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The changing epidemiology of malaria in Ifakara Town, southern Tanzania

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Summary Between 1995 and 2000 there were marked changes in the epidemiology of malaria in Ifakara, southern Tanzania. We documented these changes using parasitological and clinical data from a series of community- and hospital-based studies involving children up to the age of 5 years. There was a right shift and lowering in the age-specific parasite prevalence in the community-based cohort studies. The incidence of clinical malaria in placebo-receiving infants in additional study cohorts dropped from 0.8 in 1995 to 0.43 episodes per infant per year in 2000, an incidence rate ratio of 0.53 (95% confidence interval: 0.404, 0.70, $P < 0.0001$). At the same time, there was an increase in the total number of malaria admissions and a marked right shift in the age pattern of these admissions (median age in 1995 1.55 years *vs.* 2.33 in 2000, $P < 0.0001$). However, the burden of malaria deaths remained in infants. We discuss how these dramatic changes in the epidemiology of malaria may have arisen from the use of currently available malaria control tools. Caution is required in the interpretation of hospital-based data as it is likely to underestimate the impact of anaemia on mortality in the community, where most paediatric deaths occur. Even in low/moderate malaria transmission settings, where older children suffer most malaria episodes, targeting effective malaria control at infants may produce important reductions in infant mortality caused by malaria.

keywords *P. falciparum* malaria, epidemiology, Tanzania, children, malaria control, anaemia

Introduction

In recent years there has been a resurgence of interest in malaria research and control. This positive development stems from a better appreciation of the developmental and economic, as well as health, impacts of the disease (Sachs & Malaney 2002). WHO's Roll Back Malaria has set ambitious goals for malaria control, one of which is to halve the burden of malaria disease by 2010. To reach this target in such a limited time frame it will be necessary to use currently available malaria control tools more efficiently, tailoring specific strategies to distinct endemic settings. This paper presents observations from Ifakara, in southern Tanzania, where different approaches to malaria control have been evaluated during the past decade and where there have been major changes in the pattern of malaria in recent years.

A series of studies since the mid-1980s showed that the subsistence rice farmers of the rural Kilombero valley in southern Tanzania are subject to intense, perennial *Plasmodium falciparum* malaria transmission. Estimated entomological inoculation rates (EIR) of over 300 infectious mosquito bites per person per year have been documented (Tanner *et al.* 1986; Lyimo 1993; Smith *et al.* 1993; Charlwood *et al.* 1998). The effects of this high EIR were clearly reflected in all parasitological and clinical parameters. The age prevalence of parasitaemia showed strong age-dependency (Alonso *et al.* 1996), with parasite prevalence climbing steeply in the first 4 months of life and reaching levels of around 80% by 10 months of age (Kitua *et al.* 1996). Similar prevalences were documented in children not sleeping under mosquito nets in 1999 (Abdulla *et al.* 2001). On the paediatric ward of the district hospital, 44% of clinical malaria cases and 54% of paediatric malaria deaths were in children <1 year of age, a clear sign of intense malaria transmission (Schellenberg *et al.* 1999).

In the midst of the flood plains, the semi-urban setting of Ifakara town has been the site of a series of malaria intervention trials. The intensity of malaria transmission in this Ifakara study area (ISA) is much lower than in the surrounding villages, with an EIR of 29 (95% CI: 19, 44)

infective bites per person per year in the period 1999–2000 (Drakeley *et al.* 2003). In keeping with this, an active case detection cohort demonstrated no age-dependence of malarial disease and a maximal parasite prevalence of only 25% in 4 year olds (Schellenberg *et al.* 2003). Variations in malaria transmission have been described elsewhere (Cattani *et al.* 1986; Goncalves *et al.* 1996; Browne *et al.* 2000; Clarke *et al.* 2002) and, in Kilombero, are likely to be due to a combination of differentials in vector breeding site densities, access to curative treatment from health facilities and shops and the use of insecticide-treated mosquito nets (Drakeley *et al.* 2003). However, in recent years we observed that the pattern of malaria transmission within the ISA itself was changing. This paper documents the transforming epidemiology of malaria in the ISA between 1995 and 2000.

