A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa

6. The impact of the interventions on mortality and morbidity from malaria

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Abstract

The effects of insecticide-impregnated bed nets on mortality and morbidity from malaria have been investigated during one malaria transmission season in a group of rural Gambian children aged 6 months to 5 years. Sleeping under impregnated nets was associated with an overall reduction in mortality of about 60% in children aged 1–4 years. Mortality was not reduced further by chemoprophylaxis with Maloprim® given weekly by village health workers throughout the rainy season. Episodes of fever associated with malaria parasitaemia were reduced by 45% among children who slept under impregnated nets. The addition of chemoprophylaxis provided substantial additional benefit against clinical attacks of malaria; 158 episodes were recorded among 946 children who slept under impregnated nets but who also received chemoprophylaxis. Chemoprophylaxis reduced the prevalence of splenomegaly and parasitaemia at the end of the malaria transmission season by 63% and 83% respectively. Thus, insecticide-impregnated bed nets provided significant protection in children against overall mortality, mortality attributed to malaria, clinical attacks of malaria, and malaria infection. The addition of chemoprophylaxis provided substantial additional protection against clinical attacks of malaria and malaria infection but not against death.

Introduction

Until a safe, effective and affordable vaccine becomes widely available malaria control in Africa will continue to rely on antimalarial drugs and on reduction of human–vector contact.

Provision of facilities for the prompt treatment of presumptive cases of malaria with an effective drug remains the cornerstone of malaria control strategies in sub-Saharan Africa. However, in studies undertaken in The Gambia and in Kenya, this strategy had no significant effect on mortality in children (SPENCER *et al.*, 1987; GREENWOOD *et al.*, 1988). An alternative to presumptive treatment is the regular distribution of antimalarial drugs as prophylactics to the groups at highest risk through appropriate primary health care (PHC) schemes. The efficacy of such a strategy depends upon its operational feasibility and sustainability. In The Gambia, targeted chemoprophylaxis, integrated into a PHC programme, was successful in producing large reductions in morbidity and mortality from malaria in young children (GREENWOOD *et al.*, 1988; MENON *et al.*, 1990).

Reduction of human–vector contact has traditionally relied on house spraying with residual insecticides. In many malarious areas this strategy has had limited success because of the exophilic behaviour of vector mosquitoes, resistance to insecticides, poor co-operation by the population and because of financial and other organizational constraints. Thus, new vector control technologies are needed which are locally appropriate. In many parts of Africa, the success of strategies to reduce human–vector contact will depend largely upon the local intensity of malaria transmission, the behaviour of the vector and on whether schemes can be implemented through established PHC programmes. Bed nets have been used for protection from mosquitoes for many years (LINDSAY & GIBSON, 1988) but there have been few evaluations of their effect on malaria. In a trial carried out in The Gambia, conventional bed nets failed to reduce significantly the incidence of clinical episodes of malaria (SNOW *et al.*, 1988a). However, there has recently been growing interest in the use of insecticide impregnation of mosquito nets as a means of increasing their potential to reduce human–vector contact. This old idea is now perceived as a potentially effective malaria control strategy which could be integrated into PHC programmes.

Results from previous trials that evaluated the efficacy of insecticide-treated bed nets in preventing malaria infection and disease are often difficult to interpret and complicated by variations in the epidemiology of malaria between study areas (WHO, 1989; ROZENDAAL, 1989). In The Gambia, impregnated bed nets reduced the incidence of clinical episodes of malaria when used to protect an individual or a whole village (SNOW *et al.*, 1987, 1988b). They were easy to distribute and were well accepted by the local population.

The Gambia has an effective village-based PHC programme which can be used to deliver malaria control strategies once these have been shown to be effective. The aim of our trial has been to evaluate the feasibility and impact of treating existing bed nets with insecticide through an established PHC structure. A further aim has been to determine whether chemoprophylaxis is of additional benefit in preventing morbidity and mortality among children who sleep under a treated net.

Subjects and methods

Study area and population

The study was carried out in a rural area of The Gambia on the south bank of the River Gambia, east of the town of Soma. The study population of approximately 20 000 comprised mostly subsistence farmers belonging to the Mandinka and Fula ethnic groups. The climate of the area is characteristic of the sub-Sahel with a rainy season from July to October during which most malaria transmission occurs. Further details of the study area and population are given elsewhere (ALONSO *et al.*, 1993a).

Study design and implementation

The design of the study and the way it was implemented have been described previously (ALONSO *et al.*, 1993b). In brief, bed nets in 17 PHC villages were impregnated with permethrin (target dose 0·5 g/m^2, dose achieved 0·2 g/m^2) at the beginning of the 1989 malaria

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transmission season; 92% coverage was achieved. In addition, children aged 6 months to 5 years were individually allocated at random to receive weekly chemoprophylaxis with Maloprim® (pyrimethamine 12·5 mg+ dapsone 50 mg) or placebo given by village health workers (VHWs) throughout the rainy season. Mortality and morbidity from malaria were compared in these 2 groups of children and in a third group of children of the same age who lived in neighbouring non-PHC villages and who slept without nets, or under untreated nets, and who did not receive chemoprophylaxis.

