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Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast

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Summary New tools to prevent malaria morbidity and mortality are needed to improve child survival in sub-Saharan Africa. Insecticide treated bednets (ITBN) have been shown, in one setting (The Gambia, West Africa), to reduce childhood mortality. To assess the impact of ITBN on child survival under different epidemiological and cultural conditions we conducted a community randomized, controlled trial of permethrin treated bednets (0.5 g/m^2) among a rural population on the Kenyan Coast.

Between 1991 and 1993 continuous community-based demographic surveillance linked to hospital-based in-patient surveillance identified all mortality and severe malaria morbidity events during a 2-year period among a population of over 11 000 children under 5 years of age. In July 1993, 28 randomly selected communities were issued ITBN, instructed in their use and the nets re-impregnated every 6 months. The remaining 28 communities served as contemporaneous controls for the following 2 years, during which continuous demographic and hospital surveillance was maintained until the end of July 1995.

The introduction of ITBN led to significant reductions in childhood mortality (PE 33%, CI 7–51%) and severe, life-threatening malaria among children aged 1–59 months (PE 44%, CI 19–62). These findings confirm the value of ITBN in improving child survival and provide the first evidence of their specific role in reducing severe morbidity from malaria.

keywords malaria, childhood mortality, insecticide treated bednets, Kenya

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Introduction

The country is infested by swarms of gnats and the people have invented various methods of dealing with them . . . everyone . . . provides himself with a net, which during the day he uses for fishing, and at night fixes up round his bed, and creeps in under it before he goes to sleep. For anyone to sleep wrapped in a cloak or in linen would be useless, for gnats would bite through them; but they do not even attempt to get through the net.

Heroditus, 5th C. BC

Since Heroditus' travels to Egypt the bednet has assumed an important role in the control of malaria. *Plasmodium falciparum* malaria constitutes one of the principal barriers to further improvements in child survival in Africa today (World Bank 1993). This serious situation is becoming steadily more critical with the rapid spread of chloroquine resistance and the associated rise in malaria mortality. Despite encouraging results with a prototype malaria vaccine (Alonso *et al.* 1994) many problems remain (D'Alessandro *et al.* 1995b) and there are no prospects of a vaccine having widespread impact on malaria mortality in the short to medium term, certainly not in the next 5 years, during which period between 2 and 5 million African children can be expected to die of malaria (Greenwood 1990). The application of insecticides to bednets (mosquito nets) was first used by Russian troops during the Second World War (Blagoveschensky *et al.* 1945), but it was not until the 1980s that controlled trials demonstrated significant protection against the incidence of febrile episodes due to *P. falciparum* infection among children using non-toxic, synthetic pyrethroid-treated bednets (Snow *et al.* 1988; Graves *et al.* 1988; Sexton *et al.* 1990; Lyimo *et al.* 1991; Dapeng *et al.* 1994; Luxemburger *et al.* 1994). In the Gambia, Alonso *et al.* (1991) demonstrated that sleeping under insecticide-treated bednets (ITBN) was associated with a greater than 60% reduction in all-cause mortality among children aged 1–4 years. However, the pattern of transmission of *P. falciparum* and existing tradition of bednet use in The Gambia are not representative of malaria ecologies throughout much of sub-Saharan Africa. Understandably, donors and control agencies have been reluctant to commit limited resources to ITBN programmes without further evidence that this intervention can significantly reduce child mortality in other settings. We now report that the introduction of ITBN in a randomized controlled study in a malaria endemic area of Kenya led to major reductions in severe malaria and all-cause childhood mortality.

Materials and methods

Study area

Kilifi District lies between two creeks on the Kenyan coast, 60 km north of Mombasa. An area immediately surrounding the administrative town of Kilifi was defined in 1991 for intensive demographic and epidemiological surveillance (Snow *et al.* 1993; 1994b). The population are predominantly Wagiriama and the rural area comprises scattered homesteads separated by land farmed for subsistence and cash crops. The majority of the population live within 2 km of a bus stage which provides regular transport to the Kilifi District Hospital (KDH) (Snow *et al.* 1994a). The hospital provides paediatric in-patient services through a 35-bed paediatric ward and a 5-bed, high-dependency unit. Over 10% of children under the age of 5 years resident within the study area are admitted to the hospital each year (Snow *et al.* 1994b). Peripheral health services are limited to 3 government dispensaries and 6 private clinics although most mothers give home-based care with proprietary drugs purchased from the numerous shops in the area (Mwenesi *et al.* 1995). Prior to this intervention bednet use was uncommon; only 6% of children slept under a net in 1990 (Snow *et al.* 1992b).

