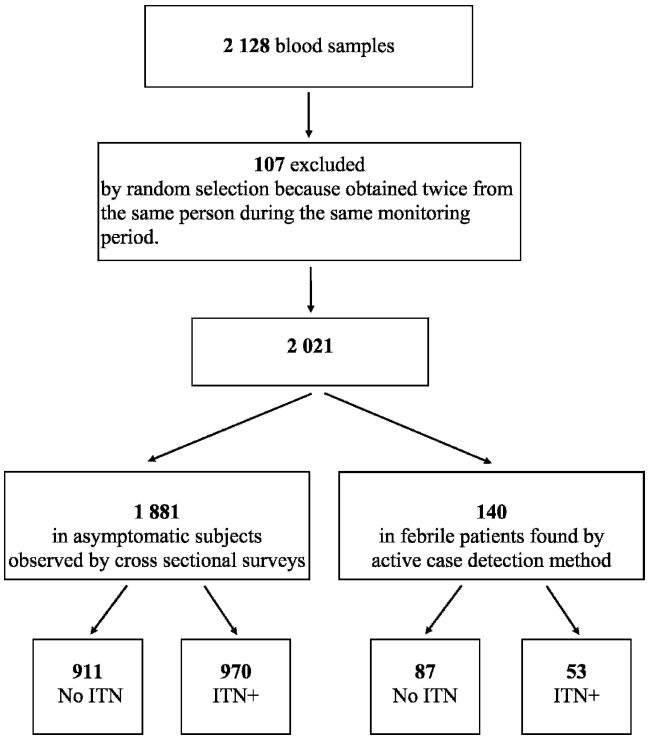

FIGURE 2. Distribution of blood samples according to clinical status and treatment by ITN.

TABLE 2
Malariometric indices and clinical malaria in the study groups in 1997 before implementation of ITN

Methodology	Parameters	Group of not treated villages in 1999		Group of treated villages in 1999		P
		n	Rate (95% CI)	*N*	Rate (95% CI)	
Cross-sectional surveys	Mean *P. falciparum* prevalence %	1,048	84.0 (77.7–90.3)	1,032	80.0 (72.8–87.2)	0.35
Cross-sectional surveys	Geometric mean parasite density (falciparum trophozoites/μL)	1,048	199 (122–325)	1,032	143 (83–246)	0.37
Active case detection	Incidence of clinical malaria episodes per child-year	1,209	2.3 (1.6–3.2)	1,136	2.9 (2.1–4.0)	0.36

(0–23 and 24–59 months) and the overall impact in reducing clinical malaria attacks was statistically significant ($P < 0.015$) (Table 4). Moreover, ITNs also tend to reduce the number of clinical malaria episodes per child during the year. In the control group, 12 (21%) out of 56 children suffered more than one malaria attack during the year, with 9 children having two episodes and 3 having 3 episodes each. In the treated group, only 3 out of 32 children suffered two malaria attacks during the year, and no child suffered 3 or more attacks.

DISCUSSION

Studies conducted during the past 20 years with insecticide-treated nets in various epidemiologic conditions have confirmed their effectiveness in reduction of the burden of malaria.[1] The extension of the range of resistance to pyrethroids in Côte d'Ivoire[2] and other countries in West Africa has called into question the continued effectiveness of treated nets and of the current strategy for malaria prevention based on promotion of the use of these nets. A trial in a village where *An. gambiae* is resistant to pyrethroids suggested that Olyset nets, which incorporate permethrin, are still effective in reducing by 50% the incidence of malaria attacks.[4] Various trials in experimental huts in Côte d'Ivoire have shown that insecticide-treated nets can still provide personal protection from biting as well as a high mortality of mosquitoes resistant to pyrethroids.[3,12,13] These data obtained in Phase II trials according to WHOPES protocol were the starting point of the current study, which corresponds to a Phase III WHOPES protocol.