Methods

Study area and population

All data reported here was collected from the ISA, described in detail elsewhere (Schellenberg *et al.* 2003). In brief, the area covers a 6-km radius of the St Francis Designated District Hospital (SFDDH) and includes the rapidly developing semi-urban area of Ifakara Town, the administrative capital of Kilombero district. The ISA was delineated as the recruitment area for a series of intervention studies in order to maximize the completeness of passive case detection, based at SFDDH, of illness episodes or adverse reactions in study participants. The total population of the study area is approximately 85 000, of whom about 2500 are infants at any one time. During the study period the annual rainfall varied between a minimum of 1290 mm in 1996 and a maximum of 1430 mm in 2000, with the exception of a high of 2066 mm in 1997 (C. Golding, personal communication).

Parasite prevalence data

Plasmodium falciparum prevalence data was available from two descriptive cohort studies (Table 1) involving children aged <5 years who were recruited from their homes using a modified EPI sampling scheme (Schellenberg *et al.* 2003). Cross-sectional data were available from March to May and October to November 1998 from the first study, which aimed to investigate the relationship between baseline multiplicity of *P. falciparum* infection and the subsequent risk of clinical malaria. The second study used a rolling cross-sectional survey to

Table 1 Summary information of studies in the Ifakara study area

	Recruitment							
Study	Sample size	Start	Duration	Timing and place	Design	Follow-up	Cross-sectional survey timing	Reference
Ironmal	832	1994	1 year	Post-delivery at SFDDH	Factorial, 4-arm, DBPCRT	4 years	Age 2, 5, 8, 18 and ~48 months	Menendez *et al.* 1997
Infanvac	1207	1996	1 year	Routine vaccinations at MCH clinic, age 1 month	2-arm DBPCRT	17 months	Age 12 and 18 months	Acosta *et al.* 1999
XPCR	611	1998	3 months	Children <5 years at home	Descriptive	8 months	At recruitment and end of follow-up	Henning L *et al.*, unpublished data
KiPAne	701	1999	9 months	Routine vaccinations at MCH clinic, age 2 months	2-arm DBPCRT*	18 months	Age 12 and 18 months	Schellenberg *et al.* 2001
ACD	618	2000	1 month	Children <5 years at home	Descriptive	1 year	Rolling CSV, ~10 children per week	Schellenberg *et al.* 2003

* All children received iron supplementation between 2 and 6 months of age.
MCH, mother and child health; DBPCRT, double-blind placebo-controlled randomized trial.

collect prevalence data while following children at home on a weekly basis to detect episodes of clinical malaria over a 1-year period (Schellenberg *et al.* 2003).

Clinical malaria incidence data

Data on the prevalence of parasitaemia and on the incidence of clinical malaria were available from placebo recipients in a series of placebo-controlled, double-blind randomized studies that recruited cohorts of infants at SFDDH or the adjacent mother and child health clinic (Table 1). The first study (Menendez *et al.* 1997) used a factorial design with iron supplements and/or chemoprophylaxis to assess the relative contributions of iron deficiency and *P. falciparum* malaria to anaemia in infants. The second trial used two arms to assess the safety and efficacy of the malaria vaccine SPf66 (Acosta *et al.* 1999) and the third trial used two arms to assess the safety and efficacy of intermittent malaria treatment in the prevention of clinical malaria and anaemia in infancy (Schellenberg *et al.* 2001).

All children in these cohort studies were recruited from the ISA and given an identity card to facilitate positive identification at the time of presentation to health facilities. Free drug treatment was provided by the project. At the time of recruitment, arrangements for clinical care of sick children were explained to mothers and written instructions were provided. The mother was encouraged to bring the child to the project clinical officer working in the Clinical Surveillance System (CSS) at any time should she be concerned about the child's well-being. The CSS, established in 1994 primarily to monitor illness episodes in children recruited to the intervention studies, monitored outpatient attendances of study children. At least one project-employed clinical officer was available to see study children 24 h a day, every day of the year, to ensure that all outpatient attendances of study children were documented. At presentation to hospital, the clinical officer used a detailed, pre-coded clinical proforma to record the history and clinical signs on examination. If there was a history of fever or a measured axillary temperature ≥37.5 °C the child would have thick blood films prepared for malaria parasite examination from a capillary blood sample. The packed cell volume (PCV) was also measured on these samples and those collected from children who appeared pale. Written informed consent was obtained before initiation of any trial procedures and study protocols were approved by the IHRDC Ethical and National Medical Research Co-ordinating Committees through the Tanzanian Commission of Science and Technology (UTAFITI).

Malaria admission data

The CSS also documented paediatric admissions of study and non-study children to SFDDH, as described in detail elsewhere (Schellenberg *et al.* 1999). Blood slide and PCV results were available from IHRDC for all children admitted only in 1995 and 2000. Data generated by the paediatric inpatient surveillance is presented to document changes in the patterns of malaria admission and death on the paediatric ward of SFDDH. We present paediatric malaria admission data only from children resident in the ISA.