The area is characterized by prolonged seasonal *P. falciparum* transmission following the long and short rains. The *An. gambiae* s.l. complex are the main vectors contributing approximately 10–30 infective bites per person per annum (Mbogo *et al.* 1995). This low intensity transmission still poses a serious threat to children in the area with one in 15 requiring hospital admission for severe, life-threatening malaria before their fifth birthday (Snow *et al.* 1993).

Enumeration and community surveillance for mortality events

An area used during previous surveys was extended by 10% to the north and west. The area was subdivided along administrative boundaries into 56 zones of approximately 1000 individuals each. Each homestead, bus-location, health facility and major landmark was mapped using a hand-held, satellite navigational system (Trimble Navigation, Europe Ltd, UK). Twenty field staff recruited from the area were trained in census techniques and the sensitive nature of mortality surveys. Within each household, residents were enumerated by recording basic demographic details on a pre-coded census schedule and

issued a unique identification number linked to the geographical position of the homestead. Residents were defined as inhabitants intending to reside for a continuous period of at least 6 months. During the initial and subsequent censuses additional information was recorded on the numbers of beds and sleeping structures within each household. Censuses were repeated every 6 months to identify in and out migrants, births and deaths. Biannual census data was supplemented with 6–8-weekly house-to-house vital registration of births and deaths. Each reported death was further investigated by a senior member of the field team to establish the precise date, place and circumstances surrounding the death.

Paediatric ward surveillance

The mother or guardian of each child admitted to the paediatric ward of KDH was interviewed on admission to establish the child's census identification number, symptom history and illness duration; this information was recorded on a proforma also used for all subsequent laboratory and clinical findings. A finger prick blood sample was taken for malaria parasitology and haematology. Each child was examined by a KEMRI physician and all clinical investigations recorded at the time of admission. On discharge a primary diagnosis was recorded following a review of all the clinical and laboratory investigations during the child's stay on the paediatric ward. Severe malaria was defined following modifications of the WHO guidelines (Warrell *et al.* 1990) used in previous studies at Kilifi (Snow *et al.* 1993). Children with *P. falciparum* patent parasitaemia and no other detected cause for their symptoms were regarded as having severe malaria if they had any of the following: (1) coma, defined as being unable to localize a painful stimulus (assessed after 1 hour following a seizure or administration of anticonvulsants and after correction of hypoglycaemia); (2) prostration, defined as being unable to breast feed or sit unassisted; (3) multiple seizures, two or more convulsions within 24 hours prior to admission; (4) severe malaria anaemia, a haemoglobin of less than 5.1 g/dl and an associated parasitaemia greater than 10 000 parasites per μl of blood; (5) hyperparasitaemia, more than 20% of red cells infected; (6) death without any of the aforementioned complications but without evidence of an alternative diagnosis.

Data handling and statistical analysis

Data entry, validation and cleaning were carried out using FoxPro (ver. 2.0, 1991, Fox Software Inc., Ohio, USA). Statistical analysis was carried out using STATA (Release 4.0, 1995, Stata Corporation, Texas, USA). All-cause mortality and disease-specific hospital admission rates were analysed on an intention-to-treat basis. Annual rates of both hospital admission and mortality were computed using as denominators the mid-pre-intervention (May 1992) and mid-post-intervention (August 1994) resident populations aged 1–59 months. An adjusted rate ratio (RR) was calculated to allow for potential confounding effects of pre-intervention rates of either morbidity or mortality and age in each zone using a multivariate Poisson regression model. Because this was a community randomized trial, the calculation of significance levels and confidence intervals must allow for the correlation within zones so a *t*-test for the significance of the RR was carried out using residuals from the regression model aggregated at the community level. A 95% test-based confidence interval for the adjusted RR was also obtained from the analysis of the aggregated residuals. Protective effcacies (PE) were calculated as 1 − RR. A detailed discussion of analysis strategies for community randomized trials is given by Donner and Klar (1993; 1994).