In 1997, a study on the relationship of malaria to rice cultivation in 12 villages in the Department of Korhogo led to the selection of 2 groups of 4 villages,[5] in which the annual incidence of infection (80%) and of malaria morbidity (about 2.6 malaria episodes per child per year) were similar and where the annual entomological inoculation rate was around 113 infective bites per person (Dossou-Yovo J, unpublished data). The implementation of ITNs in 1999 led to the coverage in 4 villages of more than 80% of beds with nets treated with lambda-cyhalothrin (15 mg a.i./m^2). Re-impregnation was done after 6 months, and coverage was sustained at about 80%. Longitudinal surveys on representative samples of children aged less than 5 clearly showed that the children in the treated communities were healthier than in the untreated communities for all parameters measured. In terms of standard malaria indices, the prevalence of infection with *P. falciparum* appeared to be reduced by 12% in the netted community, compared with the untreated. It lies in the range of 5–12% based on numerous studies that compared treated nets with no nets in areas where the vectors are susceptible to pyrethroids.[10] It should be noted that in the current study, the prevalence of infection was recorded after ascertaining that the child was asymptomatic, whereas in most other studies the symptomatic/asymptomatic status of the child has not been taken into account. Regarding clinical status, the mean haematocrit was higher in the young children in the netted villages than in the controls. The difference found was comparable to that observed in other studies.[10] Furthermore, the treated nets reduced the risk of clinical malaria attacks by 56% (95% confidence limits 25 to 75) among the children. This protection factor was comparable to the range of 46-48%.[10] It was also similar to the 49% reported in the study of the clinical impact of nets treated with lambda-cyhalothrin in Sierra Leone where the vectors were susceptible to this insecticide.[14]

Although the reduction in clinical cases observed in Korhogo in the both groups of villages from January to May was natural, following reduction in transmission during the dry season (Dossou-Yovo J, unpublished data), and although the low malaria incidence continued throughout June and July 2000 because of the late start of the rainy season in that year, the percentage impact of the treated nets on clinical incidence remained constant during both the rainy and the dry seasons. The reduction in all investigated parasitological as well as clinical parameters was correlated with a sharp reduction in malaria transmission (26 infective bites per man per year in

TABLE 3
Effect of ITN on malariometric and haematological indices in asymptomatic children observed in 1999 during cross-sectional surveys in an area of pyrethroid resistant vectors.

Parameters	Age of children	Control group		Treated group		P
		N	Rate (95% CI)	N	Rate (95% CI)	
Mean *P. falciparum* prevalence %	0–4 yrs	911	68.5 (64.9–72.1)	970	56.6 (53.0–60.2)	<0.001
Geometric mean parasite density (*falciparum* asexual forms/μL)	0–4 yrs	911	69 (53–91)	970	29 (22–38)	<0.001
Packed cell volume %	0–2 yrs	72	30.8 (29.6–31.9)	83	32.8 (31.9–33.7)	0.007

TABLE 4

Protective efficacy of ITN on episodes of clinical malaria during the active case detection in 1999-2000 in an area of pyrethroid resistant vectors.

	Control group				Treated group			
	Obs.		Malaria fever		Obs.		Malaria fever	
Surveys	n	Person-day	Attributable fraction	Incidence per child-year (95% CI)	n	Person-day	Attributable fraction	Incidence per child-year (95% CI)
July–August 1999	185	1142	13.43	4.0 (2.0, 6.7)	192	1157	4.57	1.4 (0.4 (3.5)
Sept–Oct 1999	194	1221	8.63	2.6 (1.1, 4.9)	158	953	2.47	0.9 (0.1, 2.8)
Oct–Nov 1999	195	1174	5.61	1.7 (0.6, 3.8)	196	1229	2.18	0.6 (0.1, 2.1)
Nov–Dec 1999	169	1038	7.2	2.5 (1.0, 5.1)	187	1150	5.81	1.8 (0.6, 3.9)
Jan–Feb 2000	178	1091	2.33	0.8 (0.1, 2.4)	177	1110	1.65	0.5 (0.0, 2.1)
March–Apr 2000	128	817	1.08	0.5 (0.0, 2.5)	132	852	0.72	0.3 (0.0, 2.0)
Apr–May 2000	173	1053	2.5	0.9 (0.1, 2.8)	176	1101	1.03	0.3 (0.0, 1.8)
June–July 2000	187	1108	1.09	0.4 (0.0, 1.8)	185	1146	0.0	0.0 (0.0, 1.2)
Total	1409	8644	41.87	1.8 (1.3, 2.4)	1403	8698	18.43	0.8 (0.4, 1.2)
	Rate ratio				0.43 (0.25–0.74)			
	Protective efficacy (95% CI)				56% (25–75)			
	P				< 0.01			

netted villages versus 55 in the controls) (Dossou-Yovo J, unpublished data).

The parasitological and clinical parameters observed in 1999 were lower than those of 1997. Those reductions may be attributed to the health education that we have carried out, provision of medical supplies, and recruitment of medical auxiliaries without any specific antimalaria campaign.

One hypothesis that has been proposed to explain the success of pyrethroid-treated nets in areas with pyrethroid resistance is based on the fact that the irritability of resistant mosquitoes due to pyrethroids is less than that of susceptible insects.[12,15,16] Additional studies have confirmed that the resistant mosquitoes remained a longer time on treated surfaces.[17] Thus, the time of contact of the resistant insects with a pyrethroid deposit may be so long that enough insecticide would be absorbed to reach the relatively high dose required to kill them.

The current study carried out at the community level has demonstrated that the *An. gambiae* resistance due to the *kdr* gene did not have an influence on the efficacy of malaria vector control in Northern Côte d'Ivoire, when treated nets were used. If such results are encouraging in areas of *kdr* resistance, one does not know what could happen in areas of metabolic resistance. Indeed, involvement of metabolic resistance mechanisms have been described in *An. gambiae* in North Cameroon and *An. funestus* in Kwazulu Natal.[18,19] However, the efficacy of pyrethroid-treated nets has never been evaluated in these conditions. It should be done in the future. We may be reasonably optimistic but we have to continue searching for alternative methods or insecticides to counter insecticide resistance. Careful monitoring of resistance in malaria vectors and its impact on disease control is clearly a priority in Africa where most countries rely on vector control to reduce malaria transmission and morbidity.[20]

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REFERENCES

1. Lengeler C, De Savigny D, Cattani J, 1997. *Un mur contre la malaria: du nouveau dans la prévention des décès dus au paludisme*. Ottawa, Canada: CRDI/OMS, 300 pp.
2. Chandre F, Darriet F, Manguin S, Brengues C, Carnevale P, Guillet P, 1999. Pyrethroid cross-resistance spectrum among populations of *Anopheles gambiae* from Côte d'Ivoire. *J Am Mosq Control Assoc 15:* 53–59.
3. Darriet F, Guillet P, N'Guessan RN, Doannio JMC, Koffi AA, Konan LY, Carnevale P, 1999. The impact of permethrin and deltamethrin resistance in *Anopheles gambiae* s.s. on the efficacy of insecticide-treated mosquito nets. Documents WHO/VBC/99.1002, WHO/MAL/99.1088.
4. Henry M-C, Doannio JMC, Darriet F, Nzeyimana I, Carnevale P, 1999. Efficacité des moustiquaires pré-imprégnées de perméthrine *Olyset Net*® en zone de résistance des vecteurs aux pyréthrinoïdes. II. Evaluation parasitoclinique. *Med Trop 59:* 355–357.
5. Henry M-C, Rogier C, Nzeyimana I, Assi SB, Dossou-Yovo J, Audibert M, Mathonnat J, Keundjian A, Akodo E, Teuscher T, Carnevale P, 2003. Inland valley rice production systems and malaria infection and disease in the Savannah of Côte d'Ivoire. *Trop Med Int Health 8:* 449–458.
6. Smith PG, Morrow RH, (1996). *Field Trials of Health Interventions in Developing Countries—A Toolbox*. 2nd edition. London and Basingstoke: Macmillan Press Ltd, 362 pp.
7. Armstrong Schellenberg JRM, Smith T, Alonso PL, Hayes RJ, 1994. What is clinical malaria? Finding case definitions for field research in highly endemic areas. *Parasitol Today 10:* 439–442.
8. Rogier C, Ly AB, Tall A, Cisse B, Trape JF, 1999. *Plasmodium falciparum* clinical malaria in Dielmo, a holoendemic area in Senegal: no influence of acquired immunity on initial symp-

tomatology and severity of malaria attacks. *Am J Trop Med Hyg 60:* 410–420.
9. Smith T, Hurt N, Teuscher T, Tanner M, 1995. Is fever a good sign for clinical malaria in surveys of endemic communities? *Am J Trop Med Hyg 52:* 306–310.
10. Lengeler C, 1998. Insecticide treated nets and curtains for malaria control (Cochrane Review). In *The Cochrane Library*, Issue 3, Oxford: Update Software.
11. Zeger SL, Liang K, 1986. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics 42:* 121–130.
12. Darriet F, N'Guessan R, Koffi AA, Konan L, Doannio JM, Chandre F, Carnevale P, 2000. Impact de la résistance aux pyréthrinoïdes sur l'efficacité des moustiquaires imprégnées dans la prévention du paludisme: résultats des essais en cases expérimentales avec la delthaméthrine SC. *Bull Soc Pathol Exot 93:* 131–134.
13. Asidi AN, N'Guessan R, Hutchinson RA, Traore-Lamizana M, Carnevale P, Curtis CF, 2004. Experimental hut comparisons of nets treated with carbamate or pyrethroid insecticides, washed or unwashed, against pyrethroid-resistant mosquitoes. *Med Vet Entomol 18:* 134–140.
14. Marbiah NT, Petersen E, David K, Magbity E, Lines J, Bradley DJ, 1998. A controlled trial of lambda-cyhalothrin-impregnated bed nets and/or dapsone/pyrimethamione for malaria control in Sierra Leone. *Am J Trop Med Hyg 58:* 1–6.
15. Hodjati MH, Curtis CF, 1999. Effects of permethrin at different temperatures on pyrethroid-resistant and susceptible strains of Anopheles. *Med Vet Ent 13:* 415–422.
16. Chandre F, Darriet F, Duchon S, Finot L, Manguin S, Carnevale P, Guillet P, 2000. Modifications of pyrethroid effects associated with *kdr* mutation in *Anopheles gambiae. Med Vet Entomol 14:* 81–88.
17. Hougard JM, Duchon S, Darriet F, Zaim M, Rogier C, Guillet P, 2003. Comparative performances, under laboratory conditions, of seven pyrethroid insecticides used for impregnation of mosquito nets. *Bull Who 81:* 324–333.
18. Etang J, Manga L, Chandre F, Guillet P, Fondjo E, Mimpfoundi R, Toto JC, Fontenille D, 2003. Insecticide susceptibility status of *Anopheles gambiae* s.l. (Diptera: Culicidae) in the Republic of Cameroon. *J Med Entomol 40:* 491–497.
19. Hargreaves K, Koekemoer LL, Brooke BD, Hunt RH, Mthembu J, Coetzee M, 2000. *Anopheles funestus* resistant to pyrethroid insecticides in South Africa. *Med Vet Entomol 14:* 181–189.
20. WHO/SAMC, 1999. Intensive vector control activities begin throughout southern Africa. Southern Africa Malaria Control, Information for Action Leaflet. *Malaria Vector Update 1:* 1–2.