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# Long-term effects of malaria prevention with insecticide-treated mosquito nets on morbidity and mortality in African children: randomised controlled trial

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**Abstract**

OBJECTIVE The objective is to investigate the effect of malaria control with insecticide-treated mosquito nets (ITNs) regarding possible higher mortality in children protected during early infancy, due to interference with immunity development, and to assess long-term effects on malaria prevalence and morbidity.

METHODS Between 2000 and 2002, a birth cohort was enrolled in 41 villages of a malaria holoendemic area in north-western Burkina Faso. All neonates ($n$ = 3387) were individually randomised to ITN protection from birth (group A) *vs*. ITN protection from age 6 months (group B). Primary outcome was all-cause mortality. In 2009, a survey took place in six sentinel villages, and in 2010, a census was conducted in all study villages.

RESULTS After a median follow-up time of 8.3 years, 443/3387 (13.1%) children had migrated out of the area and 484/2944 (16.4%) had died, mostly at home. Long-term compliance with ITN protection was good. There were no differences in mortality between study groups (248 deaths in group A, 236 deaths in group B; rate ratio 1.05, 95% CI: 0.889–1.237, $P$ = 0.574). The survey conducted briefly after the rainy season in 2009 showed that more than 80% of study children carried asexual malaria parasites and up to 20% had clinical malaria.

CONCLUSION Insecticide-treated mosquito net protection in early infancy is not a risk factor for mortality. Individual ITN protection does not sufficiently reduce malaria prevalence in high-transmission areas. Achieving universal ITN coverage remains a major challenge for malaria prevention in Africa.

**keywords** Africa, malaria control, children, insecticide-treated mosquito nets, immunity, mortality, morbidity, child health, birth cohort, Burkina Faso

## Introduction

Malaria is a major cause of global morbidity and mortality, with most of the burden being in sub-Saharan Africa (SSA) (Greenwood *et al.* 2005; Breman *et al.* 2006). Malaria control has received increasing attention in recent years, and the international *Roll Back Malaria* (RBM) partnership now considers insecticide-treated mosquito nets (ITNs) as a key tool in the fight against the disease (RBM_WHO 2008). This decision is supported by the recent findings from a large multi-country analysis which provided further evidence for ITNs that is also being effective under programme conditions (Lim *et al.* 2011). Consequently and massively supported by various *Global Health Initiatives*, the ITN intervention is to be rolled out continuously in SSA on a large scale. However, ITN coverage and compliance with the intervention remain major challenges for control programmes (Korenromp *et al.* 2003; Baume & Marin 2007; Noor *et al.* 2009).

A number of years ago, controversy emerged on the possible negative long-term effects of ITN protection in malaria high transmission areas of SSA. On the basis of the

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findings from a large ecological study, ITN protection in early infancy was considered as potentially leading to excess mortality in older children due to interference with immunity development (Snow *et al.* 1997). Long-term follow-up of children enrolled in African ITN studies, which were all cluster-randomised controlled trials with a longer unprotected period in the comparison group in early childhood, has so far not supported such a hypothesis (Binka *et al.* 2002; Diallo *et al.* 2004; Lindblade *et al.* 2004). The underlying hypothesis was first specifically addressed by an early follow-up of the study presented here, which is a birth cohort in which individual children were randomised to earlier or later ITN. Short-term (2 years) follow-up of children from this trial has not provided evidence for the occurrence of excess mortality (Mueller *et al.* 2006). However, ITN programmes may convert high transmission into low transmission areas with a different pattern of severe malaria and consequently mortality (Snow & Marsh 1995; Modiano *et al.* 1998; Snow *et al.* 1999). Reduced transmission intensity may in particular increase the mean age of severe malaria manifestations, with older children being more likely to develop cerebral malaria (Roca-Feltrer *et al.* 2010). Thus, long-term follow-up is required to fully address this question.

Another important aspect of the ITN intervention is the question about how much transmission and morbidity reduction can be achieved under real life conditions in rural SSA. Programmes rarely achieve full coverage, and compliance with the ITN intervention is often suboptimal due to culturally influenced risk-perceptions and socio-economic realities (Lengeler & Snow 1996; Frey *et al.* 2006; Githinji *et al.* 2010; Vanden Eng *et al.* 2010). It thus remains to be determined which degree of malaria burden reduction can be achieved with ITNs under the scenario of high malaria transmission intensity, low education levels and prevailing poverty in most of SSA (Mueller 2011).