Laboratory methods

All blood slides were read according to standardized quality-controlled procedures (Alonso *et al.* 1994) at the IHRDC laboratory. In brief, thick blood films were air-dried and stained with Giemsa before being read twice, independently, by separate slide readers. The slide reading results were compared by a computer program which generated a list of slides with conflicting results, which were then read a third time by a senior slide reader. PCVs were read using a Hawkesley haematocrit reader at IHRDC after centrifugation of capillary blood in microcapillary tubes.

Data processing and statistical methods

All data were entered twice at IHRDC, and range and internal consistency checks performed on a regular basis. The sensitivity and specificity of different malaria case definitions was assessed in infants using an estimate of the proportion of fevers attributable to malaria given different densities of *P. falciparum* parasitaemia (Smith *et al.* 1994). A measured axillary temperature of ≥37.5 °C with *P. falciparum* parasitaemia of any density had a sensitivity and specificity both >80% in infants. Admitted children were classified as malaria cases if at the time of discharge the clinician considered malaria a major diagnosis on the basis of the clinical course and laboratory results, and the blood slide result from IHRDC was positive for asexual parasites. Severe malarial anaemia was defined as a PCV < 15% in the presence of a blood slide positive for asexual *P. falciparum* parasites.

The estimates of clinical malaria incidence presented in this paper are limited to placebo recipients under 2 years of age. The incidence of malaria episodes was calculated using Poisson regression models with random effects to take into account inter-individual variation. Time at risk commenced at recruitment and ended at 1 year of age or censoring due to withdrawal or death. Children were not

considered at risk for 28 days after the start of each clinical malaria episode.

Results

Data from the community-based studies in the ISA showed a right shift and lowering in age-specific parasite prevalence, the peak prevalence of 35.8% (73/131) in 2-year olds in 1998 changing to a peak prevalence of 24% (29/92) in 4-year olds in 2000. The age-specific parasite prevalence in placebo recipients in the different intervention trials decreased by at least 50% between 1994 and 2001 (Table 2).

Table 2 Age-specific parasite prevalence in placebo recipients

	≥12 months			13–23 months		
Year*	*n*	*N*	%	*n*	*N*	%
1994–96	23	252	9.1	23	135	17.0
1996–98	31	500	6.2	31	420	7.4
2000–01	11	310	3.5	25	294	8.5
Chi-square		7.44			11.63	
P-value		0.024			0.003	

* Data sources are as follows (see Table 1): 1994–96 Ironmal, 1996–98 Infanvac, 2000–01 KiPane.

Table 3 shows that the incidence of clinical malaria in infants, detected by passive case detection, fell by 47% in placebo recipients between 1995 and 2001. The cohorts were similar in terms of haemoglobin genotype and tertiles of distance between children's homes and the hospital (data not shown). However between 1996 and 2001 reported use of a mosquito net increased from 51% (217/423) to 76% (235/310) ($\chi^2 = 45.45$, $P < 0.0001$).

Table 4 presents data on paediatric admissions under 5 years of age from the study area. Between 1995 and 2000 there was a 14% decrease in the number of non-malaria admissions. In contrast, the number of malaria admissions rose by 13% and the proportion of admissions due to malaria increased from 34% (791/2349) to 40% (892/2228) ($\chi^2 = 133.4$, $P < 0.0001$). The age distribution of malaria cases shifted significantly to the right (Figure 1), the median age increasing from 1.53 years in 1995 to 2.33 years in 2000 (Mann–Whitney Z-score $= -10.435$, $P < 0.00001$), and the proportion of malaria cases aged <1 year decreasing from 39% to 17% (Table 4). The number of malaria deaths was similar in the 2 years and, although numbers were small, there was no indication of a change in the proportion of malaria deaths occurring in infants [8/18 (44%) in 1995 and 9/21 (43%) in 2000; $\chi^2 = 0.01$, $P = 0.92$]. The overall malaria case fatality rate did not change during the course of the study, but there

Table 3 The incidence clinical malaria in infant placebo recipients detected by passive case detection

Year	No. of infants	No. of cases	Person years at risk	Incident per person year	Incidence rate ratio (95% CI)	*P*-value
1995–96	207	102	124.9	0.82	1.00	–
1997–98	603	811	1061.7	0.76	0.94 (0.76, 1.16)	0.52
2000–01	351	117	269.5	0.43	0.53 (0.40, 0.70)	<0.0001

