

Effects of insecticide-treated bednets during early infancy in an African area of intense malaria transmission: a randomized controlled trial

Olaf Müller,^a Corneille Traoré,^b Bocar Kouyaté,^b Yazoumé Yé,^b Claudia Frey,^a Boubacar Coulibaly,^b & Heiko Becher^a

Objective Insecticide-impregnated bednets and curtains have been shown by many studies to be effective against malaria. However, because of possible interactions with immunity development, treated bednets may cause no effect at all or even an increase in malaria morbidity and mortality in areas of high transmission. To clarify this issue, we did a randomized controlled trial to assess the long-term effects of bednet protection during early infancy.

Methods A total of 3387 neonates from 41 villages in rural Burkina Faso were individually randomized to receive either bednet protection from birth (group A) or from age 6 months (group B). Primary outcomes were all-cause mortality in all study children and incidence of falciparum malaria in a representative subsample of the study population.

Findings After a mean follow-up of 27 months, there were 129 deaths in group A and 128 deaths in group B (rate ratio (RR) 1.0 (95% confidence interval (CI): 0.78–1.27)). Falciparum malaria incidence was lower in group A than in group B, during early (0–5 months) and late infancy (6–12 months) (RR 3.1, 95% CI: 2.0–4.9; RR 1.3, 95% CI: 1.1–1.6) and rates of moderate to severe anaemia were significantly lower during late infancy (11.5% vs 23.3%, $P = 0.008$), but there were no differences between groups in these parameters in children older than 12 months.

Conclusion The findings from this study provide additional evidence for the efficacy of insecticide-treated nets in young children living in areas of intense malaria transmission.

Keywords Malaria/in infancy and childhood/prevention and control/transmission; Bedding and linens; Mosquito control; Randomized controlled trials; Burkina Faso (source: MeSH, NLM).

Mots clés Paludisme/chez le nourrisson et l'enfant/prévention et contrôle/transmission; Literie et linge; Lutte contre moustique; Essai clinique randomisé; Burkina Faso (source: MeSH, INSERM).

Palabras clave Paludismo/en la infancia y la niñez/prevenición y control/transmisión; Ropa de cama y ropa blanca; Control de mosquitos; Ensayos controlados aleatorios; Burkina Faso (fuente: DeCS, BIREME).

Arabic

Bulletin of the World Health Organization 2006;84:120-126.

Voir page 125 le résumé en français. En la página 125 figura un resumen en español.

Introduction

Insecticide-impregnated bednets and curtains have consistently been shown to be effective in reducing malaria morbidity and all-cause mortality in children in various malaria endemic areas.¹ However, in recent years, controversy has emerged about the long-term consequences of protecting young children with impregnated nets and curtains in areas where transmission intensity (i.e., the frequency with which a person is exposed to infective mosquito bites) is high. Because treated bednets and curtains prevent children from being bitten by mosquitos,

these interventions may affect acquisition of natural immunity to malaria. Thus, in areas of high transmission intensity, it is not clear whether treated bednets and curtains have a positive, a negative, or a neutral effect on the overall reduction of malaria morbidity and mortality.^{2–6}

The pattern of malaria morbidity, in particular the rate of severe anaemia and cerebral malaria, depends very much on transmission intensity.⁷ Concerns about increased mortality associated with bednets are based on some evidence that all-cause mortality is lower in regions

of high transmission intensity than in regions of medium transmission intensity.⁸ A possible explanation for this paradox is the assumption that if malaria transmission intensity is high, the age at which functional immunity is acquired may merge with the period of passively transferred immunity and physiological protection in the first few months of life.⁹ As insecticide-treated nets are now widely promoted in sub-Saharan Africa, millions of neonates are likely to have a much reduced rate of exposure to malaria during their first few months of life.¹⁰

^a Department of Tropical Hygiene and Public Health, Ruprecht-Karls-University Heidelberg, INF 324, 69124 Heidelberg, Germany. Correspondence to Dr Müller (email: olaf.mueller@urz.uni-heidelberg.de).

^b Centre de Recherche en Santé de Nouna, Nouna, Burkina Faso.

Ref. No. 05-023150

(Submitted: 11 April 2005 – Final revised version received: 19 September 2005 – Accepted: 20 September 2005)

To assess the benefits of insecticide-treated nets in areas of high malaria transmission intensity, we conducted a randomized controlled trial to compare all-cause mortality in children who had protection with treated nets from birth, with another group who had protection from age 6 months. We present study data after a mean follow-up period of 27 months.

