Published in final edited form as:

Am J Trop Med Hyg. 2008 August ; 79(2): 185–191.

Relationship Between Exposure, Clinical Malaria, and Age in an Area of Changing Transmission Intensity

Wendy P. O'Meara^{*}, Tabitha W. Mwangi, Thomas N. Williams, F. Ellis McKenzie, Robert W. Snow, and Kevin Marsh

Fogarty International Center, National Institutes of Health, Bethesda, Maryland; Kenya Medical Research Institute, CGMRC/Wellcome Trust Collaborative Programme, Kilifi, Kenya; KEMRI/Wellcome Trust Collaborative Programme, Nairobi, Kenya; Centre of Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, United Kingdom

Abstract

The relationship between malaria transmission intensity and clinical disease is important for predicting the outcome of control measures that reduce transmission. Comparisons of hospital data between areas of differing transmission intensity suggest that the mean age of hospitalized clinical malaria is higher under relatively lower transmission, but the total number of episodes is similar until transmission drops below a threshold, where the risks of hospitalized malaria decline. These observations have rarely been examined longitudinally in a single community where transmission declines over time. We reconstructed 16 years (1991–2006) of pediatric hospital surveillance data and infection prevalence surveys from a circumscribed geographic area on the Kenyan coast. The incidence of clinical malaria remained high, despite sustained reductions in exposure to infection. However, the age group experiencing the clinical attacks of malaria increased steadily as exposure declined and may precede changes in the number of episodes in an area with declining transmission.

INTRODUCTION

Understanding the relationship between transmission intensity, infection, and the burden of clinical malaria is important for choosing indicators to measure the long-term impact of control measures that reduce transmission. Multi-site comparisons relating transmission intensity to the incidence of clinical malaria^{1–4} and malaria mortality^{5–7} show a relationship that is complicated and nonlinear. As malaria transmission increases, there is a steep initial increase in the rate of hospital admissions with malaria, but thereafter, the risk of hospitalization rises either more slowly or plateaus at intermediate ranges of transmission intensity and may decrease slightly in areas of very high transmission.^{1,2,4}

^{*}Address correspondence to Wendy P. O'Meara, 16 Center Drive, Bethesda, MD 20892. E-mail: prudhomw@mail.nih.gov.

Disclosure: There are no competing interests to declare.

Authors' addresses: Wendy P. O'Meara, Tabitha W. Mwangi, Thomas N. Williams, and Kevin Marsh, Centre for Geographic Medicine Research–Coast, Kenya Medical Research Institute, Wellcome Trust Laboratories, P.O. Box 230, Kilifi, Kenya, Tel: 254-125-22063, Fax: 254-125-22390, E-mail: prudhomw@mail.nih.gov. F. Ellis McKenzie, 16 Center Dr., Bethesda, MD 20892. Robert W. Snow, Centre for Geographic Medicine, KEMRI-University of Oxford-Wellcome Trust Collaborative Programme, Kenyatta National Hospital Grounds, P.O. Box 43640-00100, Nairobi, Kenya.

Financial support: This investigation received financial support from The Wellcome Trust and the Kenya Medical Research Institute. WPO gratefully acknowledges the Fogarty International Center of the National Institutes for Health for funding and support. TNW is supported by The Wellcome Trust as a Senior Research Fellow (076934/Z/05/Z) and by funds awarded through the BioMalpar European Network 6 initiative. RWS is supported by the Wellcome Trust as Principal Research Fellow (079081).

Transmission intensity also affects other clinical features of malaria such as the average age at which children experience serious episodes of malaria. Children present with symptomatic malaria at a younger age in areas of high transmission than in areas with lower transmission.^{8–10} Under conditions of very low transmission, the risk of clinical disease extends into adulthood,¹¹ where risks of a clinical event are more directly related to the risks of infection than the effect of acquired clinical immunity.