Mortality and morbidity surveillance

Mortality surveillance using village reporters and the verbal autopsy technique was undertaken as described previously (ALONSO *et al.*, 1993a). Morbidity surveillance comprised cross-sectional surveys undertaken at the beginning and at the end of the malaria transmission season and active case detection by weekly morbidity surveys.

A sample of children aged 6 months to 5 years was selected in both PHC and non-PHC villages using information obtained from a census. These children were asked to take part in 2 cross-sectional surveys undertaken in June and November 1989, i.e. before, and at the end of, the main period of malaria transmission. Children were examined by a physician (P.L.A.) who recorded the presence or absence of splenomegaly with the child in the standing position. Axillary temperature was measured with an electronic thermometer and a finger-prick blood sample was obtained for measurement of packed cell volume (PCV) and for the preparation of thick and thin blood films. Blood films were stained with Giemsa's stain and examined as described previously (ALONSO *et al.*, 1993a). Children who had malaria parasitaemia received treatment with chloroquine (25 mg/kg) within 24 h.

All children aged 6 months to 5 years in the PHC villages, and all children in the same age group from 6 of the non-PHC control villages, were visited weekly throughout the main malaria transmission season. Each child was visited on the same day each week, either in the early morning or in the late afternoon. The mother was interviewed and a short questionnaire completed on the health of the child and the use of health services during the previous week. The child's axillary temperature was then recorded with an electronic thermometer. A blood film was taken if the child's temperature was 37·5°C or higher.

In PHC villages, mothers of febrile children were advised to take their child to the VHW for treatment. Febrile children from the 6 non-PHC villages who were found to have peripheral parasitaemia were given prompt treatment with chloroquine by Medical Research Council (MRC) field assistants.

During September 1989, a stratified cross-sectional survey of chloroquine consumption was carried out. Urine samples were tested for chloroquine using an enzyme-linked immunosorbent assay (ELISA) (SHENTON *et al.*, 1988).

Statistical methods

For the June and November cross-sectional surveys, a stratified, simple random sample was drawn from the census for both PHC and non-PHC villages. The sampling fractions were approximately 1:3 in PHC villages and 1:4 in non-PHC villages. The 8 strata comprised the 4 districts into which the study area was divided and 2 age groups (dates of birth: 1 July 1986–31 December 1988 and 1 January 1984–30 June 1986 respectively). Since both samples were self-weighting, and because the within-stratum variances were the same as between-stratum variances, an unweighted analysis was carried out. The standard errors and confidence intervals presented were corrected for the finite population correction.

The results of weekly morbidity surveys were used to calculate the incidence rate of clinical episodes of malaria. Rates were calculated using 2 alternative definitions of a clinical episode: (i) fever (axillary temperature ≥37·5°C) with any parasitaemia and (ii) fever with parasitaemia of 5000 per μL or greater. Rates were calculated per 1000 child-weeks at risk. Children found to have fever and parasitaemia were removed subsequently from the denominator (number at risk) and the numerator (number of episodes). A relative rate (RR) was used to compare children in PHC villages who had been individually allocated at random to receive Maloprim® or placebo and from this figure the protective efficacy of chemoprophylaxis was calculated as 1−RR.

To compare the incidence of malaria in children in PHC villages receiving weekly placebo and in children from 6 paired neighbouring, non-PHC villages, rates were calculated for each village and the 2 groups compared using Wilcoxon's rank sum test. The confidence intervals for the protective efficacy are calculated from the mean and standard error of log rate ratios of each pair.

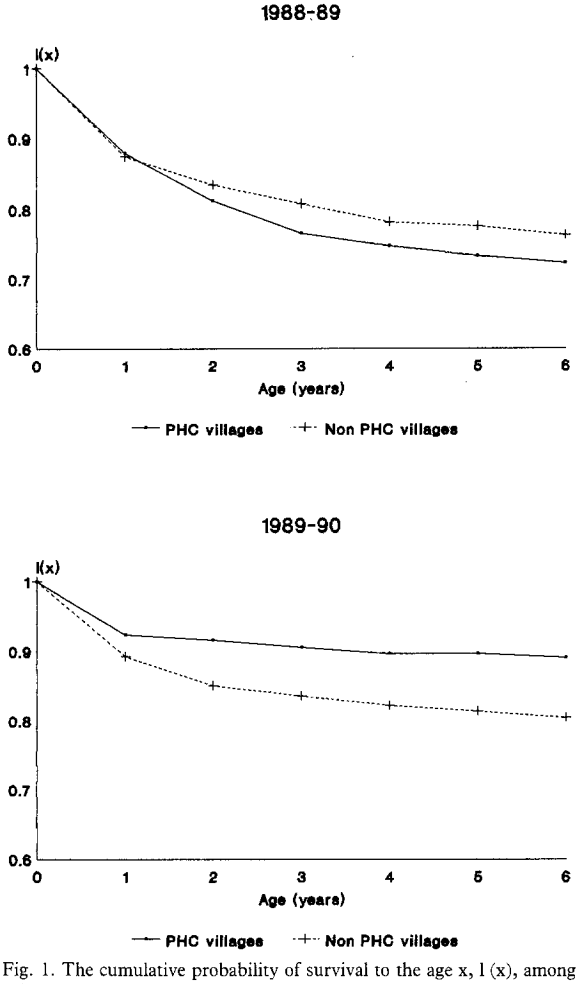

Fig. 1. The cumulative probability of survival to the age x, l (x), among children in primary health care (PHC) and in non-PHC villages before and after the introduction of malaria control measures in PHC villages in The Gambia, 1988–1989 and 1989–1990.