Randomization and delivery of intervention

Ethical clearance was granted by the Kenyan Medical Research Institute's ethical review committee. The community were informed of the trial by means of public meetings throughout the study area and through smaller meetings with administrative chiefs, sub-chiefs, other influential community leaders and village health committees. Special care was taken to explain the nature of the randomization process and that those selected to serve as controls would receive nets at the end of the trial. Preliminary analysis of severe malaria hospital presentation and mortality data collected 2 years prior to intervention (1991–1993) showed significant differences

between the north, south-east and south-west divisions of the study area (data not shown). To rationalize the randomization process these three divisions were used as strata in the sampling of zones. Zones were randomly selected within each stratum to achieve equal numbers of children in each arm of the trial, resulting in 28 intervention and 28 control zones.

Investigations were made during the pre-intervention phase to assess the optimal size and colour preferences of bednets for this community. An overall preference for green nets was expressed especially in houses where domestic fires were common and in view of the restrictions on washing placed by the insecticide. Large nets without borders or opening slits (190 × 180 × 150 cm; 100 denier polyester) were imported from Thailand (Siam-Dutch Co., Thailand). These nets were impregnated with 28.5 ml permethrin 25% emulsifiable concentrate (Imperator 25, Zeneca, UK) diluted with 500 ml of water to achieve a target dose of 0.5 g permethrin per m^2 of netting. Bednets were distributed between June and July 1993 to each intervention household and issued according to the 'bed' registers of each house. Distribution was accompanied by pre-tested demonstrations of correct hanging and care of nets by trained field staff. Education in bednet use was continued the following day by government public health technicians who reviewed net hanging and held discussion meetings with small groups of mothers. Posters and school-based bednet plays and interactive learning sessions continued to be used throughout the trial (Marsh *et al.* in press). Local bednet committees were formed through the existing primary health care system to identify, resolve or report subsequent bednet issues, losses and difficulties within their communities. Every 6 months, immediately before the rains in April and October, householders were asked to wash their bednets in preparation for reimpregnation on a preset day. Bednets were reimpregnated at a dose of 0.5 g/m^2 permethrin at each homestead by field staff.

Results

Following the re-enumeration of the population in June 1993, 2760 households were identified in the 28 zones allocated to receive ITBN and between June and July 1993 pre-impregnated bednets were issued to 17 742 (96%) of the 18 478 beds registered during the census. Subsequent re-enumerations identified new households and new net requirements for in-migrants and births. Successful reimpregnations of nets were achieved for 88, 91 and 85% of nets in October 1993, April 1994 and October 1994, respectively. In April 1995 only 80% of the 19 092 intervention nets were successfully reimpregnated. ITBN use among control children was less than 1% during the second year of the trial.

Approximately 220 randomly selected intervention children were sampled every 6 weeks during the first year and twice during the second year of the trial to assess bednet use by direct observation using early morning (0430–0700 h) visits. During the dry, hot season (January–March) 65% of intervention children were found to be using the net correctly and during the wet, cooler months of highest malaria transmission observed bednet use was 77% among the target childhood population.

Concentrations of permethrin on nets were assessed by high performance liquid chromatography (HPLC) on 72 randomly selected netting swatches: 65% of samples had active, cis-permethrin concentrations in excess of 0.5 g/m^2. The indoor resting densities of *Anopheles gambiae* s.l. were reduced ninefold in zones where ITBN were issued compared to control zones (Mbogo *et al.* in press) and the prevalence of *P. falciparum* infection among infants sleeping under ITBN was reduced by 50% (Snow *et al.* in press).

Mortality rates

Table 1 shows the mortality rates for the intervention and control arms of the trial during the pre-intervention period (April 1991–May 1993). Following the intervention in July 1993 mortality rates over the 2-year post-intervention period (August 1993–July 1995) were significantly reduced among children aged 1–4 years living in the 28 intervention zones compared to their contemporary control: adjusted PE 33% (95% CI 7–51%, P=0.02). Reductions were also observed for children aged 1–59 months (adjusted PE 30%, 95% CI 7–47%, P=0.02).