Table 4 Malaria and non-malaria admissions and deaths of children <5 years from the Ifakara study area

	1995	2000	Chi-square	*P*-value
Malaria admissions				
Total	791	892		
No. of malaria admissions age <1 year (%)	305 (38.6)	155 (17.4)	94.7	<0.00001
No. of malaria deaths (case fatality rate*)	18 (2.3)	21 (2.4)	0.02	0.9
Malaria deaths, <1 year (case fatality rate)	8 (2.6)	9 (5.8)	2.93	0.09
No. of malaria admissions with PCV < 15% (%)	38 (5.4)	13 (1.5)	19	<0.001
Non-malaria admissions				
Total	1558	1336		
No. of non-malaria admissions age <1 year (%)	796 (51.1)	630 (47.2)	6.6	0.16
No. of non-malaria deaths (case fatality rate*)	109 (7.1)	88 (6.6)	0.23	0.63
Non-malaria deaths, <1 year (case fatality rate)	72 (9.2)	54 (8.6)	0.116	0.73

* Denominators are less than total number of cases as the outcome was unknown for those who absconded or who were referred. Non-malaria deaths: absconded 18 in 1955 and six in 2000. Malaria deaths: absconded two in 1995 and nine in 2000.

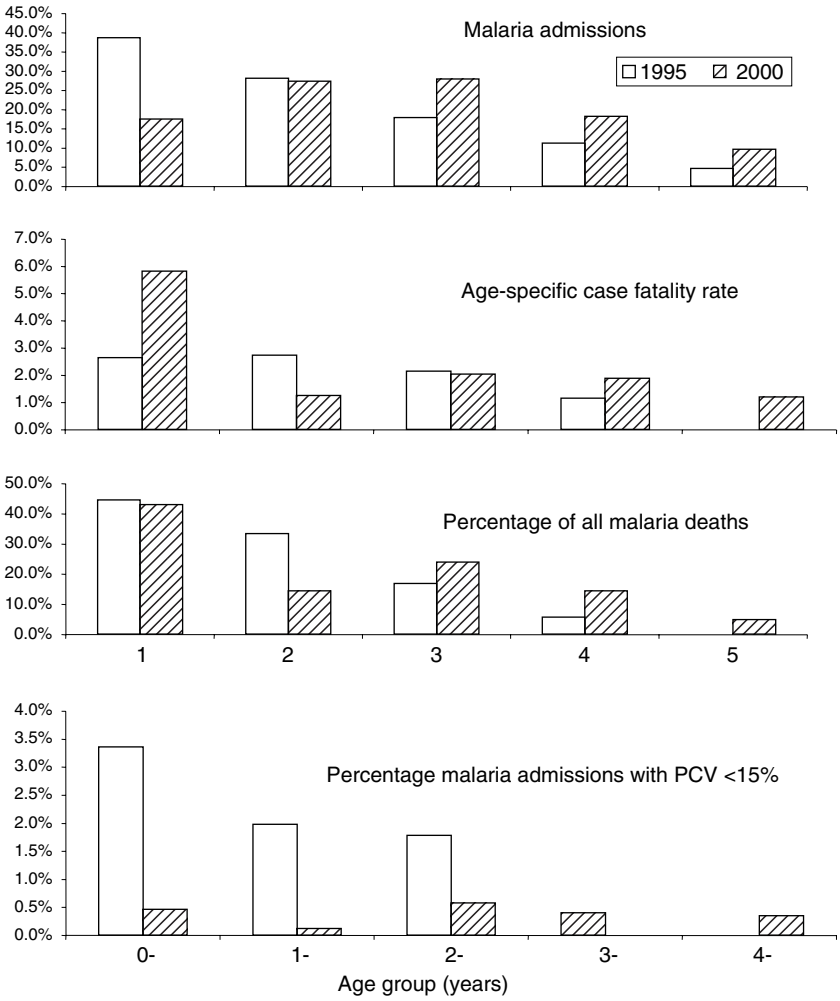

Figure 1 Malaria admissions to SFDDH 1995 and 2000: changes in age distribution, case fatality rate and anaemia.

was an apparent increase in the malaria case fatality rate in infants. The proportion of malaria cases presenting with a PCV < 15% fell from 5.4% to 1.5%. In contrast, there was little change in the age distribution of non-malaria admissions or in their overall – or infant-specific – case fatality rates (Table 4).

Discussion

The pattern of *P. falciparum* infection and disease changed in the ISA between 1995 and 2000. The prevalence of parasitaemia and the incidence of clinical malaria fell by around 50% in infants and were accompanied by a right shift in the age pattern of parasite prevalence in the community and clinical disease in the hospital. Taken together, these data suggest that the intensity of *P. falciparum* transmission may have decreased during the study period. However, the overall effect of this change on the health of children in Ifakara remains to be established, and the reasons for the change are not yet clear.

The apparent decrease in the intensity of transmission was associated with an increase in the number of malaria cases. Setting the data in the context of an annual population growth of 2.6% shows that the 791 malaria admissions in 1995 would increase to 899 by 2000, suggesting that the increase in malaria admissions was in line with the underlying population growth. However, as the total number of admissions from the study area decreased during the same period, possibly the result of the introduction of user charges at SFDDH in 1997, it is likely that the increase in the number of malaria admissions was a real phenomenon. This is also made more likely as the procedures to identify malaria cases, the criteria for admission and the malaria case definition did not change

during the study period. Our findings are thus consistent with an earlier report of higher malaria admission rates in areas with low-moderate transmission than in areas with higher transmission, documented by concomitant observations from five hospitals in settings with different malaria endemicity (Snow *et al.* 1997). It was speculated that these observations resulted from changes in the interplay between incident infections stimulating the acquisition of immunity in the young child while protected from the worst effects of infection by passively acquired maternal immunity. The authors raised the possibility of adverse consequences resulting from the reduction in malaria transmission in Africa. Our results could be interpreted similarly: an increase in the number of malaria cases in the face of a stable case fatality rate suggests an increase in the total number of malaria deaths. However, we caution against such conclusions because these hospital-based studies may not adequately reflect the situation in the community, where most paediatric deaths occur. A reduction in the intensity of transmission may have led to a reduction in the number of deaths in infants who would never have made it to hospital.

The hospital-based malaria case fatality rate in Ifakara in 1995, when anaemia was common, is likely to be considerably lower than the case fatality rate in the community at the same time. This is because of variation in the efficacy and availability of different curative interventions in the two settings, which produces a disparity between hospital and community malaria case fatality rates. The extent of this disparity may vary according to the predominant manifestation of malaria, which is largely age-dependent. For example, severe malarial anaemia is particularly common in infants subject to intense malaria transmission and may develop rapidly with only vague symptomatology, leading to initiation of care seeking when the child is relatively ill. The most effective treatment, early blood transfusion, is usually only available in hospitals, and the outlook for a child far from a transfusion centre is bleak. However, timely blood transfusion may be so effective at saving life that a reduction in infant malaria cases admitted to hospital, secondary to a reduction in life-threatening malarial anaemia, may not lead to a reduction in infant malaria deaths in hospital, a notion supported by our findings. It follows that reducing the number of infant malaria cases may produce important mortality reductions in the community in the absence of a decrease in inpatient infant mortality. The principle that reducing the intensity of transmission has beneficial effects on child health and survival is also supported by the impact on mortality of insecticide-treated materials in areas of intense transmission (Habluetzel *et al.* 1997; Armstrong Schellenberg *et al.* 2001; Phillips-Howard *et al.* 2003).

Despite the relatively small number of infant malaria admissions in 2000, and the predominance of malaria cases in older children, infants suffered more malaria deaths than any other age group. The increased malaria case fatality rate of younger children in our study is in keeping with the observation that young age increases the risk of an adverse outcome in Malawian children with cerebral malaria (Molyneux *et al.* 1989). Our finding is also consistent with a study of Gambian children with malaria and increased lactic acid concentrations, who were at increased risk of death and significantly younger than normolactaemic malaria cases (Krishna *et al.* 1994). This raises the possibility that malaria mortality is highest in children who are younger than those who bear the brunt of malaria disease, a possibility that has practical implications in terms of the target group for preventive malaria control strategies. In particular, the benefits of delivering malaria control interventions alongside routine vaccinations in the first year of life may be greater than suggested by the age pattern of malaria episodes.

Although the overall malaria case fatality rate remained unchanged, there was an ostensible increase in the case fatality rate amongst infants, despite the small numbers. This is likely to be due to the marked decrease in severe malaria-anaemia, which is relatively easily treated by blood transfusion in the hospital setting, thus leaving more complex clinical management problems in small children.

Many factors probably contributed to the change in the epidemiology of malaria in Ifakara and we cannot provide a comprehensive review of all elements that may have been involved. Changes in the level of exposure to *P. falciparum* probably started early in our study as the increase in malaria in 1–4-year olds in 2000 suggests that these children did not receive sufficient parasitological challenge as infants to develop a protective immune response. The absence of comparable entomological data from the study area makes it impossible to exclude a change to a less efficient vector. It is also possible that the changes documented were secular, or even cyclic, variations, although meteorological data from the area reveal no apparent trends. The Kilombero valley, particularly the ISA, was subject to considerable economic development, with an increase in the number of shops and goods available and a general improvement in the quality of housing, which has been associated with reduced risks of anaemia in the area (Kahigwa *et al.* 2002). This development has not been accompanied by major in-migration to the study area, as evidenced by the fact that >97% of families invited to participate in the studies reported here had been residing in the area for at least 2 years. Liberalization of the health sector has resulted in a number of private providers opening clinics and drug stores in the

ISA, although we do not have any indication that these have significantly affected the health-seeking behaviour of the population towards the SFDDH and it is difficult to reconcile these changes with an increase in malaria admissions. The influence of the continuous presence of the research team in the study area is hard to gauge. Several malaria-related studies have been conducted in the area and 6.8% and 10.9% of the under 5-year-old community was directly involved in studies in 1995 and 2000, respectively. However it seems unlikely that the small number of infants receiving an efficacious intervention would account for: (i) the reduced incidence of clinical malaria in placebo recipients in successive trials, (ii) the change in parasite prevalence in the interventionless community-based studies, or (iii) the increase in malaria admissions seen in older children. It is possible that altered patterns of care-seeking behaviour in study children influenced the community at large, but if this effect was marked one would also expect changes in the pattern of non-malaria admissions. There have, however, been two obvious developments in the timeframe of the study with community-wide, malaria-related implications: a change in the first-line malaria treatment and an increased use of mosquito nets.

The Kilombero District Health Team bases malaria control on early effective treatment of malaria cases and the reduction in man–vector contact by promoting the use of insecticide-treated mosquito nets. In 1995–96 the first-line antimalarial treatment was chloroquine, which had a 7-day parasitological efficacy of only 35% in the area (Hatz *et al.* 1998). Appreciation of the falling efficacy of chloroquine led to its abandonment and the increased use of the former second-line treatment, sulphadoxine–pyrimethamine, which had a 7-day parasitological efficacy of 75% in 1999 (Schellenberg *et al.* 2002), and was formally made the first-line malaria treatment in 2000 (MoH Tanzania 2000). The changes we documented are likely to be at least partly due to the change from a low-efficacy, short half-life antimalarial to a high efficacy, and long half-life treatment. The improved efficacy would likely reduce the proportion of malaria cases requiring admission and the sustained protection afforded by the long half-life may have also reduced the reservoir of infection.

Mosquito nets, especially those treated with insecticide, have been shown by meta-analysis to reduce all-cause mortality, severe malaria, clinical malaria and *P. falciparum* parasitaemia by up to 18%, 45%, 48% and 24%, respectively (Lengeler 2000). Estimates show that <20% of households used a mosquito net in the ISA in 1995. Within a few years this figure had increased to over half the study children, but very few of these would have been regularly treated with insecticide. By 2000, the availability of mosquito nets and insecticide had increased, and their costs decreased, due to developments in the private sector and a social marketing programme of nets and insecticide (Armstrong Schellenberg *et al.* 1999). The enhanced net coverage and insecticide usage is likely to have played a role in changing the epidemiology of malaria, although increasing coverage from half to three quarters of infants would not be expected, on the basis of the meta analysis, to reduce the incidence of clinical malaria by half.

In conclusion, the ISA is an area of moderate, perennial *P. falciparum* transmission, surrounded by areas of more intense transmission. In recent years, there have been significant changes in the epidemiology of malaria in the ISA. Changing the first line antimalarial treatment, increasing use of insecticide-treated mosquito nets and socio-economic development are likely to have played a part in these changes. Reductions in malaria disease in one age group were accompanied by an increase in another age group, and no apparent change in the age-pattern of malaria deaths. There is thus a need to evaluate malaria control activities to assess whether reductions in malaria morbidity translate into reductions in malaria mortality. The observation that infants suffered more malaria deaths than any other age group in 2000 raises the possibility that an important impact on mortality may be gained by delivering preventive anti-malaria interventions to infants, even when the burden of malaria disease falls on older children.

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