Results

Mortality

The impact of the 2 interventions on overall mortality and on cause-specific mortality has been presented previously (ALONSO *et al.*, 1991); it is summarized in life table format in Fig. 1, which compares the cumulative probabilities of surviving to age *x* in PHC and non-PHC villages during the year in which insecticide-treated bed nets and chemoprophylaxis were introduced into PHC villages, with the probabilities of survival during the previous year. During the pre-intervention year mortality

Table 1. Mortality rates for infants (deaths/1000 live births) and children aged 1–4 years (deaths/1000 per year), and probability of dying by age 5 (5q0), for one year before and one year after the introduction of interventions into primary health care (PHC) villages

Age (years)	Villages PHC	Non-PHC	Rate ratio PHC/non-PHC[a]	P[b]
Pre-intervention				
<1	115·5 (65/563)[c]	127·1 (46/362)[c]	0·91 (0·6–1·3)	NS[e]
1–4	47·6 (81/1700)[d]	31·5 (37/1176)[d]	1·51 (1·0–2·2)	0·03
5q0	267·5	224·6	–	–
Post-intervention				
<1	73·5 (41/558)[c]	105·1 (37/352)[c]	0·7 (0·5–1·1)	NS[e]
1–4	9·0 (16/1787)[d]	24·2 (30/1240)[d]	0·37 (0·2–0·7)	0·001
5q0	104·4	186·7	–	–

[a]95% confidence interval in parentheses.
[b]χ^2 test.
[c]Deaths/live births.
[d]Deaths/approximate mid-year population.
[e]Not significant.

was higher in PHC than in non-PHC villages. Following the introduction of the malaria control measures into PHC villages, this situation was reversed. Mortality rates during the pre-intervention and post-intervention years are shown for infants and for children aged 1–4 years in Table 1, together with probabilities of dying by age 5 years. There were 19 deaths among children under 5 years old resident in PHC villages and allocated to receive either Maloprim® or placebo during the post-intervention year. Ten of these children had received Maloprim® (mortality rate 10·5 per 1000) and 9 had received placebo (mortality rate 9·5 per 1000) (χ^2=0·05; degrees of freedom [d.f.]=1; P=0·83) (RR=0·91, 95% confidence interval=0·37,2·22). The effects of season on mortality in intervention and in control villages are shown in Fig. 2. The reduction in mortality recorded in PHC villages during the post-intervention year was most marked during the rainy season.

The post-mortem questionnaire technique was used to try to establish causes of death among study children. The overall reduction in mortality observed after inter-

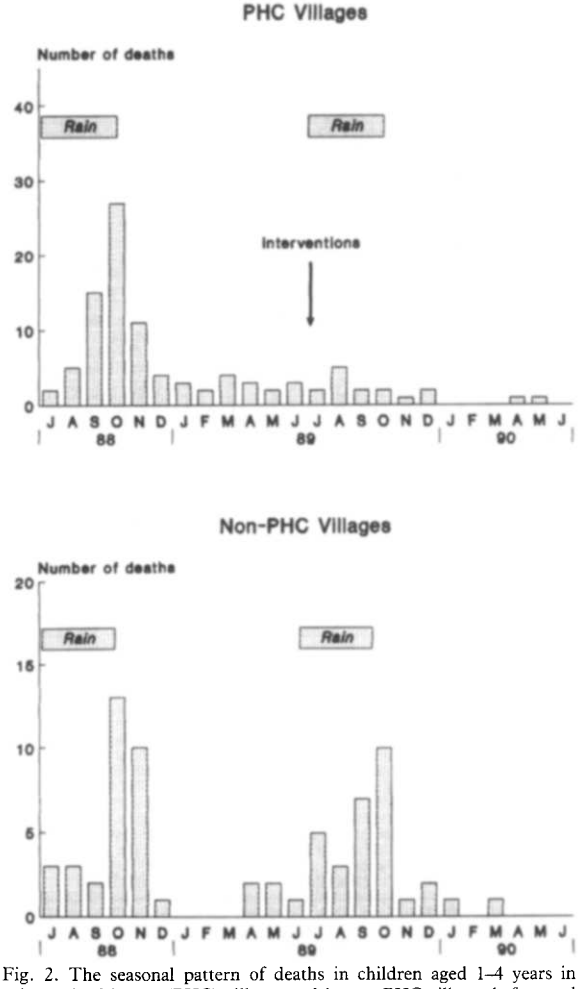

Fig. 2. The seasonal pattern of deaths in children aged 1–4 years in primary health care (PHC) villages and in non-PHC villages before and after the introduction of malaria control measures into PHC villages.