Table 1 Crude overall rates of paediatric admission and mortality per 1000 children aged 1–59 months of age per annum living in 28 zones allocated to receive ITBN and 28 zones selected to serve as controls 2 years prior to intervention (May 1991–April 1993) and 2 years post-intervention (August 1993–July 1995)

	Intervention zones (28) May 91–Apr 93 Pre-	Intervention zones (28) Aug 93–Jul 95 Post-	Control zones (28) May 91–Apr 93 Pre-	Control zones (28) Aug 93–Jul 95 Post-
Total childhood population aged 1–59 months over 2 years	11 172	11 566	11 484	11 432
Mortality rates p.a.				
1–59 months of age	15.8 (176)	9.4 (109)	14.9 (171)	13.2 (151)
1–4 years of age	13.0 (118/9058)	7.4 (70/9466)	11.7 (109/9330)	10.9 (104/9556)
Paediatric admission rates 1–59 months of age p.a.				
All admissions	74.8 (836)	67.7 (783	90.2 (1036)	92.6 (1059)
P. falciparum negative admissions	29.6 (331)	36.1 (418)	36.1 (414)	35.6 (407)
P. falciparum positive admissions	44.0 (491)	31.0 (358)	52.8 (606)	56.6 (647)
Primary diagnosis malaria admissions	37.3 (417)	27.8 (322)	44.7 (513)	50.6 (579)
Malaria admissions with *P. falciparum* parasite density $\geqslant$ 20 000/μl	21.8 (244)	16.6 (192)	26.3 (302)	32.3 (369)
Severe malaria admissions	15.0 (168)	11.0 (127)	18.5 (212)	20.0 (229)
Acute respiratory tract infection admissions	14.8 (165)	16.2 (187)	17.1 (196)	17.7 (202)
Gastroenteritis admissions	4.8 (54)	5.7 (66)	5.9 (68)	6.7 (77)

Figures in parentheses represent total numbers of cases

Severe paediatric morbidity

During the pre-intervention period (May 1991–April 1993), 836 children aged between 1 month and 5 years were admitted to the paediatric ward at KDH from the intervention zones and 1036 children were admitted from the control zones. The rates of hospital admission for children resident in the 28 intervention zones were lower than those described for children from the 28 control zones (Table 1) and were allowed for in the analysis of the post-intervention data.

Crude admission rates during the post-intervention period (August 1993–July 1995) were lower among children aged 1–59 months living in intervention zones (68 per 1000 children aged 1–59 months p.a.) compared to children living in control zones (93 per 1000 children aged 1–59 months p.a.) (Table 1). Greater differences were observed for admissions due to malaria; a total of 322 children with malaria were admitted during the 2 years of the intervention from the 28 zones where ITBN were issued (28 per 1000 children 1–59 months p.a.) and 579 malaria admissions from the 28 control zones (51 per 1000 children 1–59 months p.a.). The adjusted protective efficacy (shown in Table 2) of ITBN in reducing the rates of paediatric malaria admissions after controlling for pre-intervention differences in malaria admission rates and age in the regression model was 41% (95% CI 20–57%, P=0.001). No significant effects of ITBN on admission rates for conditions such as ARI (P=0.73) or diarrhoea (P=0.29) were noted during this trial (Tables 1 and 2).

Two hundred and twenty-nine children were admitted to KDH with severe malaria during the intervention phase of the trial (August 1993–July 1995) from the 28 control zones compared to only 127 from the 28 intervention zones. The admission rates for severe, life-threatening malaria were significantly reduced by 44% (95% CI 19–62%, P=0.004) allowing for confounding variables within the regression model.

Discussion

It is now clear that optimal use of ITBN by children living in malaria endemic areas, similar to those of both The Gambia (Alonso *et al.* 1991) and the Kenyan coast, can significantly improve their chances of survival through childhood. The results from

Table 2 Unadjusted and adjusted protective efficacies (95% CI) of overall rate ratios shown in Table 1