This article presents data on the long-term morbidity and mortality effects of ITN malaria prevention in a large cohort of children from a malaria holoendemic area of Burkina Faso.

## Methods

### Study area

The study took place in 41 villages of the research zone of the *Centre de Recherche en Santé de Nouna* (CRSN) in north-western Burkina Faso. The area, which is populated mainly by subsistence farmers of different ethnicities, was holoendemic for malaria during the time of enrollment of study children (Mueller *et al.* 2001). Most of the malaria cases and related mortality occur during or briefly after the rainy season which lasts from June until October (Hammer *et al.* 2006; Becher *et al.* 2008). The rainy season is followed by a relatively cold dry season from November to February and a hot dry season from March to May. The study area is served by 13 peripheral health centres and the district hospital in Nouna town (Kouyaté *et al.* 2007). Access to malaria prevention and treatment has been rather limited in recent years, with about one quarter of young children having been reported to use untreated nets during the rainy season before the beginning of the trial, with 28% of households possessing ITNs in 2007 and with only 15% of children with malaria having received artemisinin-based combination therapy (ACT) within 24 h in 2010 (Traoré 2004; Kouyaté *et al.* 2007; Mueller *et al.* 2008; Tipke *et al.* 2009; De Allegri *et al.* 2011).

### Study design and procedures

The study design and initial study procedures have been published before (Mueller *et al.* 2006). The main objective of the study was to test if protection of young infants with ITNs in areas of high malaria transmission would be associated with differences in all-cause mortality. In brief, a birth cohort of $N = 3387$ children was enrolled (NCT00355225) between June 2000 and December 2002 from 41 villages of the rural CRSN study area, with children individually randomised to two interventions: ITN protection from birth onwards (group A, $N_A = 1695$) and ITN protection from month 6 onwards (group B, $N_B = 1692$). Parents and caretakers were advised to protect the children consistently throughout their childhood with the ITN. Primary outcomes of the study were all-cause mortality (all children) and malaria incidence (sub-sample of $N_S = 420$ children in six sentinel villages). Secondary outcomes were other clinical and parasitological parameters from the sub-sample of study children. Over the first 3.5 years, data were collected through active longitudinal surveillance (all-cause mortality, malaria incidence) and through bi-annual cross-sectional surveys (e.g. malaria prevalence, malaria parasitaemia, anaemia).

The children were protected with 100 denier green family-size first-generation ITNs (PermaNet, Vestergaard Frandsen), which were annually re-impregnated by CRSN staff during the first years of the study, whereas later re-impregnation services were offered by the district authorities with support from the CRSN. Re-impregnation coverage was high during the first years of the intervention, and the entomological efficacy was proven (Mueller *et al.* 2004, 2006). Good compliance of study children with ITN use during the first years of the intervention was demonstrated (Frey *et al.* 2006). This is supported

by observations on a subsample of 210 study children from three sentinel villages, who were followed up for compliance during their first year of life (unpublished data).

### First follow-up study

The first assessment of mortality in study children was based on data collection through existing village informants and specific CRSN staff after a mean follow-up period of 27 months. During this period, 98% of study children were reported to use ITNs during the rainy season (Frey *et al.* 2006). At that time, 129 deaths had occurred in group A and 128 deaths in group B (Mueller *et al.* 2006). At the same time, malaria incidence was shown to be significantly lower in group A compared with group B children in the first year of life, but there were no differences in year 2 and 3 (Mueller *et al.* 2006).

### Second follow-up study

The second assessment of mortality in study children was based on data collection from a complete census of the original study population in the 41 study villages. This census took place in April/May 2010 through a specific CRSN study team, which addressed all the original households of study cohort members using a standard questionnaire. Questions were asked about vital and migration status of respective study children. When the child was still present in the village, mosquito net possession and pattern of use, ITN treatment status, ITN type (verified by observation) and clinical history were further asked. Most interviews (89%) were conducted with the mother or father of the study child.

In addition, a cross-sectional survey was conducted on the original study children of the six sentinel villages in November 2009. Systematic collection of demographic, parasitological and clinical data as well as mosquito net use took place using standard CRSN procedures (Mueller *et al.* 2001, 2006). Laboratory technicians and field staff were kept blind regarding group allocation of study children. All reported mosquito nets were verified by observation.