These relationships have been defined largely from comparisons of clinical data collected over time at different transmission settings paired with cross-sectional data on transmission intensity collected at single time points^{1,2,4–7} or on the basis of heterogeneity of exposure within a single site over a short time span.^{12,13} The natural experiment has not been described where systematic declines in parasite exposure from birth over time are compared with the average age of a clinical event and the overall childhood risks of malaria. Here we describe the clinical epidemiology of pediatric malaria from a single site on the Kenyan coast over a 16-year period in the context of declining transmission intensity.

MATERIALS AND METHODS

Study area

Ngerenya is a community of 13,800 people located in the northern part of Kilifi district on the coast of Kenya. Details of the study location have been described elsewhere.^{14,15} Malaria transmission in Ngerenya is highly seasonal after the long rains in April–June and the short rains in October–November each year. The main malaria vectors are *Anopheles gambiae* s.l., with minor contributions from *An. funestus*.¹⁶ In Ngerenya, the entomologic inoculation rate (EIR) was estimated to be 10 infectious bites per year during the early 1990s. More recent evidence suggests that current transmission may be much lower.¹⁷

Bednet use in the early 1990s was estimated to be < 6%.¹⁸ An insecticide-treated net (ITN) trial was initiated in June 1993,¹⁹ and ITNs were distributed to some parts of Ngerenya. At the conclusion of the study in 1994, treated nets were distributed to all families. ITNs and re-treatment were available through social marketing campaigns in the retail sector until 2004 but uptake was low.²⁰ In 2000, a survey showed that 70% of children younger than 10 years old had nets, but only 10% of them were properly treated.²¹ In 2005, ITNs became available through government clinics at highly subsidized rates.²² Although the percentage of children sleeping under a treated net in Ngerenya at the end of the surveillance period is not known, a free mass distribution campaign was undertaken by the District Health Management Team in September 2006, which significantly increased the ITN coverage across Kilifi district.²³

Chloroquine was the first-line antimalarial therapy until 1998 when the Ministry of Health implemented a switch to sulphadoxine-pyrimethamine (SP).²⁴ At the time of the switch, > 50% of childhood fevers were treated first with drugs purchased at local shops. A shopkeeper training program was active during the switch to SP to increase antimalarial access in the community through the informal retail sector.²⁵ Artemether-lumefantrine replaced SP in government clinics in September 2006 and has since been offered to pediatric patients free of charge through the public health sector.²⁶ Currently, the Ngerenya community is served locally by one government dispensary, one private clinic, and one private dispensary.

Hospital admissions

Ngerenya is situated ~15 km to the north of Kilifi District Hospital (KDH), which serves as the first referral center for the majority of patients requiring hospitalization. KDH operates a 35-bed pediatric ward and a smaller pediatric high dependency unit. Patients arriving at the hospital are seen first in the outpatient area and admitted to the ward if they are considered too

ill to be treated as an outpatient. Clinical examination, demographic details (including address), laboratory studies, discharge diagnoses, and outcome are recorded in a central database for each child admitted.^{27,28} A routine blood slide is taken on all admissions and is examined by microscopy for malaria parasites. Primary and secondary discharge diagnoses are assigned by a medical officer on review of all clinical notes and laboratory studies made during the child's stay in the hospital. Children admitted to the ward are between birth and 12 years of age. All children identified at the time of admission as a resident in a household in Ngerenya are included in this analysis.

Here we consider three case definitions of malaria. First, any child admitted to hospital with slide-confirmed parasitemia. Second, any child admitted to hospital with slide-confirmed parasitemia and a primary or secondary discharge diagnosis of malaria. Third, any child admitted to the hospital with a parasitemia of $> 2,500$ parasites/ μL . This latter definition provides the most specific definition of clinical malaria free of the subjective bias of assigning a diagnosis.²⁹ Slide-negative children are all those admitted without evidence of peripheral malaria infection.

Annual rates of pediatric hospital admissions from the Ngerenya area are reported per 1,000 children ages 0–12 years which are residents of Ngerenya. The denominators were computed from census enumeration data collected three times per year from 2002 to 2006. Within each year, the number of children was estimated by interpolating to the midpoint of that year using the five nearest census rounds. Before 2002, the number of children was estimated by fitting the mid-year points from 2002 to 2006 with a linear regression and extrapolating to earlier years.