	Unadjusted PE (%)	Adjusted PE (%) CI	*P*-value for adjusted PE
Mortality rates p.a.			
1–59 months of age	29	30 (7,47)	0.02
1–4 years of age	32	33 (7,51)	0.02
Paediatric admission rates 1–59 months of age p.a.			
All admissions	27	22 (−2, 41)	0.08
P. falciparum negative admissions	−2	−5 (−21, 9)	0.55
P. falciparum positive admissions	45	42 (21, 57)	0.001
Primary diagnosis malaria admissions	45	41 (20, 57)	0.001
Malaria admissions with *P. falciparum* density ⩾20 000/μl	49	46 (25,61)	<0.001
Severe malaria admissions	45	44 (19, 62)	0.004
Acute respiratory tract infection admissions	8	9 (−53, 46)	0.73
Gastroenteritis admissions	15	19 (−19, 45)	0.29

these 2 studies also demonstrate the importance of malaria as a cause of childhood mortality across sub-Saharan Africa. The introduction of a single, malaria-specific intervention significantly reduced all-cause mortality by 63% in The Gambia. In Kilifi, all-cause mortality was reduced by 33%; however, even this must underestimate the effect of malaria as a failure to ensure complete net treatment (14%) and the failure of children to sleep under nets (23%) means that the maximum expected reduction in malaria specific events is around 66%. Whatever the case, these reductions provide us with our best estimate of malaria's minimum contribution to childhood mortality (1–4 years) in Africa and suggest that previous estimates of the toll of malaria on African children's survival have been grossly underestimated (Greenwood 1990).

The massive apparent contribution of malaria to all-cause childhood mortality raises the question of whether the major effect of control is the direct prevention of severe (life-threatening) clinical episodes of malaria or a reduction in the putative secondary immunosuppressive effects of malaria. Previous studies have indicated a concomitant reduction in deaths due to acute respiratory tract infections (Alonso *et al.* 1991). However these observations were based on the technique of verbal autopsy applied to deaths in the community and we have since shown that this approach is not capable of distinguishing between malaria and other common severe childhood infections (Snow *et al.* 1992a). Hospital-based surveillance to detect severe morbidity has not been used previously during randomized controlled trials of new malaria interventions. Our study population (where over 10% of the childhood population are admitted to hospital each year) provided a unique opportunity to examine the impact upon well defined disease categories. The availability of pre-intervention information on admission rates by location within the study area enabled us to control for pre-existing hospital utilization differences within the study population. Malaria accounts for approximately 50% of the admissions to the paediatric ward at Kilifi posing the single largest clinical burden on the hospital (Snow *et al.* 1994b). We have shown that the introduction of a programme of ITBN can reduce paediatric malaria admissions by 41%. Categorization of malaria patients according to severity or increasing parasite densities circumvents some of the problems associated with the accurate diagnosis of malaria in areas where asymptomatic infection is common and malaria shares presenting symptoms with other common childhood diseases (O'Dempsey *et al.* 1993; Redd *et al.* 1992). A 44% reduction in severe malaria morbidity associated with the use of ITBN was shown in our study (Tables 1 and 2). It is striking that there were no significant reductions in either non-malaria admissions overall or in any other specific syndrome. This does not preclude the possibility that part of the protective effect of malaria control is indirect, but it does again emphasize the enormous

importance of acute, life-threatening malaria.

The intervention was delivered under optimum trial conditions; nevertheless, we were unable to achieve 100% reimpregnation coverage and nets were used correctly by young children in only 77% of direct observations during the periods of peak mosquito abundance. Despite these shortcomings ITBN were efficacious in reducing both child mortality and severe, life-threatening malaria which raises the question of whether efficacy under these trial conditions can be translated into 'real-life' effectiveness under national programme conditions. The first effectiveness study was recently reported by D'Alessandro *et al.* (1995a) where the impact upon childhood mortality of ITBN was measured through the National Primary Health Care System in The Gambia. That study still demonstrated a 25% reduction in all-cause childhood mortality despite all the programme's inadequacies. Doubts have been raised about the acceptance of such an intervention in areas where bednet use is uncommon. Although the Kilifi community were previously unfamiliar with bednets, nets were well accepted and no significant adverse effects were reported following insecticide treatment.

Given the rapidly emerging anti-malaria drug resistance in sub-Saharan Africa, malaria mortality can be expected to increase beyond its already unacceptable level. Although recent studies have given encouragement to the drive to develop malaria vaccines, these will not form part of comprehensive malaria control efforts for many years. Meanwhile ITBN provide our best hope for the reduction of severe and complicated paediatric malaria and significant improvements in child survival on the African continent. A large part of malaria endemic sub-Saharan Africa has disease ecologies similar to The Gambia or the Kenyan coast and national control programmes, donors and aid organizations working in such areas should seriously consider the implementation of ITBN as part of existing child survival initiatives such as EPI+ (World Bank 1993; Snow *et al.* 1995).

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