### Statistical analysis

Binary exposure variables between groups were compared with chi-square tests. Mortality rates by group and by age were calculated using exact person-years of observation. For survival analysis, Cox regression was used with group and gender as co-variables. A possible time-dependent effect of treatment group was also investigated using Poisson regression analysis in which the rate ratios between groups by age were modelled. SAS 9·2 software (SAS Institute Inc., Cary, NC, USA.) was used for statistical analysis.

Migration date was used as censoring time in survival analysis. For $n$ = 328 children, this date was unknown and therefore a computed date was used equal to the mean between the last known date of presence and the end-of follow-up date.

### Ethical aspects

The study was approved by the Ethics Committee of the Heidelberg University Medical School and the Ministry of Health in Burkina Faso. Community consent was achieved through negotiations with the district health authorities and local population in the 41 villages. Individual oral consent from the parents and care takers of study children was a prerequisite for participation. ITNs were provided free of charge, and all sick children were treated appropriately in the field or referred to the next higher health service level when necessary.

## Results

A total of 3387 neonates (1673 girls and 1714 boys) were enrolled into the study (1695 group A, 1692 group B) (Mueller *et al.* 2006). During the April/May 2010 census, information on all households of study children was successfully collected. A total of 443/3387 (13.1%) study children had migrated outside the study area, and 484/2944 (16.4%) of study children had died (Figure 1).

### ITN characteristics

Table 1 shows the ITN characteristics of study children in the year 2010 by group. Overall, 2234/2460 (90.8%) study children owned a mosquito net, 80% of these still being the original study ITN. Only a few owned socially marketed ITNs (Serena) or other nets. More than half of the mosquito nets used in the study population had been re-treated during the last 2 years. Reported regular ITN protection in study children was around 90% during the rainy season and the cold dry season, but decreased to one third during the hot dry season. As the survey took place at the height of the hot dry season, the reported mosquito net protection during the last night was correspondingly low. There were no major differences in ITN characteristics between group A and B.

### Mortality

By May 2010, mean (median) follow-up in the study population was 7.3 (8.3) years (range 0–9.9 years),

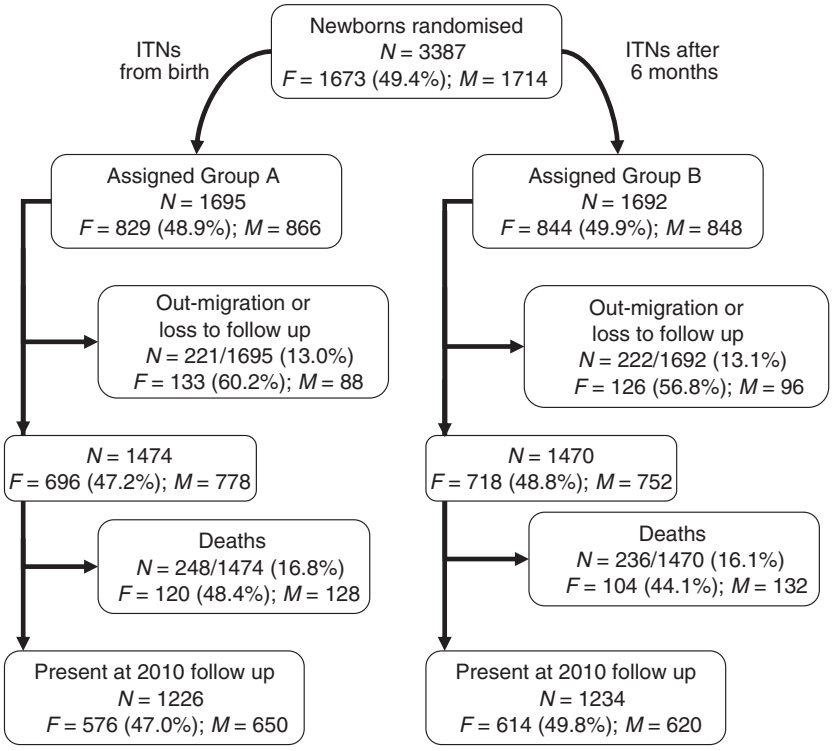


**Figure 1** Trial profile.

| | Group A (%) | Group B (%) |
|---|---|---|
| Mosquito net ownership (%) | 1116/1226 (91.0) | 1118/1234 (90.6) |
| Original study ITN (%) | 889/1116 (79.7) | 884/1118 (79.1) |
| New ITN (Serena) (%) | 97/1116 (8.7) | 102/1118 (9.1) |
| Other type of mosquito net (%) | 130/1116 (11.7) | 131/1118 (11.7) |
| Re-treated last 2 years (%) | 683/1116 (61.2) | 639/1118 (57.2) |
| Regular net use, rainy season (%) | 1099/1116 (98.5) | 1103/1118 (98.7) |
| Regular net use, cold dry season (%) | 991/1116 (88.8) | 987/1118 (88.2) |
| Regular net use, hot dry season (%) | 394/1116 (35.3) | 356/1118 (31.8) |
| Mosquito net use last night (%) | 370/1116 (33.1) | 327/1118 (29.3) |

**Table 1** Insecticide-treated mosquito net (ITN) characteristics in the population of study children

corresponding to 24 799 person years (PY), 12 334 PY in group A and 12 464 PY in group B. At that time, overall 484/2944 (16.4%) children had died, 248 in group A and 236 in group B (Figure 1). A total of 450/2944 (15.3%) children died under the age of five and represented the great majority of recorded deaths (450/484, 93.0%). The highest relative percentage of deaths occurred in infancy (171/484, 35.3% (Table 2)). The mean age at death was 1.8 year (95% CI 1.6–2.1 year) in group A and 1.9 year (95% CI of 1.7–2.1 year) in group B. The median age at death was 1.4 year in all cases.

Cox regression showed no statistical differences in mortality between the study groups (rate ratio 1.05, 95% CI: 0.889–1.237; $P = 0.570$). In an overall comparison, women had a non-significant better survival than males (rate ratio 0.88, 95% CI: 0.748–1.042 $P = 0.15$). There were slightly non-significant gender differentials in mortality between study groups (rate ratio = 1.175,

**Table 2** Mortality in children of a birth cohort in rural Burkina Faso by study group

| | Group A | | | Group B | | | |
|---|---|---|---|---|---|---|---|
| Age | *N* died | Person years | Annual rate* | *N* died | Person years | Annual rate* | Rate ratio (95% CI) |
| <1 yr | 86 | 12 334 | 6.97 | 85 | 12 464 | 6.82 | 1.02 (0.76–1.38) |
| 1 to <2 yr | 67 | 12 294 | 5.45 | 62 | 12 421 | 4.99 | 1.09 (0.77–1.54) |
| 2 to <3 yr | 48 | 12 187 | 3.94 | 42 | 12 330 | 3.41 | 1.16 (0.76–1.76) |
| 3 to <4 yr | 24 | 12 063 | 1.99 | 15 | 12 209 | 1.23 | 1.62 (0.86–3.16) |
| 4 to <5 yr | 8 | 11 956 | 0.67 | 13 | 12 137 | 1.07 | 0.62 (0.25–1.48) |
| 5 to <6 yr | 6 | 11 763 | 0.51 | 9 | 11 920 | 0.76 | 0.68 (0.23–1.87) |
| 6 to <7 yr | 3 | 11 456 | 0.26 | 2 | 11 634 | 0.17 | 1.52 (0.25–11.56) |
| 7 to <8 yr | 3 | 10 994 | 0.27 | 4 | 11 241 | 0.36 | 0.77 (0.15–3.48) |
| 8 to <10 yr | 3 | 13 761 | 0.22 | 4 | 14 078 | 0.28 | 0.77 (0.15–3.50) |
| Total | 248 | 12 334 | 2.01 | 236 | 12 464 | 1.89 | 1.01 (0.88–1.16) |

Yr, year; *N*, number.
*Annual mortality rate per 1000 persons-years.

95% CI: 0.920–1.500, $P = 0.196$ for women and 0.950, 95% CI: 0.759–1.188, $P = 0.650$ for males). Mortality was slightly higher in group A in the first 4 years of life, and slightly higher in group B thereafter (Table 2 and Figure 2). However, no significant age-dependent effect of treatment was detected, and this observation should be attributed to chance (*P*-value for interaction between age and treatment group = 0.62).

A total of 341/484 (70.4%) of deaths occurred at home and 79/484 (16.3%) occurred in a medical facility; of those, 47/79 (59.5%) in a peripheral health station and 31/79 (39.2%) in a hospital. For 64/484 (13.2%), the information was missing.

### Morbidity

Reported number of children hospitalised since birth was 255/3387 (7.5%), 124/1695 (7.3%) in group A and 131/1692 (7.7%) in group B. There were a total of 339 hospitalisations (range one to five per child), with the majority of children having been hospitalised only once (198/255, 77.6%). Most hospitalisations took place in a peripheral health station (277/339, 81.7%), only 55/339 (16.2%) occurred in a hospital. Fever, vomiting and convulsions were the main reasons for hospitalisation, without differences between study groups (data not shown).

From the initial 420 sentinel children followed longitudinally until the end of 2003, 311 (74.0%) children were present at the time of the survey in November 2009 (150 group A, 161 group B) and 59 (14.0%) were absent due to migration or loss to follow up. A total of 50 out of 361 (13.9%) children had died. Table 3 gives the main findings from the survey. In 2009 mean age of study children was 8.7 years (median 8.8 years). Reported mosquito net protection during last night was high, and 89% of the nets

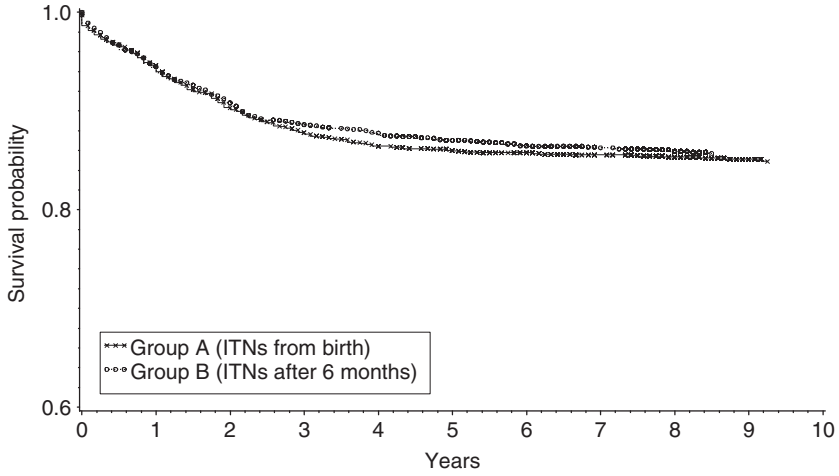


**Figure 2** Survival curve of children of a birth cohort in rural Burkina Faso by study group.

**Table 3** Demographic to clinical characteristics of the children in the six sentinel villages ($N$ = 311 children)

| Characteristics | Group A ($n$ = 150) | Group B ($n$ = 161) |
|---|---|---|
| Demographic data | | |
| Women | 78/150 (52%) | 78/161 (49%) |
| Mean age (years), range | 8.7 (7.1–9.7) | 8.6 (7.1–9.7) |
| Mosquito net data | | |
| Mosquito net protection last night | 135/149 (91%) | 137/159 (86%) |
| Parasitological data | | |
| Malaria trophozoites | 117/150 (78%) | 133/161 (83%) |
| *Plasmodium falciparum* trophozoites | 114/150 (76%) | 131/161 (81%) |
| Mean *P. falciparum* trophozoite density/$\mu$l (range) | 1754 (80–21 440) | 1742 (80–33 600) |
| Clinical data | | |
| Weight in kg (range) | 23.4 (15–38) | 23.0 (15–32) |
| Fever (≥37.5 °C axillary) | 37/143 (26%) | 45/160 (28%) |
| Mean haemoglobin g/dl (range) | 10.7 (7.1–13.4) | 10.7 (7.2–13.9) |
| Falciparum malaria | | |
| (fever + ≥1 parasites/$\mu$l) | 27/143 (19%) | 35/160 (22%) |
| (fever + ≥2000 parasites/$\mu$l) | 7/143 (5%) | 10/160 (6%) |

were ITNs of still good quality (data not shown). Around 80% of children had detectable malaria trophozoites, mostly *Plasmodium falciparum*. Fever prevalence was also high, and depending on the definition, between 6% and 20% had clinical malaria. There were no significant differences in any of the survey parameters between study groups.

## Discussion

Our study was designed to specifically test the controversial hypothesis published in the year 1997 that ITNs possibly increase childhood mortality if used during early infancy in malaria endemic areas (Snow *et al.* 1997). This hypothesis was based on the assumption that under high enough transmission intensity, the short period of passive malaria immunity due to maternal antibodies and foetal haemoglobin largely merges with an already extensive exposure to the different *P. falciparum* strains, allowing for safe immunity development of the exposed young infant (Snow *et al.* 1997). We had previously shown that the cohort children protected with ITNs since birth had significantly lower malaria antibody titres than children only protected from month 6 onwards (Wakilzadeh 2009). Moreover, compliance with the ITN intervention was good during the first study years, with 66% and 98% of children having been protected during the dry and rainy season respectively (Frey *et al.* 2006), and continuous testing for ITN efficacy in the main malaria vectors has provided no evidence for measurable pyrethroid resistance in the study area (unpublished data). The main findings from our large and representative study conducted in a malaria holoendemic area of rural SSA thus clearly show that ITN use in early infancy is not a risk factor of public health importance for excess mortality. However, it has to be considered that this study has only tested the specific hypothesis related to reduced exposure in early infancy. Thus, other aspects of immunological rebound associated with decreasing transmission intensity may still play a role in endemic areas where ITNs are used for malaria prevention.

We had recently shown a 23% decrease in malaria prevalence in children under 5 years of age between 1999 and 2009 in the Nouna study area, which was likely attributed to the increased ITN household coverage (Beiersmann *et al.* 2011). However, malaria prevalence and malaria morbidity remained high in the older children of this cohort despite good ITN coverage. One possible explanation for this surprise finding could be the differences in the sleeping behaviour of older and younger children, who may thus have been more exposed to mosquito bites. Moreover, the fact that the study took place in an environment where nets were generally less often used may also have played a role (Okrah *et al.* 2002; Traoré 2004). Before the study took place, the overall net use in young children was 9% in the dry season and 16% in the rainy season (Traoré 2004). Another possible explanation could be the occurrence of malaria rebound due to decreased immunity.

Our findings on most deaths occurring in children under the age of 5 years and mainly without sufficient access to health services support many similar reports and call for major efforts to strengthen primary health care services in SSA (Greenwood *et al.* 2005; Mueller 2011). In our birth

cohort followed up under real life conditions, a total of 450/2944 (15.3%) children under the age of 5 years had died. These mortality data are consistent with the data from the ongoing HDSS-based mortality surveillance in the study area that showed significantly decreased childhood mortality over the past two decades (Sié *et al.* 2010), supporting similar trends in most developing regions (Bhutta *et al.* 2010).

Long-term compliance with the ITN intervention was surprisingly good in our study cohort, which could be due to the initial strong advice parents had received. However, with the exception of the study households in the six sentinel villages, there was no further systematic contact to such households in the years after the provision of the ITN. Self-reported mosquito net protection was high during the rainy season and the cold dry season, but not during the hot dry season when many people sleep outside houses, which confirms the findings from an earlier evaluation of ITN compliance in this study (Frey *et al.* 2006). The observation that ITN use is usually less common than ITN ownership has frequently been reported and can be attributed to many behavioural and cultural determinants (Alaii *et al.* 2003; Korenromp *et al.* 2003; Baume & Marin 2007; Thwing *et al.* 2008; Iwashita *et al.* 2010). However, compliance has currently to be considered being responsible for a smaller part of the ITN coverage gap, as only half of all households in SSA reported to have at least one ITN in 2011 (WHO 2011).

High coverage ITN programmes have been associated with major reductions in malaria morbidity and all-cause mortality in young children (D'Alessandro *et al.* 1995; WHO 2009, Lim *et al.* 2011). In addition to the effect of individual protection, this is likely due to the mass effect of the intervention on vector mosquitoes in communities with high ITN coverage (Binka *et al.* 1998; Ilboudo-Sanogo *et al.* 2001; Maxwell *et al.* 2002; Hawley *et al.* 2003; Killeen *et al.* 2007). Malaria prevalence was still high in our study cohort despite high individual coverage with the ITN intervention, which supports the importance of achieving universal coverage in malaria high transmission settings (Mueller 2011).

Long-term follow-up has to be considered difficult in such a setting. In our study, the percentage of children which migrated with their family out of the study area and which could not be followed-up were 13%, both in treatment groups A and B. This is a relatively low number, and we do not think it could have introduced a bias in our results. All reported deaths were cross-checked with the underlying Health and Demographic Surveillance System (HDSS) of the study area, and there were only few conflicting data. Overall, we believe data quality of our study is good. The observed slightly lower mortality in women is consistent with the observed mortality pattern in the HDSS (Sié *et al.* 2010).

In conclusion, ITN protection in early infancy is not a risk factor for mortality at older ages. Individual ITN protection does not sufficiently reduce malaria prevalence in high-transmission areas. Achieving universal ITN coverage remains a major challenge in malaria endemic regions.

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