Clinical episodes in the community

In September 1998, longitudinal surveillance of a cohort was initiated in Ngerenya. The cohort and all monitoring activities are described in detail elsewhere.¹⁵ Briefly, households within the study area were chosen randomly, and children in each household were enrolled. Selection continued until the required number of children was enrolled. Four hundred twenty-three children between birth and 8 years of age were initially recruited, and newborns were enrolled continuously during each year. The axillary temperature of each child was measured by a field worker during weekly home visits. Any child with a temperature $\geq 37.5^\circ\text{C}$ or a history of fever was referred to the study clinic, and transportation costs were paid as part of the study. At the clinic, a blood film was made to check for parasites. Clinical outpatient malaria is defined as a temperature $\geq 37.5^\circ\text{C}$ measured at home or at the clinic and any parasitemia. Children who were unwell between weekly visits were also brought to the clinic, but here we have only included actively detected cases to control for differences in utilization rates.

Community cross-sectional prevalence

Age-stratified parasite prevalence data were available from several community cross-sectional surveys undertaken in February 1993 (C. Nevill, personal communication), March/August 1995¹ and since 1998 from bi-annual surveys in May and October among the longitudinal cohort in Ngerenya.¹⁵ Infants were recruited continuously into the cohort and therefore represent an independent sample from year to year.

Cross-sectional parasite prevalence in children is a well-established proxy measure for transmission intensity. Infant parasite prevalence correlates closely to the force of infection,³⁰ thus reflecting annual difference in transmission intensity. Although it is a more sensitive indicator of transmission intensity than prevalence in older children because of early saturation and long duration of infections,³¹ it becomes less sensitive as transmission declines,³² unless extremely large numbers of infants are examined serially during a year. We report the parasite

prevalence in infants 1–11 months of age as a measure of contemporary community parasite exposure. We also included data on the prevalence of infection among children 5 years of age (60–71 months) to supplement information provided for infants.

For infant parasite prevalence estimates, multiple surveys done in the same calendar year are pooled to give a single estimate in that year. For 5 year olds in the cohort (from 1998 onward), only one survey (May) in each year is used to estimate prevalence in 5 year olds to avoid any child contributing twice to the annual estimate. The use of a single age band of 1 year (5 year olds) also avoids any child appearing in prevalence estimates in consecutive years.

During all community-based surveys and clinic visits, thick and thin blood films were made from finger-prick samples. Slides were air-dried, after which the thin film was fixed in 100% methanol. Both films were stained for 10 minutes with 10% Giemsa stain and examined by light microscopy. One hundred fields were examined before a slide was declared negative.

Analysis

Comparisons of parasite prevalence estimates in infants between years were performed using a two-sided test for proportions. Trends in parasite prevalence with time were evaluated using a χ^2 test for trend. Confidence intervals (CIs) for prevalence estimates and incidence of clinical malaria in the community are exact binomial 95% CIs and CIs for rates, respectively. The probability of measuring a prevalence of zero was calculated using a hypergeometric distribution. Linear regression was used to explore the relationship between year and incidence of clinical episodes and between year and mean age of admission. Differences in age of slide-positive and slide-negative admissions within a single year were tested for significance by the Mann-Whitney test. Statistical analyses were performed using Stata 9.0 (Stata Corp., College Station, TX).

Ethical approval

Studies and data collection methods were approved by the Kenyan Medical Research Institutes ethical review committee.

RESULTS

Parasite prevalence

Data from cross-sectional surveys conducted in Ngerenya were available from 1993, 1995, and 1998–2005 (Table 1). Parasite prevalence in infants declined from 19% to undetectable levels over the surveillance period. Over the first half of the surveillance period, the prevalence dropped by nearly half and continued to decline to undetectable levels in the next 6 years. Similarly, prevalence in 5 year olds declined to one third of its starting value by 2003 and dropped precipitously to undetectable levels in the next year, at the same time that infection in infants also dropped below detection. The overall prevalence in children ages 0–9 in 1993 was 59.1% (95% CI: 51.8– 66.1%, $N = 193$) and fell to 2% by 2005 (95% CI: 0.6–4.6%, $N = 252$).

Prevalence estimates for infants and 5 year olds reported here are sub-samples of larger surveys conducted in each year selected for age (1–11 months or 5 years of age) and location of residence (Ngerenya). The number of infants and children in each survey meeting these criteria are small ($N = 12$ –69, median = 39), which limited statistical power to detect any annual declines in parasite prevalence that may have existed. However, parasite prevalence at the end of the surveillance period was significantly lower than in 1993 in both infants and 5 year olds ($P = 0.0159$ and $P < 0.00001$, respectively) and the trend of declining prevalence over the 15-year surveillance period was also significant in both groups ($P = 0.0061$ and $P = 0.0001$ for infants and children, respectively).

There is a possibility that the prevalence in infants remained constant at 2% from 2002 onward. The probability of measuring a prevalence of zero in infants in 2004 and 2005 if the true prevalence remained at 2% is 0.43–0.65, but the probability of measuring a prevalence > 2% is 0.14 in 2004 and 0.29 in 2005 and the probability of measuring a prevalence greater than the upper 95% CI for 2003 is < 0.01. In other words, the size of the sample may have prevented detection of a low, but stable prevalence, but the probability that an increase in prevalence was not detected is small.

Incidence of malaria episodes in the community

An average of 481 (range, 229–774) children younger than 8 years of age and residents of Ngerenya were monitored continuously over 8 years for fever during weekly home visits. Infants were recruited into the cohort each year, and children were dropped from the analysis on their ninth birthday. The annual incidence of malaria episodes detected in these children and treated at the study clinic are shown in Figure 1. Incidence varied by an order of magnitude over the 8-year period, from a maximum of nearly 1 episode per child per year in 2001 to < 0.1 in more recent years. Overall, there was a significant decline in clinical episodes of fever and parasites ($P = 0.006$). The greatest reduction was observed between 2003 and 2004, when incidence dropped > 5-fold from 0.73 to 0.13 episodes per person year at risk (PYAR).

Incidence of hospital admissions

The total number of children 0–12 years of age living in Ngerenya was estimated to be 4,426 in 1991 and rose to 6,748 in 2006. The incidence of hospital admissions of these children ranged from 20 to 40 hospitalizations per year per 1,000 children (Figure 2A). Slide-positive admission rates decreased from a maximum of 22.6 per 1,000 children in 1994 to < 2 per 1,000 in 2006. Linear regression showed a significant decline in slide-positive admissions with time between 1991 and 2006 ($P = 0.001$). However, there was no significant trend in malaria admission from 1991 through 2003 ($P = 0.16$), indicating that reductions in incidence of hospitalized malaria were concentrated in the last 3 years. The proportion of admissions that were slide positive decreased very slowly, if at all, between 1991 and 2003, but dropped sharply between 2003 and 2004 (Figure 2B).

In every year, 90% of slide-positive admissions had a discharge diagnosis of malaria, and 82% of slide-positive admissions had a parasitemia > 2,500 parasites/ μ L (data not shown). These proportions remained consistent from year to year, and thus these alternate definitions of malaria morbidity show trends that are identical to those of the slide-positive admissions.

Mean age of hospital admissions

Over the 15 years of admissions recorded at KDH, the mean age of admission with a positive blood smear among children from Ngerenya increased from 2.9 to 4.9 years of age (Figure 3). The overall trend of age by year for slide positive admissions from 1991 to 2006 was positive and highly significant ($P < 0.00001$). The mean age of clinical cases and the trend in mean age with time was virtually identical when alternate case definitions (discharge diagnosis of malaria or parasitemia > 2,500 parasites/ μ L) were applied (data not shown). In contrast, the mean age of slide-negative admissions fluctuated from year to year but did not change consistently over the same time period ($P = 0.3$).

DISCUSSION

The relationship between malaria exposure, infection, and disease must certainly be governed by biological relationships, but relating them through epidemiologic measurements has proven challenging. Studies that describe clinical malaria as a function of transmission intensity rely on comparisons across ecologic zones and pair clinical data collected over months or years

with a single cross-sectional measure of transmission intensity.^{1,2,4-7} They relate disease burden to a static snapshot of transmission in a geographical location with an unknown history of transmission. Such comparisons may not accurately predict the patterns of clinical malaria in an area experiencing changes in transmission intensity. Sixteen years of surveillance in a community in coastal Kenya has generated a more comprehensive picture of the impact of reduced exposure on the clinical burden of disease and the age groups experiencing that burden.

Previous analyses have predicted that the rate of hospitalized malaria is insensitive to changes in transmission intensity over a wide range of values.^{2,3,33} A multi-site analysis of hospitalized malaria cases as a function of parasite prevalence in children 0–9 years of age predicted that the incidence of malaria cases is bi-phasic; it initially increases with parasite prevalence, or exposure, reaching a peak near 20% prevalence, and declines slightly with increasing prevalence.⁴ Similarly, longitudinal observations from Ngerenya also showed a non-linear relationship between infant parasite prevalence and the incidence of hospitalized malaria (Figure 4; data from Figure 2A and Table 1). From 1993 to 2003, infant parasite prevalence declined from 19% to a few percent, and the prevalence in 5 year olds declined by two thirds. Despite significant reductions in exposure to infection, the incidence of hospitalized malaria did not change significantly over the same interval. From 2003 onward, further decreases in parasite prevalence were accompanied by a sharp reduction in hospital admissions, suggesting that Ngerenya fell below the threshold exposure level required to see a significant reduction in hospital admissions. Overall prevalence in children 0–9 years of age in 1993 was 59% and at the end of the surveillance period was 2%, well below the theoretical threshold of 20% predicted in earlier studies. The incidence of malaria in the community showed the same pattern as hospitalized malaria, with evidence of a threshold crossed between 2003 and 2004. The reductions in both prevalence and incidence of disease were maintained over the last 3 years of surveillance.

The mean age of slide-positive admissions rose steadily from the late 1990s, a change that seems to have preceded the abrupt decrease in the number of malaria admissions observed between 2003 and 2004 (Figure 4). This observation is in agreement with earlier studies where communities with much higher mean ages of malaria morbidity still experienced the same total malaria morbidity as those with a much lower mean age.^{2,3,34} Ifakara, Tanzania has reported decreasing prevalence and incidence of disease in young children with an associated increase in age of malaria admissions, but age data from only two time points during a 5-year period are compared and do not provide insight into the dynamics of changes in age as a function of exposure.³⁵

It could be argued that the incidence of hospitalized clinical malaria began to decrease in the late 1990s, with an anomalous year in 2003. However, the observation that the proportion of admissions with malaria remained stable until 2003 suggests that the decrease began after 2003, and certainly 2004 was the first year that malaria admissions were lower than any previous year in the surveillance period. This is further supported by the consistency between the incidence of malaria in the community and the incidence of hospitalized malaria; both show dramatic declines between 2003 and 2004, the same time the prevalence in the cohort dropped below detection.

Only one entomologic measure of transmission is available from this area during the surveillance period¹⁶; thus, trends in exposure are inferred from cross-sectional prevalence. We cannot separate out the possible initial effects of the widespread introduction of an effective antimalarial drug (SP) from 1998 in directly reducing the apparent prevalence, from the expected downstream effect of such a reduction on transmission. However, it seems unlikely that initial reductions in prevalence of asymptomatic parasitemia caused by the introduction of SP would have been maintained in the face of rising resistance to SP without sustained

reductions in transmission. This, together with the concurrent changes in mean age of disease and, later, incidence of malaria admissions, provides strong evidence in support of a true reduction in exposure to infection.

Longitudinal surveillance in a community with declining exposure to malaria infection confirms predictions about the relationship between transmission intensity and incidence of clinical malaria episodes derived from comparisons across ecological zones. Data from Ngerenya show for the first time the direct relationship between changing transmission intensity and the mean age of clinical disease. Our results suggest that changes in the mean age of clinical disease may be a more contemporary measure of change in transmission intensity than the incidence of disease, particularly over a wide range of intermediate values of transmission. These results give new insights into the dynamics of exposure, disease, and age incidence of malaria relevant to malaria control measures designed to reduce transmission.

Finally, it should be noted that the data reported here relate to only a part of Kilifi district and that, although the incidence of hospitalized malaria has certainly fallen in the district as a whole,²³ the magnitude of the changes reported here is larger, as one might expect in a part of the district that has traditionally been regarded as having lower transmission than other areas.^{15, 17}

Acknowledgements

This work was published with the permission of the Director of KEMRI. The authors thank all the clinical, field, demography, and laboratory staff at the KEMRI/Wellcome Trust Programme who made this study possible. The KEMRI/Wellcome Trust Programme is a member of the INDEPTH Network of demographic surveillance sites.

References

1. Snow RW, Omumbo JA, Lowe B, Molyneux CS, Obiero JO, Palmer A, Weber MW, Pinder M, Nahlen B, Obonyo C, Newbold C, Gupta S, Marsh K. Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa. *Lancet* 1997;349:1650–1654. [PubMed: 9186382]
2. Trape JF, Quinet MC, Nzingoula S, Senga P, Tchichelle F, Carme B, Candito D, Mayanda H, Zoulani A. Malaria and urbanization in Central Africa—the example of Brazzaville. 5. Pernicious attacks and mortality. *Trans R Soc Trop Med Hyg* 1987;81:34–42. [PubMed: 3455565]
3. Snow RW, Deazavedo IB, Lowe BS, Kabiru EW, Nevill CG, Mwankusye S, Kassiga G, Marsh B, Teuscher T. Severe childhood malaria in 2 areas of markedly different falciparum transmission in East Africa. *Acta Trop* 1994;57:289–300. [PubMed: 7810385]
4. Marsh K, Snow RW. Malaria transmission and morbidity. *Parassitologia* 1999;41:241–246. [PubMed: 10697862]
5. Smith T, Killeen G, Lengeler C, Tanner M. Relationships between the outcome of *Plasmodium falciparum* infection and the intensity of transmission in Africa. *Am J Trop Med Hyg* 2004;71:80–86. [PubMed: 15331822]
6. Smith TA, Leuenberger R, Lengeler C. Child mortality and malaria transmission intensity in Africa. *Trends Parasitol* 2001;17:145–149. [PubMed: 11286800]
7. Snow RW, Marsh K. Will reducing *Plasmodium falciparum* transmission alter malaria mortality among African children? *Parasitol Today* 1995;11:188–190.
8. Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, Olomi R, Cox J, Nkya W, Lemnge M, Greenwood BM, Riley EM. Association of transmission intensity and age with clinical manifestations and case fatality of severe *Plasmodium falciparum* malaria. *JAMA* 2005;293:1461–1470. [PubMed: 15784869]
9. Idro R, Aloyo J, Mayende L, Bitarakwate E, John CC, Kivumbi GW. Severe malaria in children in areas with low, moderate and high transmission intensity in Uganda. *Trop Med Int Health* 2006;11:115–124. [PubMed: 16398762]

10. Modiano D, Sirima BS, Sawadogo A, Sanou I, Pare J, Konate A, Pagnoni F. Severe malaria in Burkina Faso: influence of age and transmission level on clinical presentation. *Am J Trop Med Hyg* 1998;59:539–542. [PubMed: 9790426]
11. Baird JK, Basri H, Weina P, MaGuire JD, Barcus MJ, Picarema H, Elyazar IR, Ayomi E, Sekartuti. Adult Javanese migrants to Indonesian Papua at high risk of severe disease caused by malaria. *Epidemiol Infect* 2003;131:791–797. [PubMed: 12948380]
12. Smith T, Charlwood JD, Kitua AY, Masanja H, Mwankusye S, Alonso PL, Tanner M. Relationships of malaria morbidity with exposure to *Plasmodium falciparum* in young children in a highly endemic area. *Am J Trop Med Hyg* 1998;59:252–257. [PubMed: 9715941]
13. Beier JC, Oster CN, Onyango FK, Bales JD, Sherwood JA, Perkins PV, Chumo DK, Koech DV, Whitmire RE, Roberts CR, Diggs CL, Hoffman SL. *Plasmodium falciparum* incidence relative to entomological inoculation rates at a site proposed for testing malaria vaccines in Western Kenya. *Am J Trop Med Hyg* 1994;50:529–536. [PubMed: 7911282]
14. Snow RW, Schellenberg J, Peshu N, Forster D, Newton C, Winstanley PA, Mwangi I, Waruiru C, Warn PA, Newbold C, Marsh K. Periodicity and space-time clustering of severe childhood malaria on the coast of Kenya. *Trans R Soc Trop Med Hyg* 1993;87:386–390. [PubMed: 8249058]
15. Mwangi TW, Ross A, Snow RW, Marsh K. Case definitions of clinical malaria under different transmission conditions in Kilifi District, Kenya. *J Infect Dis* 2005;191:1932–1939. [PubMed: 15871128]
16. Mbogo CNM, Snow RW, Khamala CPM, Kabiru EW, Ouma JH, Githure JI, Marsh K, Beier JC. Relationships between *Plasmodium falciparum* transmission by vector populations and the incidence of severe disease at 9 sites on the Kenyan coast. *Am J Trop Med Hyg* 1995;52:201–206. [PubMed: 7694959]
17. Mbogo CM, Mwangangi JM, Nzovu J, Gu WD, Yan GY, Gunter JT, Swalm C, Keating J, Regens JL, Shililu JI, Githure JI, Beier JC. Spatial and temporal heterogeneity of anopheles mosquitoes and *Plasmodium falciparum* transmission along the Kenyan coast. *Am J Trop Med Hyg* 2003;68:734–742. [PubMed: 12887036]
18. Snow RW, Peshu N, Forster D, Mwenesi H, Marsh K. The role of shops in the treatment and prevention of childhood malaria on the coast of Kenya. *Trans R Soc Trop Med Hyg* 1992;86:237–239. [PubMed: 1412642]
19. Nevill CG, Some ES, Mungala VO, Mutemi W, New L, Marsh K, Lengeler C, Snow RW. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Trop Med Int Health* 1996;1:139–146. [PubMed: 8665377]
20. Snow RW, McCabe E, Mbogo CNM, Molyneux CS, Some ES, Mung'ala V, Nevill CG. The effect of delivery mechanisms on the uptake of bed net re-impregnation in Kilifi District, Kenya. *Health Policy Plan* 1999;14:18–25. [PubMed: 10351466]
21. Mwangi TW, Ross A, Marsh K, Snow RW. The effects of untreated bednets on malaria infection and morbidity on the Kenyan coast. *Trans R Soc Trop Med Hyg* 2003;97:369–372. [PubMed: 15259458]
22. Noor AM, Amin AA, Akhwale WS, Snow RW. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. *Plos Medicine* 2007;4:1341–1348.
23. Okiro EA, Hay SI, Gikandi PW, Sharif SK, Noor AM, Peshu N, Marsh K, Snow RW. The decline in paediatric malaria admissions on the coast of Kenya. *Malar J* 2007;6:151. [PubMed: 18005422]
24. Shretta R, Omumbo J, Rapuoda B, Snow RW. Using evidence to change antimalarial drug policy in Kenya. *Trop Med Int Health* 2000;5:755–764. [PubMed: 11123822]
25. Marsh VM, Mutemi WM, Willetts A, Bayah K, Were S, Ross A, Marsh K. Improving malaria home treatment by training drug retailers in rural Kenya. *Trop Med Int Health* 2004;9:451–460. [PubMed: 15078263]
26. Amin AA, Zurovac D, Kangwana BB, Greenfield J, Otieno DN, