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Mortality in a seven-and-a-half-year follow-up of a trial of insecticide-treated mosquito nets in Ghana

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Abstract

A 17% efficacy in preventing all-cause mortality in children aged 6–59 months was previously reported from a cluster-randomized controlled trial of insecticide-treated mosquito nets (ITNs) carried out in the Kassena-Nankana District of northern Ghana from July 1993–June 1995. A follow-up until the end of 2000 found no indication in any age group of increased mortality in the ITN group after the end of the randomized intervention. These results should further encourage the use of ITNs as a malaria control tool in areas of high endemicity of *Plasmodium falciparum*.

Keywords: malaria, *Plasmodium falciparum*, control, insecticide-treated nets, Ghana

Introduction

Randomized controlled trials have demonstrated the efficacy of insecticide-treated mosquito nets (ITNs) and curtains against mortality in children aged < 5 years in a series of African field sites (ALONSO *et al.*, 1991; D'ALESSANDRO *et al.*, 1995; BINKA *et al.*, 1996; NEVILL *et al.*, 1996; HABLUETZEL *et al.*, 1997). However, it has subsequently been suggested that, other things being equal, long-term transmission control in areas of high endemicity may reduce acquisition of clinical immunity and hence only delay severe disease or death, possibly even increasing overall mortality (SNOW & MARSH, 1995; TRAPE & ROGIER, 1996; SNOW *et al.*, 1997).

The original trials ran for only 1–2 years each. At the end of these periods, the efficacy of the intervention was considered proven and the control groups were provided with nets or curtains, thus these trials could not be used to demonstrate the effects of long-term transmission control. One of the original trials of ITNs (BINKA *et al.*, 1996) was carried out in the Kassena-Nankana District of northern Ghana and demographic surveillance at this site continues. We now report on a $7\frac{1}{2}$-year follow-up of this trial. The analysis considers firstly, whether the gains in child survival during the trial were maintained during this longer follow-up period, and secondly, in which age groups the effects on mortality were apparent.

Methods

Kassena-Nankana District, in the Upper East Region of Ghana lies at the northern edge of the country between latitudes 10°30′–11°00′ N and longitudes 1°00′–1°30′ W. Malariological surveys have consistently found the area to be holoendemic for *Plasmodium falciparum* malaria (COLBOURNE & WRIGHT, 1955; BINKA *et al.*, 1994).

A census of the study area was conducted in 1992, and in June 1993 the entire population was enrolled in a cluster-randomized trial of ITNs (BINKA *et al.*, 1996). Ninety-six clusters covered the whole district. A total of approximately 31 000 permethrin-impregnated (50% EC Zeneca, UK) mosquito nets were provided free of charge to residents of over 6035 compounds in the 48 intervention clusters.

Intervention compounds were subsequently visited every 6 months during the 2 years of initial follow-up to reimpregnate the mosquito nets. At the end of this period, ITNs were provided to the control clusters, and thereafter there was no difference in the interventions offered to the 2 groups. Efforts to maintain ITN coverage have not been successful and recent malariological surveys report patterns of infection typical of holoendemic *P. falciparum* malaria with prevalence in children of over 80% in the wet season (OWUSU-AGYEI *et al.*, 2002).

Births, deaths, immigration, and emigration were, and continue to be, recorded in a database (the Navrongo Demographic Surveillance System (NDSS)) and updated every 90 d (BINKA *et al.*, 1999).

Using the NDSS database we identified the cohort of people who were present at the start of the trial and followed them up until they either died or emigrated (Table). To ensure that all members of the cohort were comparable in terms of exposure to the intervention people who were born, or immigrated after the start of the trial, were not included. Hence fewer children 6–59 months of age were included than in the original 2-year follow-up, and the cohort was smaller than the *de jure* population of the district.

Results

The original analyses found that the ITN clusters enjoyed a 17% reduction in all-cause mortality in children aged 6–59 months (95% confidence interval 0–31%) (BINKA *et al.*, 1996). This effect was reproduced in our cohort analyses and was clearly limited to children aged < 2 years at the start of the trial (Figure and Table) and hence < 4 years by the end of the 2-year follow-up. There was no indication in any group that the benefits of reducing malaria exposure for the 2-year period of the trial were lost during the subsequent follow-up period. In particular, in the age group 6–11 months of age at baseline, the cohort analysis found a significant protective efficacy during the 2-year period of the trial (confidence interval not overlapping with 0, see Table) but there was minimal difference between the control and ITN groups in mortality in this age group during the subsequent $5\frac{1}{2}$ years of follow-up (Table).

Discussion

When pilot trials of residual insecticide spraying in highly endemic malaria areas were abandoned, there was no evidence of subsequent increases of mortality above baseline levels in transiently protected groups (MOLINEAUX, 1985). Similarly, a 6-year follow-up of the trial of insecticide-treated curtains in Burkina Faso found no evidence of delayed adverse effects on mortality. The possibility that such effects exist has nevertheless been a concern that has tempered recent enthusiasm for ITNs. We found no evidence for such delayed effects and concluded that if they do exist they are small, and that ITN use should be strongly promoted for young children in highly endemic areas.

The health benefits of reduced exposure to malaria

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Table. Numbers of people at risk and age-specific mortality during the $7\frac{1}{2}$-year follow-up of a trial of insecticide-treated mosquito nets in Ghana

Age at baseline	ITN clusters: Individuals at risk	ITN clusters: Deaths	ITN clusters: Incidence (I_1)[a]	Control clusters: Individuals at risk	Control clusters: Deaths	Control clusters: Incidence (I_0)[a]	Incidence difference[b] (I_1-I_0) (95% CL)
Trial period (July 1993–June 1995)							
< 6 months	1120	86	42·1	1195	111	52·3	−10·7 (−24·4; 2·4)
6–11 months	1085	66	33·3	1074	89	46·5	−13·2 (−26·4; 0·1)
1 year	1527	57	19·7	1530	69	23·8	−4·4 (−11·8; 3·3)
2–4 years	5226	107	10·6	5266	104	10·3	0·3 (−2·6; 3·1)
5–9 years	7034	74	5·4	6944	75	5·6	−0·2 (−2·0; 1·7)
10–19 years	10496	85	4·3	10322	74	3·9	0·4 (−1·0; 1·7)
20–39 years	13545	205	8·1	13084	197	8·1	−0·1 (−1·8; 1·7)
40–59 years	10220	398	20·1	10000	406	21·0	−1·1 (−4·4; 2·0)
⩾ 60 years	4822	536	59·3	4980	549	58·7	−0·2 (−8·4; 8·8)
Overall	49347	3054	12·3	48504	2986	12·3	
Follow-up period (July 1995–December 2000)							
< 6 months	924	49	11·2	941	40	9·1	2·0 (−2·3; 6·0)
6–11 months	930	34	7·5	869	30	7·0	0·6 (−3·1; 4·0)
1 year	1383	40	5·5	1386	36	4·9	0·6 (−1·7; 2·9)
2–4 years	4844	101	4·0	4845	100	3·9	0·0 (−1·1; 1·2)
5–9 years	6574	104	3·1	6499	102	3·0	0·0 (−0·9; 0·8)
10–19 years	9018	126	3·0	8778	107	2·6	0·3 (−0·4; 1·1)
20–39 years	11810	348	5·7	11411	333	5·7	0·0 (−1·0; 1·0)
40–59 years	9615	1079	21·7	9373	1057	21·9	−0·4 (−3·1; 2·1)
⩾ 60 years	4249	1173	57·9	4402	1181	56·2	1·2 (−6·1; 8·2)
Overall	55075	1614	15·5	54395	1674	16·3	

ITN, insecticide-treated net; 95% CL, 95% confidence limits.
[a]Deaths per 1000 person-years-at-risk.
[b]Calculated from a Poisson model (fitted in the programme Winbugs) including a random effect term to allow for heterogeneity in mortality rates between clusters.

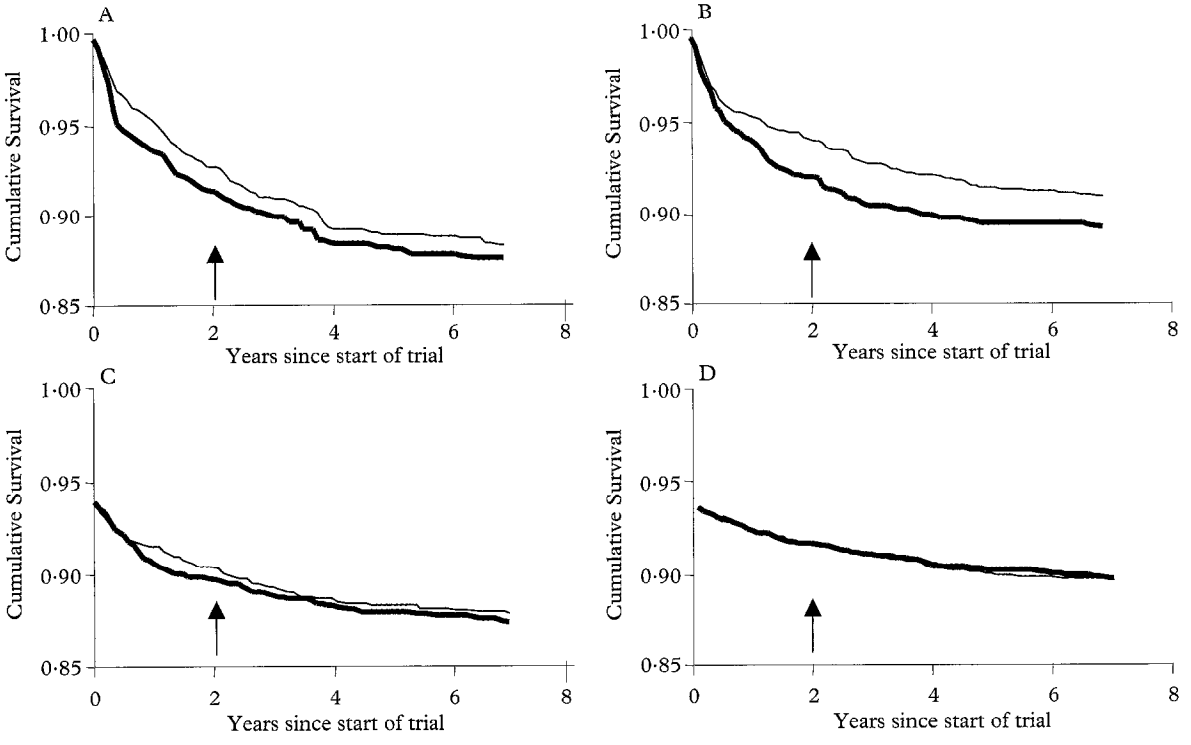

Figure. Kaplan–Meier estimates of cumulative survival. Key: thick lines, control group; thin lines, insecticide-treated net (ITN) group; vertical arrows, the date when ITNs were given to the control group. Age groups at the start of the trial: (A) < 6 months; (B) 6–11 months; (C) 1 year; (D) 2–4 years.

in older people in highly endemic areas remain to be established and young children (and pregnant women) should remain the main targets of ITN programmes. However, the reduction in malaria transmission resulting from preventing mosquitoes feeding on older children and adults in any case contributes to survival of young children in the same community. The use of ITNs should thus be promoted as widely as possible in malaria-endemic areas.

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Book Review

The Behavioural Ecology of Parasites. E. E. Lewis, J. F. Campbell & M. V. K. Sukhdeo (editors). Wallingford: CABI Publishing, 2002. ix + 385pp. Price £65.00. ISBN 0-85199-615-9.

The last significant multi-author monograph on behavioural aspects of the interactions between parasites and their hosts was *Parasites and Behaviour* in 1994, edited by Michael Sukhdeo. In this new text Sukhdeo and his co-editors Edwin Lewis and James Campbell tackle a basically similar subject area in an intriguingly expanded fashion.

As well as pulling together the new findings of the last 8 years related mainly to parasites of vertebrates, *The Behavioural Ecology of Parasites* broadens the scope of its interlocking reviews by including treatments of plant–parasitic and entomopathogenic nematodes, insect parasitoids, seed-feeding insects, and social parasitism in insects.

The more extensive biological landscape of associative interactions surveyed in 16 chapters enables the international mix of authors to demonstrate how widely relevant are the behavioural imperatives of host–parasite systems. The eclecticism of the subject range is patterned by being drawn together in 4 substantive sections 'Foraging for Hosts', 'Host Acceptance and Infection', 'Interactions among Parasites within Hosts', and 'Parasite–Host Interactions'. These sections catalogue, among other topics, the bewildering range of behavioural adaptations in space and time that parasites employ to locate and infect their hosts, the behavioural repertoires of parasites within or on their hosts, and parasite manipulation of host behaviour.

The systems reviewed show a refreshing diversity but give due weight to host–parasite pairings of agricultural, veterinary and human clinical significance. There is much here to interest parasitologists, ecologists, ethologists, and entomologists.

One is left feeling, as one reaches the end of this stimulating book, that it has defined the bounds of a crucial set of organismal interactions, fascinated us with the sheer biological exuberance of parasitic adaptations, but has rarely satisfied our desire for understanding of underlying mechanisms. When our knowledge includes a molecular explanation of the 'fatal attraction' for cat odour elicited in rats infected with *Toxoplasma*, this subject will have truly come of age.

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