Methods

Study area

The trial took place in the 41 villages of the rural research zone of the Centre de Recherche en Santé de Nouna (CRSN) in Nouna Health District, north-western Burkina Faso. The Nouna area is a dry orchard savannah, populated mainly by subsistence farmers of various ethnic groups. Childhood mortality is high, with significant variation between villages.¹¹ Malaria is holoendemic but highly seasonal in the study area; the rainy season lasts from July until October and the main transmission period is between July and December.¹² The number of infective bites per person per year — i.e., the annual Entomological Inoculation Rate (EIR) — varies between 100 and 1000 in the different study villages.¹³ Formal health services are limited to four rural health centres and the district hospital in Nouna town. As a consequence, malaria control relies mainly on home-based treatment with chloroquine, the official first-line treatment drug in Burkina Faso.¹⁴ Treated bednets and curtains were not available in the study area until the start of this trial, and about one quarter of young children were usually protected with untreated bednets in the study villages during rainy seasons.^{13, 15}

Participants

From June 2000, mothers of all neonates born in the 41 CRSN study villages were approached about inclusion of their child in the trial. Recruitment was done by three fieldworkers who were regularly informed about births by village informants during their twice-weekly visits to study villages. Village informants are volunteers selected by the community to facilitate the communication with the CRSN. Inclusion criteria were recruitment within 2 weeks of birth, and being a permanent resident in the study villages.

Study design

The study was designed as a randomized controlled effectiveness trial. All

neonates from the 41 study villages were individually randomized to receive either protection with treated bednets and curtains from birth until their fifth birthday (group A) or protection from age 6 months until their fifth birthday (group B).

Outcomes

Primary outcomes of the study were all-cause mortality in all study children and falciparum malaria incidence in a subsample of study children. Methods for subsample selection are outlined later in Procedures.

Secondary outcomes were clinical and parasitological variables in a subsample of study children; specifically, moderate-to-severe anaemia (erythrocyte volume fraction (haematocrit) $\leq 24\%$), palpable spleen, and other morbidity. We also recorded the existence of species-specific positive blood-films, species-specific malaria parasite densities, haematocrit values, and body weight during cross-sectional follow-up visits.

Sample size

When the trial began in 2000, data from the demographic surveillance system showed infant and childhood mortality rates in the study area were 67.4 and 27.9 per 1000, respectively.¹⁶ To be able to detect a 25% mortality difference between the intervention and control group in a given year with 80% power and at a significance level of 5%, we calculated that we would need to include 1450 children in each group. To allow for a 15% loss to follow-up, 1700 children per group would be needed. We assumed that there would be a mean of two falciparum malaria episodes per child per year; thus, a sample size of 210 children per group with a mean observation time of 3 years would enable us to detect a difference in falciparum malaria incidence of 11% with 80% power and at a significance level of 5%.

Randomization

Fieldworkers were provided with 20 closed opaque envelopes, containing equal numbers of intervention allocations. Randomizing envelopes were prepared by the study physician. A simple sign (+ for group A, – for group B) indicated the study allocation. Whenever the number of envelopes was reduced to 10, another 10 envelopes containing equal group numbers were added.

Procedures

Children were protected with green family-size treated bednets and curtains (PermaNet, Vestergaard Frandsen, Denmark). The choice of colour and size of the nets was based on the results from preceding qualitative interviews in the study villages (data not shown). Delivery of the nets was within 2 weeks of recruitment in group A and within 4 weeks of age 6 months in group B.

To measure levels of compliance with the treated-net intervention, we interviewed mothers of study participants and made direct night-time observations during cross-sectional surveys in all study children from 15 of the 41 study villages. Compliance was close to 100% during the rainy season and around 70% during the dry season, with no differences between group A and B. Details will be published elsewhere.

Standard WHO bioassays and deltamethrin concentration measurements were done on random samples of study nets at the beginning of the trial.¹⁷ Because first-generation PermaNets are known to have insufficient long-term effectiveness, all nets used during the trial were reimpregnated by the mothers under supervision of study staff with 0.4 g deltamethrine (K-O TAB, Aventis) before the beginning of the rainy season each year. Retreatment coverage was always above 95%, and the efficacy against *Anopheles* mosquitoes of reimpregnated bednets was shown to be good.¹⁸

Moreover, in early November 2002, we did morning pyrethrum spray catches in a random sample of 33 households with study children aged younger than 6 months' from three villages and noted differences in the mean number of mosquitos in rooms with insecticide-treated nets (0.9 (95% confidence interval (CI): 0.18–1.56)) compared with rooms without such nets (4.2 (95% CI: 1.12–7.22)). Finally, the condition of all participants' bednets and curtains was assessed by the field supervisors during the annual reimpregnation exercises. By mid 2003, 16% of study nets had a few (<4) holes, 8% had multiple (≥ 4) holes, 2% were torn, 1% were burnt, but only 0.1% were considered unusable; there were no differences in the condition of nets between group A and B.

Collection of all-cause mortality data took place through continuous information on all deaths of study children by the village informants.

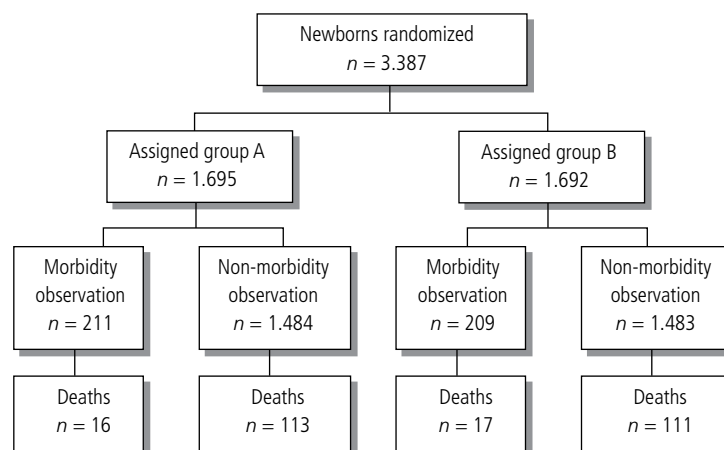
Morbidity was measured in subgroups of the first 70 children recruited from six study villages ($n = 420$). These children were seen every second day by village-based field staff, who systematically took their axillary temperature with an electronic thermometer (Digital Classic, Hartmann, Germany) and filled in a structured questionnaire in accordance with reports from parents about their child's symptoms and any treatment received.

Fieldworkers were trained to take finger-prick blood samples and to prepare thick and thin blood films in case of fever ($\geq 37.5^\circ\text{C}$) or a history of fever in the past 48 hours; They were also trained in provision of presumptive malaria treatment, as outlined in national guidelines. Fieldworkers were visited twice-weekly by the study nurse who checked their work, collected completed forms and blood slides, examined and treated sick children, and regularly reported to the study physician. Study children who were too ill to be treated at home were referred to governmental health services.

In addition to longitudinal morbidity surveillance, cross-sectional surveys were undertaken twice a year in all children in the morbidity surveillance subgroup. Surveys took place during low (January to June) and high (July to December) malaria transmission periods. Demographic data (age, sex, ethnicity), parasitological data (thin and thick blood films) and clinical data (medical history, symptoms, temperature, spleen size by Hackett score, bodyweight, haematocrit) were systematically collected during surveys.

Blood was taken by fingerprick, and haematocrit was measured with a portable microhaematocrit centrifuge (Compur Microspin, Bayer Diagnostics, Germany). Blood films were kept in closed slide boxes until they were transported to the CRSN laboratory in Nouna town. After Giemsa staining, all films were examined by two experienced laboratory technicians. Thick and thin blood films were analysed for the species-specific parasite density per μl by counting against 200 white blood cells and multiplying by 50 (we took into consideration the higher number of white blood cells in early infancy). Slides were declared negative if no parasites were found on the thick film after 15 minutes of searching. All lab technicians were unaware of group assignments. We randomly selected 10% of blood films

Fig. 1. Trial profile



WHO 05.162

for re-examination at the laboratory at the Heidelberg School of Tropical Medicine. Concordance was 100% for all slides with a parasite density above 5000 per μl blood. In slides with lower parasite densities, 7% of slides were false-negatives and 11% were false-positives.

Statistical analysis

Field data forms were checked manually by supervisors for completeness before independent computer entry (Microsoft ACCESS, version 97) at CRSN. All data were checked for range and consistency. Any differences were resolved by checking against original case records.

Analysis was by intention-to-treat. Primary and secondary outcomes were systematically compared for the total observation period as well as within three age groups (<6 months, 6–12 months, >12 months). A falciparum malaria episode was defined as fever (axillary temperature $\geq 37.5^\circ\text{C}$) accompanied by ≥ 5.000 *P. falciparum* parasites per μl (in the presence or absence of *P. malariae* or *P. ovale* parasites), with no other obvious cause for the fever. This case definition is similar to that used in a previous trial.¹³ We also analysed data using other common case definitions for mild and heavy malaria infections (i.e., fever plus any parasite count and fever plus a parasite count of 100.000/ μl or more, respectively).

Analysis of longitudinal data

The morbidity analysis was based on the subsample of 420 children from the six villages as described previously. We used Poisson regression analysis to model the group effect on number of episodes

of malaria or other morbidity. We calculated relative risks, 95% confidence intervals and *P*-values. To avoid inclusion of recrudescing malaria episodes, the individual observation time was defined as the time interval from first to last day of observation minus 20 days for each defined falciparum malaria episode. The log observation time was used as an offset term.

We compared all-cause mortality between the overall study groups as well as between the age-defined study subgroups using a Cox proportional hazards model. Extra Poisson variation was accounted for in confidence interval estimation. Vital status was assessed for all children until 31 December 2003.

Analysis of data from cross-sectional surveys

We compared clinical and parasitological variables in both groups with subgroup analysis by age group. We used χ^2 tests and, in case of small numbers, Fisher's exact test-to-test differences for categorical variables. *t*-tests were used to compare arithmetic means.

We used SAS software (version 9.1) for all analyses.

Ethics approval

This study was approved by the Ethics Committee of the Heidelberg University Medical School and the Ministry of Health in Burkina Faso. Before recruiting participants, we explained the trial in detail to all district authorities. Village meetings were held to explain the purpose, methods, benefits and risks of the study to the population. Oral informed consent was sought from the parents

or caretakers of study children. Treated bednets and curtains were paid for by the project, and all sick study children received appropriate counselling and treatment in the village free of charge, or they were referred to governmental health services.

Results

By the end of December 2002, 3387 neonates (1673 girls and 1714 boys) were enrolled in the study. 1695 were randomly assigned to protection from birth in group A and 1692 were assigned to protection from age 6 months in group B (Fig. 1). There were 888, 684, 711, 552 and 552 enrolments during the periods June–December 2000, January–June 2001, July–December 2001, January–June 2002 and July–December 2002, respectively; none of the parents or caretakers refused consent for their children to participate. Mean age at enrolment was 8.5 days. 1684 (99.4%) children in group A received their treated bednets within 2 weeks of birth; likewise, 1678 (99.2%) participants in group B received their bednets within 4 weeks of age 6 months. In accordance with the intention-to-treat analysis, we did not exclude any children from the study after randomization.

Table 1. Number of deaths and mortality by age and study group

Age	Group A			Group B		
	Person-years	Deaths	Mortality ^a	Person-years	Deaths	Mortality ^a
0–5 months	791	49	61.9	791	53	67.0
6–12 months	813	27	33.2	800	25	31.3
>12 months	2169	53	24.4	2142	50	23.3
Total	3773	129	34.2	3733	128	34.3

^a Deaths per thousand person-years.

Mortality

By 31 December 2003, mean follow-up in the study population was 26.6 months (range 0.1–42.3), corresponding to 7506 person years (PY), with no differences between group A (3773 PY) and group B (3733 PY). At 31 December 2003, 257 (7.6%) children had died (137 boys and 120 girls). There were 102 deaths in the 0–5 months age group, 52 in 6–12 month-olds, and 103 in participants aged more than 12 months with no differences between study groups (RR 1.0 (95% CI: 0.78–1.27) Fig. 1, Table 1).

Morbidity

Longitudinal data

By 31 December 2003, the 420 study children from the six morbidity observa-

tion villages had been followed up for a mean of 31.8 months (range 0.1–42.3), with no differences between study groups (32.0 months in group A and 31.6 months in group B). Specific information on study outcomes was available from 68% of observation days.

Overall, there were significantly fewer episodes of falciparum malaria in group A than in group B (881 vs 941; RR 1.11 (95% CI: 1.01–1.22); $P = 0.02$). This difference was attributed to significantly fewer episodes of falciparum malaria in group A than in group B during the period from age 0–5 months (26 vs 77; RR 3.11 (1.99–4.85); $P < 0.0001$) and from month 6–12 (152 vs 187; RR 1.33 (95% CI: 1.07–1.64); $P = 0.01$). We did not note any differences between groups in children older than 12 months (703 vs 677; RR 0.99 (95% CI: 0.89–1.10); $P = 0.85$). We obtained similar between-group differences when using the definition for mild malaria, but we noted no differences when using the definition for heavy infections (Table 2).

There were no differences between groups A and B in the carer-reported prevalence of fever, lack of appetite, vomiting, diarrhoea and cough. However, in young infants (0–5 months), fever was much less prevalent in group A than in group B (689 vs 820 fever days, RR 1.23 (95% CI: 1.11–1.35); $P < 0.0001$).

Cross-sectional survey data

We undertook six cross-sectional surveys on the 420 study children from the six morbidity observation villages (in March 2001, November 2001, March 2002, October 2002, March 2003 and November 2003).

In all, 290 children (152 in group A, 138 in group B) aged 0–5 months, 273 children (137 in group A, 136 in group B) aged 6–12 months, and 406 children (205 in group A, 201 in group B) older than 12 months were examined.

Table 2. Number of falciparum malaria episodes by age and study group^a

Malaria definition	Group A (no. of episodes)	Group B (no. of episodes)	Rate ratio ^a	95% CI ^b	P-value ^c
Mild infection^d					
0–5 months	93	166	1.90	1.47–2.45	<.0001
6–12 months	264	302	1.25	1.06–1.47	0.01
>12 months	943	941	1.03	0.94–1.13	0.50
Total	1300	1409	1.14	1.06–1.23	0.0005
Study definition^e					
0–5 months	26	77	3.11	1.99–4.85	<.0001
6–12 months	152	187	1.33	1.07–1.64	0.01
>12 months	703	677	0.99	0.89–1.10	0.85
Total	881	941	1.11	1.01–1.22	0.02
Heavy infection^f					
0–5 months	1	2	2.04	0.19–22.5	0.56
6–12 months	7	8	1.19	0.43–3.29	0.73
>12 months	30	21	0.72	0.41–1.26	0.25
Total	38	31	0.84	0.52–1.35	0.46

^a CI = confidence interval.

^b Observation time was 122 266 child days for group A and 117 398 child days for group B; for analysis of incidence of falciparum malaria, children were removed from numerator and denominator for 20 days after malaria episodes.

^c Calculated with Poisson regression model.

^d Fever and ≥ 1 parasite.

^e Fever and ≥ 5000 parasites.

^f Fever and $\geq 100\,000$ parasites.

There were no between-group differences in bodyweight, fever or malaria prevalence. Hackett scores, prevalence of *P. falciparum* and anaemia, and mean *P. falciparum* parasite densities were significantly lower, while haematocrit values were significantly higher in group A than in group B in children aged 6–12 months. However, there were no differences between groups in the 0–5 month age group or in children older than 12 months, with the exception of lower *P. falciparum* prevalence rates in group A than in group B in older children (Table 3).

Discussion

We found no evidence for a difference in all-cause mortality during follow-up of young children being protected (group A) compared to those not being protected (group B) with insecticide-treated nets during early infancy (0–5 months) in an area of intense malaria transmission in Burkina Faso.

Our data do not support findings from an ecological study on the frequency of severe childhood malaria as a proxy indicator for malaria mortality in sub-Saharan hospitals that had suggested that insecticide-treated nets were dangerous when used to protect young infants living in hyperendemic or holoendemic malaria areas.⁷

Instead, our data support results from extended follow-ups of three large cluster-randomized trials of treated nets in sub-Saharan areas of intense malaria transmission.^{19–21} These trials were not, however, specifically designed to address the issue of possible delayed or rebound mortality.

Moreover, that infant mortality in the study cohort was 30% lower than that recorded by the demographic surveillance system, and that *P. falciparum* prevalence was 25% lower in our study group than in previous studies of the same population before the intervention (data not shown) provides some evidence about the overall efficacy of treated nets in real-life conditions.¹ However, our mortality data can not be fully compared with data from the Nouna demographic surveillance system because different methods were used for data collection.¹⁶

The second main finding from this study is an overall significantly lower falciparum malaria morbidity in group A than in group B, which supports the

Table 3. Clinical and parasitological data from cross-sectional surveys

Symptoms and signs by age group	Group A	Group B	P-value
0–5 months			
Mean bodyweight (kg) (SD) ^a	5.60 (1.45)	5.63 (1.28)	0.68
Spleen enlargement ^b	39/163 (24%)	36/146 (25%)	0.88
Fever	3/158 (2%)	5/140 (4%)	0.48
Malaria (%)	1/146 (1%)	0/129 (0%)	1.0
Mean haematocrit (SD)	33.0 (5.8)	32.2 (5.2)	0.68
Moderate-to-severe anaemia	10/156 (6.4%)	11/137 (8.0%)	0.59
<i>P. falciparum</i> parasitaemia $\geq 1/\mu\text{l}$	65/146 (45%)	67/129 (52%)	0.22
Mean density <i>P. falciparum</i> (SD)	558 (3007)	599 (1559)	0.11
6–12 months			
Mean bodyweight (kg) (SD)	7.40 (1.09)	7.25 (1.03)	0.24
Spleen enlargement	51/150 (34%)	91/170 (54%)	<0.001
Fever	5/140 (4%)	5/160 (3%)	1.0
Malaria	1/134 (1%)	2/158 (1%)	1.0
Mean haematocrit (SD)	29.9 (4.2)	28.4 (4.4)	0.0025
Moderate-to-severe anaemia	16/139 (11.5%)	37/159 (23.3%)	0.0081
<i>P. falciparum</i> parasitaemia $\geq 1/\mu\text{l}$	74/134 (55%)	111/158 (70%)	0.0079
Mean density <i>P. falciparum</i> (SD)	1647 (8797)	2225 (3784)	<0.0001
>12 months			
Mean bodyweight (kg) (SD)	9.78 (1.33)	9.70 (1.24)	0.30
Spleen enlargement ^b	224/756 (30%)	225/723 (31%)	0.53
Fever	43/676 (6%)	49/657 (7%)	0.43
Malaria	19/666 (3%)	19/640 (3%)	0.90
Mean haematocrit (SD)	29.4 (2.8)	29.1 (2.8)	0.25
Moderate-to-severe anaemia	93/669 (13.9%)	102/654 (15.6%)	0.38
<i>P. falciparum</i> parasitaemia $\geq 1/\mu\text{l}$	342/666 (51%)	370/640 (58%)	0.019
Mean density <i>P. falciparum</i> (SD)	4053 (8946)	3540 (6001)	0.22

^a SD = standard deviation.

^b Hackett score >1.

efficacy of treated bednets in the prevention of malaria, particularly in young children in sub-Saharan Africa.¹ Rates of falciparum malaria and anaemia were lower in group A than in group B during the first year of life, but there were no differences in older children after a follow-up period of up to 3.5 years. Differences in malaria prevalence were significant in the 0–5 months and 6–12 months age groups, while other malaria variables showed significant differences only in the 6–12 months age group. Differences in malaria prevalence during early infancy are clearly explained by the fact that children in group B were not protected by treated nets during their first 6 months of life. The differences in malaria morbidity noted during late infancy (6–12 months) might be explained by a better development of the immune system under conditions of low-to-moderate transmission intensity. Similar findings are reported from studies on the effects of intermittent preventive treatment for malaria in infants.²² However, our findings differ from observations of rebound morbidity associated with

malaria chemotherapy in young children in sub-Saharan Africa.²³ This difference could be explained by the fact that the treated nets lower, but do not completely avoid, malaria transmission unlike the more complete protection associated with chemoprophylaxis. The exposure to malaria parasites of children protected with treated nets in hyperendemic or holoendemic areas seems to be sufficient for the development of protective immunity.

To our knowledge this is the first major trial of insecticide-treated nets that uses individual randomization rather than a cluster-randomized trial design. Because of the design of our trial and the coexistence of group A and group B children in all study villages, differences in malaria exposure during the first 6 months of life have to be attributed to the protective effects of the bednet itself, together with the repellent effect of the insecticide, and not to a possible mass effect of bednet use.^{24–26} However, that such a mass effect was not seen in all areas of sub-Saharan Africa where major trials of treated nets have been implemented must be considered.²⁷ In our study, a

major mass effect is not likely to have occurred given the incomplete coverage with insecticide-treated nets, our finding of fewer mosquitoes in rooms with treated nets compared with those without nets, and the demonstrated effects of the intervention on malaria morbidity.

This study was a large randomized controlled trial in a representative population of young African children, with sufficient power to detect mortality and morbidity differences associated with the intervention. The insecticide-treated nets were shown to be effective against the local vector, compliance with the intervention was shown to be good, case detection has been intense and individual randomization made systematic errors unlikely. Although the confidence inter-

val for the mortality comparison between groups shows a difference that, in theory, is of public health importance, there was no trend towards increasing mortality in older study children. Follow-up for all-cause mortality is planned through the existing demographic surveillance system until all study children have reached their 5th birthday. However, the largest effects of the intervention would have been expected in early childhood; this assumption is supported by malaria parasite prevalence rates having remained above 50%, despite good compliance with the net intervention in the young children of this study cohort.

Our findings provide additional evidence for the efficacy of insecticide-treated bednets and curtains in areas

of intense malaria transmission. There should be no further delay of large-scale implementation of insecticide-treated bednets in sub-Saharan Africa. ■

Acknowledgements

We are grateful to all families of study children. We thank Justin Tiendrebeogo for dedicated field work supervision, Gabriele Stieglbauer for careful data management and programming and Ulrich Mansmann for statistical support.

Funding: The study was supported by the Sonderforschungsbereich 544 (Control of Tropical Infectious Diseases) at the Ruprecht-Karls-University Heidelberg.

Competing interests: none declared.

Résumé

Effets de l'utilisation de moustiquaires de lit imprégnées d'insecticide au cours des premiers mois de la vie dans une zone à transmission palustre intense en Afrique : essai contrôlé randomisé

Objectif De nombreuses études ont démontré l'efficacité contre le paludisme des moustiquaires de lit et des rideaux imprégnés d'insecticide. Toutefois, en raison d'interactions possibles avec le développement de l'immunité, les moustiquaires de lit peuvent n'avoir aucun effet réducteur sur la morbidité et la mortalité palustres dans les zones à forte transmission ou même les aggraver. Pour éclaircir cette question, on a donc réalisé un essai contrôlé randomisé visant à évaluer les effets à long terme de la protection assurée par les moustiquaires de lit au cours des premiers mois de la vie.

Méthodes Au total, 3387 nourrissons de 41 villages de zones rurales du Burkina Faso ont été tirés au sort individuellement pour être protégés par une moustiquaire de lit soit dès la naissance (groupe A) soit à partir de l'âge de 6 mois (groupe B). Les résultats préliminaires concernaient la mortalité toutes causes confondues pour l'ensemble des enfants inclus dans l'étude et l'incidence du

paludisme à falciparum dans un sous-échantillon représentatif de la population étudiée.

Résultats Après un suivi de 27 mois en moyenne, on a enregistré 129 décès dans le groupe A et 128 décès dans le groupe B, soit un rapport de 1,0 (intervalle de confiance 95 % (IC) : 0,78-1,27). L'incidence du paludisme à falciparum était plus faible dans le groupe A que dans le groupe B, aussi bien entre 0 et 5 mois qu'entre 6 et 12 mois (RR 3,1, IC 95 % : 2,0-4,9 ; RR 1,3, IC 95 % : 1-1,6) et les taux d'anémie modérée à grave étaient sensiblement plus faibles entre 6 et 12 mois (11,5 % contre 23,3 %, $p = 0,008$), mais aucune différence n'a été constatée entre les groupes pour ces paramètres chez les enfants de plus de 12 mois.

Conclusion Les résultats de l'étude apportent une preuve supplémentaire de l'efficacité des moustiquaires imprégnées d'insecticide dans la protection du jeune enfant vivant dans une zone à transmission palustre intense.

Resumen

Efecto de los mosquiteros tratados con insecticida durante la lactancia temprana en una zona de África de alta transmisión de malaria: ensayo controlado aleatorizado

Objetivo Numerosos estudios han demostrado que los mosquiteros y cortinas tratados con insecticida son eficaces contra la malaria. Sin embargo, debido a una posible interacción con el desarrollo de inmunidad, los mosquiteros tratados pueden no tener efecto alguno o incluso aumentar la morbilidad y la mortalidad por malaria en las zonas de alta transmisión de la enfermedad. A fin de aclarar este interrogante, realizamos un ensayo controlado aleatorizado para evaluar los efectos a largo plazo de la protección con mosquiteros durante la lactancia temprana.

Métodos Se distribuyó aleatoriamente a 3387 recién nacidos de 41 aldeas de la Burkina Faso rural para que recibieran protección mediante mosquiteros a partir ya fuese del nacimiento (grupo A) o de los 6 meses de edad (grupo B). Los resultados primarios fueron la mortalidad por todas las causas en todos los niños estudiados, y la incidencia de malaria por falciparum en una submuestra representativa de la población estudiada.

Resultados Después de un seguimiento medio de 27 meses, se contabilizaron 129 defunciones en el grupo A y 128 defunciones en el Grupo B (razón de tasas (RR): 1,0 (intervalo de confianza (IC) del 95%: 0,78-1,27)). La incidencia de malaria por falciparum fue menor en el Grupo A que en el Grupo B, durante la lactancia temprana (0-5 meses) y durante la lactancia tardía (6-12 meses) (RR: 3,1, IC95%: 2,0-4,9; RR: 1,3, IC95%: 1,1-1,6), y las tasas de anemia moderada o grave fueron significativamente inferiores durante la lactancia tardía (11,5% frente a 23,3%, $P = 0,008$), pero las variables consideradas no difirieron entre los grupos en los niños mayores de 12 meses.

Conclusión Los resultados de este estudio aportan nuevos datos indicativos de la eficacia de los mosquiteros tratados con insecticida en los niños pequeños que viven en zonas de alta transmisión de malaria.

Arabic

References

- Lengeler C. Insecticide treated bed nets and curtains for preventing malaria. *Cochrane Database Syst Rev* 2004;4: CD000363.
- Snow RW, Marsh K. Will reducing *P. falciparum* transmission alter malaria mortality among African children? *Parasitol Today* 1995;11:188-90.
- Trape JF, Rogier C. Combating malaria morbidity and mortality by reducing transmission. *Parasitol Today* 1996;12:236-40.
- Lengeler C, Smith TA, Armstrong-Schellenberg J. Focus on the effect of bednets on malaria morbidity and mortality. *Parasitol Today* 1997;13:123-24.
- Marsh K, Snow RW. Malaria transmission and morbidity. *Parassitologia* 1999;41:241-6.
- Smith TA, Leuenberger R, Lengeler C. Child mortality and malaria transmission intensity in Africa. *Parasitol Today* 2001;17:145-9.
- Modiano D, Sirima BS, Sawadogo A, Sanou I, Pare J, Konate A, et al. Severe malaria in Burkina Faso: influence of age and transmission level on clinical presentation. *Am J Trop Med Hyg* 1998;59:539-42.
- Snow RW, Omumbo JA, Lowe B, Molyneux CS, Obiero JO, Palmer A, et al. Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa. *Lancet* 1997;349:1650-4.
- Snow RW, Nahlen B, Palmer A, Donnelly CA, Gupta S, Marsh K. Risk of severe malaria among African infants: direct evidence of clinical protection during early infancy. *J Infect Dis* 1998;177:819-22.
- Müller O, Jahn A. Expanding insecticide-treated mosquito net coverage in Africa: tradeoffs between public and commercial strategies. *Trop Med Int Health* 2003;8:853-6.
- Sankoh OA, Ye Y, Sauerborn R, Müller O, Becher H. Clustering of childhood mortality in rural Burkina Faso. *Int J Epidemiology* 2001;30:485-92.
- Müller O, Becher H, van Zweenen AB, Ye Y, Diallo DA, Konate AT, et al. Effect of zinc supplementation on malaria morbidity among West African children: a randomized double-blind placebo-controlled trial. *BMJ* 2001;322:1567-72.
- Traoré C. Epidemiology of malaria in a holoendemic area of rural Burkina Faso. [PhD thesis]. Heidelberg: Ruprecht-Karls-University; 2003.
- Müller O, Traoré C, Kouyaté B, Becher H. Malaria morbidity, treatment seeking behaviour, and mortality in a cohort of young children in rural Burkina Faso. *Trop Med Int Health* 2003;8:290-6.
- Okrah J, Traoré C, Palé A, Sommerfeld J, Müller O. Community factors associated with malaria prevention by mosquito nets: an exploratory study in rural Burkina Faso. *Trop Med Int Health* 2002;7:240-8.
- Kynast-Wolf G, Stieglbauer G, Kouyaté B, Yé Y, Gbangou A, Sauerborn R, et al. Mortality patterns, 1993-2001, in sub-Saharan Africa: results from a demographic surveillance system in Nouna, Burkina Faso. *SFB Discussion Paper Series* 2003: Available from: <http://www.hyg.uni-heidelberg.de/SFB544/pub.html>. Accessed 16 November 2005.
- Müller O, Ido K, Traoré C. Evaluation of a prototype long-lasting insecticide-treated mosquito net under field conditions in rural Burkina Faso. *Trans Roy Soc Trop Med Hyg* 2002;96:483-4.
- Müller O, Frey C, Traoré C, Kouyaté B. Retreatment of long-lasting ITNs under field conditions in rural Burkina Faso. *J Trop Ped* 2004;50:380-1.
- Binka FN, Hodgson A, Adjuik M, Smith T. Mortality in a seven-and-a-half-year follow-up of a trial of insecticide-treated mosquito nets in Ghana. *Trans Roy Soc Trop Med Hyg* 2002;96:597-9.
- Diallo DA, Cousens SN, Cuzin-Quattara N, Nebie I, Ilboudo-Sanogo E, Esposito F. Child mortality in a West African population protected with insecticide-treated curtains for a period of up to 6 years. *Bull World Health Organ* 2004;82:85-91.
- Lindblade KA, Eisele TP, Gimnig JE, Alaii JA, Odhiambo F, ter Kuile FO, et al. Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide-treated bednets. *JAMA* 2004;291:2571-80.
- Schellenberg D, Menendez C, Aponte JJ, Kahigwa E, Tanner M, Mshinda H, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. *Lancet* 2005;365:1481-3.
- Greenwood BM, David PH, Otoo-Forbes LN, Allen SJ, Alonso PL, Armstrong Schellenberg JR, et al. Mortality and morbidity from malaria after stopping malaria chemoprophylaxis. *Trans Roy Soc Trop Med Hyg* 1995;89:629-33.
- Binka FN, Indome F, Smith T. Impact of spacial distribution of permethrin-impregnated bed nets on child mortality in rural northern Ghana. *Am J Trop Med Hyg* 1998;59:80-5.
- Howard S, Omumbo J, Nevill C, Some ES, Donnally CA, Snow RW. Evidence for a mass community effect of insecticide treated bed nets on the incidence of malaria on the Kenyan coast. *Trans R Soc Trop Med Hyg* 2000;94:357-60.
- Hawley WA, Phillips-Howard PA, ter Kuile FO, Terlouw DJ, Vulule JM, Ombok M, et al. Community-wide effects of permethrin-treated bednets on child mortality and malaria morbidity in western Kenya. *Am J Trop Med Hyg* 2003;68 Suppl:121-7.
- Lindsay SW, Alonso PL, Armstrong Schellenberg JRM, Armstrong Schellenberg JR, Greenwood BM, Mills A. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. Impact of permethrin-impregnated bed nets on malaria vectors. *Trans R Soc Trop Med Hyg* 1993;87 Suppl:45-51.