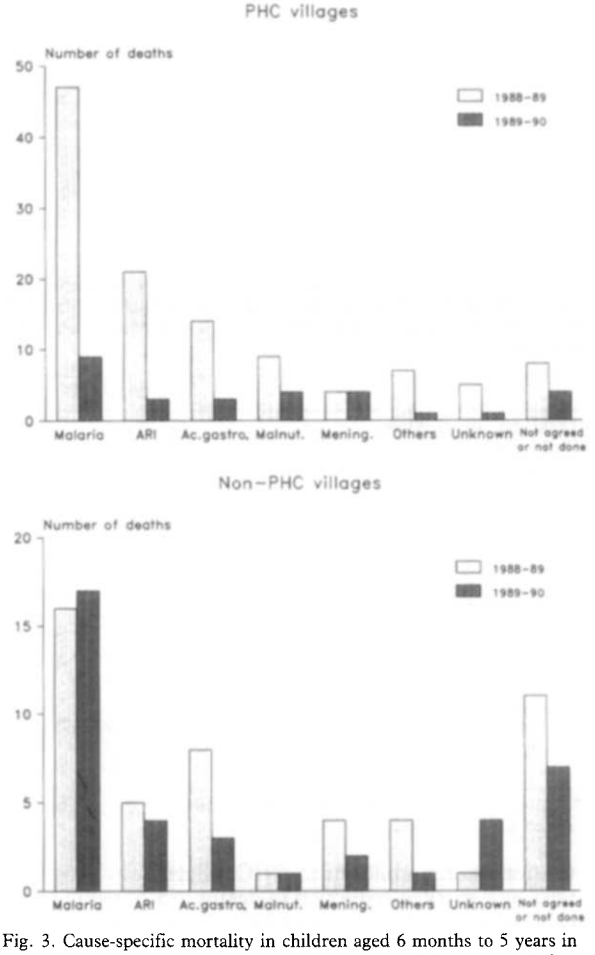

Fig. 3. Cause-specific mortality in children aged 6 months to 5 years in primary health care (PHC) villages and non-PHC villages, before (1988–1989) and after (1989–1990) the introduction of malaria control measures into PHC villages. ARI=acute respiratory infections, Ac. gastro.=acute gastroenteritis, Mening.=meningitis.

Table 2. Mortality rates attributable to malaria for infants (deaths/1000 live births) and children aged 1–4 years (deaths/1000 per year) for one year before and one year after the introduction of interventions into primary health care (PHC) villages

Age (years)	PHC	Non-PHC	Rate ratio PHC/non-PHC[a]	*P*
Pre-intervention				
<1	19·5 (11/563)[b]	2·8 (1/362)[b]	7·07 (0·9–54·6)	0·03[d]
1–4	20·6 (35/1700)[c]	11·1 (13/1176)[c]	1·86 (1·0– 3·5)	0·05[e]
Post-intervention				
<1	3·6 (2/558)[b]	2·8 (1/352)[b]	1·26 (0·1–13·9)	NS[d]
1–4	3·4 (6/1787)[c]	11·3 (14/1240)[c]	0·3 (0·1– 0·8)	0·01[e]

[a]95% confidence interval in parentheses.
[b]Deaths/live births.
[c]Deaths/approximate mid-year population.
[d]Fishers exact test; NS=not significant.
[e]χ^2 test.

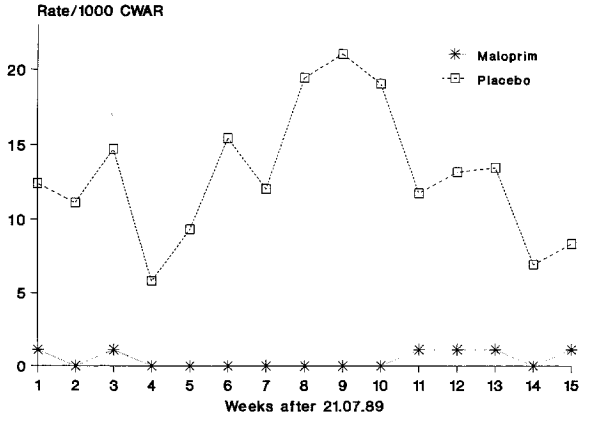

Fig. 4. The incidence of clinical attacks of malaria (fever+parasitaemia) in children aged 3–59 months who slept under impregnated nets and who received either Maloprim® or placebo; CWAR=child-weeks at risk.

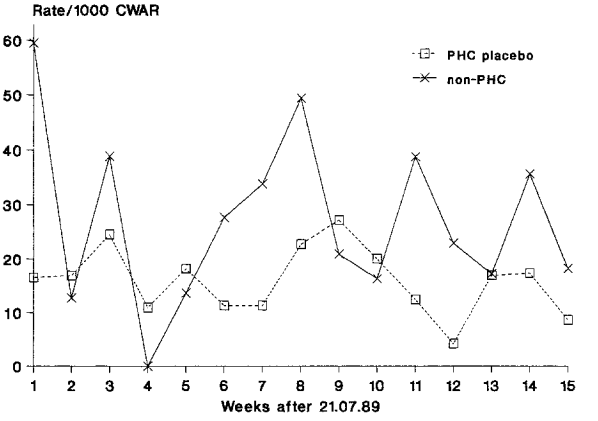

Fig. 5. The incidence of clinical attacks of malaria (fever+parasitaemia) in children who slept under impregnated nets but did not receive chemoprophylaxis and in children who slept under non-impregnated nets or who did not use nets; CWAR=child-weeks at risk.

Table 3. The results of weekly morbidity surveys of children aged 6 months to 5 years who slept under insecticide-treated bed nets and received chemoprophylaxis with Maloprim® or a placebo

	Maloprim®	Placebo
Total no. of children	952	946
Child-weeks at risk	13445	12227
Temperature <37·5°C	13115	11814
Temperature ≥37·5°C	330	413
Children with fever		
Blood film collected	317	405
No. of parasites	311	247
Parasitaemia <5000 μL	2	50
Parasitaemia ≥5000 μL	4	108
Rates per 1000 child-weeks at risk		
Fever	24·5	33·8
Fever+low parasitaemia	0·4	12·9
Fever+high parasitaemia	0·3	8·8
Protective efficacies[a]		
Fever	27% (16%,37%)	
Fever+low parasitaemia	97% (92%,99%)	
Fever+high parasitaemia	97% (91%,99%)	

[a]Protective efficacy=100 (1−relative rate); 95% confidence intervals in parentheses.

vention among children in PHC villages was accompanied by a marked reduction in deaths attributed to malaria (Table 2). However, in PHC villages there were reductions also in deaths attributed to other causes, particularly acute lower respiratory tract infections, which were not seen in control non-PHC villages (Fig. 3).

Morbidity surveillance

The incidence of clinical episodes of malaria among children in PHC villages who received either weekly Maloprim® or placebo is illustrated in Fig. 4. and summarized in Table 3. Among children who slept under insecticide-treated bed nets, the addition of chemoprophylaxis resulted in a 97% protective efficacy against clinical episodes associated with any parasitaemia or with high density parasitaemia.

The incidence of clinical episodes was also compared

Table 4. The results of weekly morbidity surveillance of children in 6 paired primary health care (PHC) villages and non-PHC villages. Only children in PHC villages who received placebo are included in this analysis

Village pairs	Fever[a]+parasitaemia[b] Rate ratio[c]	Protective efficacy	Fever[a]+high parasitaemia[b] Rate ratio[c]	Protective efficacy
1	0·784	22%	0·915	8%
2	0·579	42%	0·155	84%
3	0·193	81%	0·257	74%
4	0·489	51%	0·579	42%
5	0·734	27%	0·650	35%
6	0·872	13%	0·659	34%
Overall protective efficacy[d]	45% (14%,65%)		54% (21%,74%)	
Wilcoxon rank sum test	*P*<0·01		*P*<0·01	

[a]Temperature ≥37·5°C.
[b]*P. falciparum* parasitaemia only; high parasitaemia: ≥10 parasites/high power field (≥5000/μL approximately).
[c]Rate ratio=PHC/non-PHC values.
[d]Protective efficacy was calculated from the mean log rate ratio of village pairs.

Table 5. Findings in a cross sectional survey undertaken in primary health care (PHC) villages and non-PHC villages in June 1989 before the malaria transmission season[a]

	Villages		
	PHC		Non-PHC
	Maloprim	Placebo	
Splenomegaly	28% (24%,31%)[103/374]	28% (24%,32%)[100/359]	28% (24%,32%) [96/344]
Parasitaemia[b]	32% (28%,36%)[124/390]	28% (24%,32%)[107/381]	33% (29%,38%)[117/353]
High parasitaemia[b]	5% (3%,6%) [18/390]	5% (3%,7%) [18/381]	3% (1%,5%) [11/353]
Fever[c]	10% (8%,13%) [40/390]	9% (6%,11%) [33/383]	12% (9%,15%) [43/354]
Fever[c]+parasitaemia[b]	3% (2%,5%) [12/390]	2% (1%,4%) [9/383]	5% (3%,7%) [18/354]
Fever[c]+high parasitaemia[b]	1% (0%,2%) [2/390]	1% (0%,2%) [3/383]	0% (0%,1%) [0/354]
Packed cell volume	32·6% (32·2%,32·9%)	32·7% (32·3%,33·2%)	32·9% (32·5%,33·4%)

[a]Means with 95% confidence intervals in parentheses and actual numbers in square brackets.
[b]*P. falciparum* parasitaemia only; high parasitaemia: ≥10 parasites/high power field (≥5000/μL approximately).
[c]Temperature ≥37·5°C.

Table 6. Findings in a cross-sectional survey undertaken in primary health care (PHC) villages and non-PHC villages in November 1989 at the end of the malaria transmission season following the introduction of malaria control interventions into PHC villages[a]

	Villages		
	PHC		
	Maloprim	Placebo	Non-PHC
Splenomegaly	14% (11%,17%)[50/359]	37% (33%,42%)[129/346]	57% (52%,62%)[166/290]
Parasitaemia[b]	3% (2%,5%) [12/367]	26% (22%,30%) [94/357]	43% (38%,48%)[129/300]
High parasitaemia	11% (0%,1%) [2/367]	9% (7%,12%) [33/357]	18% (14%,22%) [53/300]
Fever[c]	0% (0%,1%) [1/367]	2% (1%,3%) [6/357]	9% (6%,12%) [28/302]
Fever[c]+parasitaemia[b]	0% (0%,1%) [0/367]	1% (0%,3%) [5/357]	7% (4%,9%) [20/302]
Fever[c]+high parasitaemia[b]	0% (0%,1%) [0/367]	1% (0%,3%) [4/357]	6% (4%,8%) [18/302]
Gametocytes[d]	2% (1%,4%) [8/367]	8% (5%,11%) [29/357]	15% (11%,19%) [45/300]
Packed cell volume	33·4% (33·0%, 33·8%)	32·2% (31·9%, 32·6%)	30·6% (30·1%, 31·1%)
Change (June–November)	+0·80% (+1·23%,+0·38%)	−0·52% (−0·04%,−1·00%)	−2·41% (−1·88%,−2·94%)

[a]Means with 95% confidence intervals in parentheses and actual numbers in square brackets.
[b]*P. falciparum* parasitaemia only; high parasitaemia: ≥10 parasites/high power field (≥5000/μL approximately).
[c]Temperature ≥37·5°C.
[d]*P. falciparum* gametocytes only.

between children from PHC villages who received placebo and children from neighbouring non-PHC villages The results are illustrated in Fig. 5 and summarized in Table 4. The protective efficacy of insecticide-treated bed nets compared with untreated nets was 45% for clinical episodes associated with any parasitaemia and 54% for clinical episodes associated with high density parasitaemia.

Pre- and post-intervention clinical surveys

A summary of the results of the 2 cross-sectional surveys are presented in Tables 5 and 6. In the pre-intervention (dry season) survey, there was no difference in the prevalence of any malariometric index between the 2 groups of children from PHC villages who had been allocated to receive either weekly Maloprim® or placebo during the forthcoming malaria transmission season, or between these children and those resident in non-PHC villages. In the post-intervention survey, there were significant differences in all the measured indices between the 2 groups of children who received weekly chemoprophylaxis, the prevalence of splenomegaly was reduced by 63%, and the prevalence of parasitaemia and high parasitaemia by 88% and 94%, respectively, compared with children who received placebo.

Following the interventions there were also significant differences in the prevalence of malariometric indices between children in non-PHC villages and children in PHC

Table 7. Malaria among users of untreated bed nets or treated bed nets and among non-users of bed nets in primary health care villages

	No nets[a]	Nets not dipped	Nets dipped[b]
Frequency[c]	3·2% (31/960)	4·4% (42/960)	86·4% (829/960)
Parasitaemia[d]	54·5% (6/11) *	29·4% (5/17)	24·4% (75/307)
Fever[e]+parasitaemia[f]	24·3 (9/371)**	17·3 (9/520)	12·3 (135/11017)
Fever[e]+high parasitaemia[f]	18·9 (7/371)***	7·7 (4/520)	8·4 (93/11017)

[a]Significance of difference between no nets and dipped nets is indicated thus: *Fisher's exact test, $P=0·03$; **Relative rate=2·0 (95% CI: 1·0,3·9) ($\chi^2=4·1$; d.f.=1; $P=0·04$); ***Relative rate=2·2 (95% CI: 1·0,4·8) ($\chi^2=4·5$; d.f.=1; $P=0·03$).
[b]Only children who received placebo are included.
[c]Status not known for 58 children (6·0%).
[d]Prevalence of *P. falciparum* asexual parasitaemia at the November 1989 survey.
[e]Temperature ≥37·5°C.
[f]Episodes/1000 child-weeks at risk; high parasitaemia ≥10 parasites/high power field (≥5000/μL approximately).

villages. The most relevant comparison was between children from non-PHC villages and children from PHC villages who received placebo. The prevalence of splenomegaly among children in PHC villages who slept under impregnated nets and who received weekly placebo was reduced by 35% compared to children in non-PHC villages, while the prevalence of parasitaemia and of high density parasitaemia were reduced by 39% and 48% respectively.

Bed net use and malaria

In PHC villages there were some children who did not use a net and others whose nets were not dipped. The results of the weekly morbidity surveillance and the cross-sectional surveys in these groups of children are presented in Table 7. The incidence of clinical malaria was similar among children who had a treated bed net and among those with an untreated bed net ($\chi^2=1{\cdot}0$; d.f.=1; $P=0{\cdot}31$). However, children who did not use a net had significantly more malaria than children using dipped nets ($\chi^2=4{\cdot}1$; d.f.=1; $P=0{\cdot}04$).

In the June cross-sectional survey, there was no difference in the prevalence of splenomegaly or parasitaemia between children resident in PHC villages who had a net and in those who did not. However, in the November survey, children without nets had a significantly higher prevalence of parasitaemia than children with dipped nets (Fisher's exact test, $P=0{\cdot}03$) (Table 7). There was no difference in the prevalence of parasitaemia or splenomegaly between children with treated and untreated nets living in PHC villages.

The relation between the condition of the net and morbidity from malaria was also investigated. At the time when bed nets were counted, the condition of the net was assessed and classified into one of 3 broad categories: intact, holed with fewer than 5 holes, and holed with 5 or more holes. In the June survey, there was no relationship between the condition of the net and the prevalence of parasitaemia. However, in November, the prevalence of splenomegaly and parasitaemia increased as the condition of the net worsened (χ^2 for trend=3·8; $P=0{\cdot}05$; $\chi^2=5{\cdot}56$; $P=0{\cdot}02$ respectively). No significant trend was found between the incidence of clinical malaria and the condition of the net.

Washing of bed nets and malaria

The incidence of clinical malaria and the prevalence of malariometric indices were similar in children whose insecticide-treated bed nets were washed during the malaria transmission season and in children whose treated nets had not been washed (Table 8).

Compliance with chemoprophylaxis and malaria

Compliance with drug administration was monitored as described previously (ALONSO *et al.*, 1993b). Compliance with drug administration was not associated significantly with age or sex, nor was it significantly different in the children who died compared with those who were alive and resident in the study area at the end of the season ($\chi^2=0{\cdot}02$; d.f.=1; $P>0{\cdot}20$).

Chloroquine consumption

During September 1989, a stratified cross-sectional survey was carried out to obtain urine samples from children in each of the 3 study groups. Chloroquine was demonstrated by ELISA in 19% (33/171) of samples obtained from children in the PHC-Maloprim® group, in 30% (51/169) from those in the PHC-placebo group, and in 35 % (54/156) from those in the non-PHC group (Maloprim® vs placebo $\chi2=5{\cdot}4$; d.f.=1; $P=0{\cdot}02$; placebo PHC vs non-PHC $\chi^2=0{\cdot}7$; d.f.=1; not significant).

Table 8. The effect of washing of bed nets on malaria morbidity at the end of the rainy season

	Unwashed	Washed once	Washed twice
Fever+parasitaemia[a]	14·0	9·6	12·5
Fever+high parasitaemia[b]	9·2	7·4	8·9
Spleen rate[c]	35%	35%	36%
Parasite rate[d]	25%	24%	21%
High parasite rate[e]	7%	9%	7%

[a]Episodes/1000 child-weeks at risk. χ^2 for trend=1·1; d.f.=1; $P=0{\cdot}29$. χ^2 for heterogeneity=3·7; d.f.=2; $P=0{\cdot}17$. Fever: temperature ≥37·5°C; *P. falciparum* parasitaemia only.
[b]Episodes/1000 child-weeks at risk. χ^2 test for trend=0·2; d.f.=1; $P=0{\cdot}69$. χ^2 for heterogeneity=0·9; d.f.=2; $P=0{\cdot}65$. Fever: temperature ≥37·5°C; high parasitaemia: *P. falciparum* only, ≥10 parasites/high power field (≥5000/μL approximately).
[c]χ^2 for trend=0·0, $P=0{\cdot}99$.
[d]χ^2 for trend=0·2, $P=0{\cdot}64$.
[e]χ^2 for trend=0·03, $P=0{\cdot}86$.

Discussion

We found a sharp reduction in child mortality following the introduction of the combined malaria intervention of insecticide-treated bed nets and targeted chemoprophylaxis. This was probably due to the introduction of treated bed nets, since children who received chemoprophylaxis had no apparent additional protection from death, regardless of the level of compliance. However, caution is needed in accepting this interpretation. In 1991, interventions with chemoprophylaxis and treated nets were repeated in PHC villages. During the 1991 rainy season, when malaria transmission was less intense, there were fewer deaths in both PHC and non-PHC villages than during the previous year but a similar selective advantage for PHC villages compared to non-PHC villages was observed. However, in contrast to the finding in 1990, children who received chemoprophylaxis and slept under a treated net had less chance of dying than those who slept under a treated net and received placebo (P. L. Alonso *et al.*, paper in preparation).

The reduction in overall mortality produced by the interventions was greater than expected. During the pre-intervention year, malaria was thought to be responsible for approximately 40% of deaths among children aged 1–4 years but the interventions produced a reduction in mortality close to 60%. There are a number of possible explanations for this finding. Firstly, it is possible that the verbal autopsy technique underestimates the contribution of malaria to mortality. Recent studies undertaken in another part of The Gambia (J. Todd *et al.*, unpublished observations) have shown that malaria frequently gives rise to a raised respiratory rate so that it is likely that some malaria deaths were, incorrectly, considered as deaths from acute respiratory infection. Secondly, it could be argued that the fall in mortality seen in PHC villages was due to concomitant improvements in health care or living standards in the intervention villages associated with the trial. This seems unlikely as the fall in mortality closely followed the introduction of the interventions and was restricted to the malaria transmission season. Thirdly, it is possible that insecticide-treated bed nets are a non-specific intervention effective against other vector-born diseases. This also seems unlikely as sleeping sickness has disappeared from The Gambia, kala-azar is extremely uncommon, and arbovirus infections are rarely fatal except during epidemics. A reduction in flies, and hence in enteric infections, is a possibility, but seems unlikely. Lastly, impregnated nets may have been more effective than expected because malaria is an important indirect cause of death in The Gambia. The fact that, following the introduction of the interventions, a large reduction was seen, not only in malaria deaths but also in deaths attributed to acute respiratory infections, supports this view. Similarly, in Guyana, successful malaria eradication campaigns led to a reduction in deaths from pneumonia (GIGLIOLI, 1972).

In field trials, there is legitimate concern about the impact that the observers may have on the results. We do

not believe that active weekly morbidity surveillance had any significant impact on mortality. Children in PHC villages received antimalarial treatment only from a VHW or health centre. Moreover, urine tests indicated that the level of chloroquine consumption was lowest among PHC children who received weekly Maloprim®, and highest among children from non-PHC villages. The use of health services in both PHC and non-PHC villages remained similar to that described in the pre-intervention year; after intervention, 65% and 67% of deaths in non-PHC and PHC villages respectively occurred at home.

The impact of the interventions on morbidity and on the prevalence of malaria infection has been assessed by means of cross-sectional malaria surveys and through a system of active case detection. Insecticide-treated bed nets reduced the incidence of fever episodes associated with parasitaemia by 45% and were even more effective at reducing those associated with high parasitaemia. These findings are similar to those reported by SNOW *et al.* (1988b) in a nearby area. The slightly lower protection we found may have been due to a higher intensity of transmission in the new study area or to the fact that, in the present trial, net impregnation was done through the PHC scheme and not by the investigators. Among children in PHC villages who slept under treated bed nets, the addition of chemoprophylaxis had a dramatic effect on the incidence of clinical episodes of malaria.

Results from the cross-sectional survey carried out in June, before the malaria transmission season began, showed no difference in the prevalence of malaria between PHC and non-PHC villages. Following introduction of the interventions, significant differences emerged. Insecticide-treated bed nets reduced the prevalence of splenomegaly and malaria parasitaemia by about 40%, and the prevalence of high density parasitaemia by 50%. Among the group of children protected by an insecticide-treated bed net, the addition of malaria chemoprophylaxis led to even greater reductions in these indices. Measurement of the PCV is a good indicator of malaria morbidity in The Gambia. In our trial, the mean PCV of children resident in non-PHC villages fell by an average of 2·4% over the malaria season. Children who slept under a treated net experienced only a minor drop, while those who received additional prophylaxis increased their mean PCV during the malaria transmission season.

The results of the cross-sectional surveys and the weekly surveillance suggested that the combination of the 2 interventions was so effective that, unlike chemoprophylaxis alone (GREENWOOD, 1991), the combined interventions might impair the development of natural immunity.

Permethrin, the pyrethroid insecticide used in this trial, is removed by washing and it was estimated that half of the amount on the net was lost after each wash (LINDSAY *et al.* 1991). At the time when the trial was discussed with the study population, and also when the interventions were implemented, villagers were asked to refrain from washing their nets after treatment with insecticide until the end of the malaria transmission season. This recommendation was followed partially, and the frequency with which people usually washed their nets was reduced. However, more than 50% of nets were washed at least once during the transmission season. None the less, the incidence of malaria was not increased among those who had washed their nets. Similarly, there was no evidence that the protective efficacy of the treated bed nets was reduced over time. In a previous Gambian trial, SNOW *et al.* (1988b) found that insecticide-treated nets were more effective at the beginning of the transmission season than at the end, but this might have been due to a change in the pressure of infection rather than to a decline in the insecticidal property of the nets. It is possible that, even after washing, treated nets have sufficient insecticide remaining to have a protective effect against mosquitoes seeking a bloodmeal. Alternatively, the impregnation of the mattress, on which bed nets were dried after treatment, may have been sufficient to deter mosquitoes from entering the house to feed.

We found that, in PHC villages, the small group of children whose bed nets were not treated with insecticide had a similar incidence of malaria to those whose nets were treated, whereas those with no nets at all had a higher prevalence of malaria parasitaemia. This effect may have been due to confounding factors; for example, children without nets had a lower compliance with chemoprophylaxis than those with nets. However, it is possible that mass treatment of bed nets with insecticide provides a degree of community protection which extends to those with treated nets that have been washed and to those with untreated nets, but not to those without nets. It is possible that children in PHC villages without a net were at an increased risk of malaria due to deflection of mosquitoes.

Approximately one-third of the children who were protected directly or indirectly by insecticide treated bed nets suffered a malaria episode during the transmission season, while children who were additionally receiving Maloprim® had practically no malaria. However, both groups of children experienced very similar levels of mortality, suggesting that insecticide-treated bed nets have a greater protective effect against life-threatening malaria infections than against uncomplicated infections. Insecticide-treated bed nets are only moderately effective at reducing the prevalence of infection; they are better at reducing clinical episodes and most effective at preventing deaths. How this graded effect is achieved is uncertain, nor has the exact way in which insecticide-treated nets achieve their protective effect been determined.

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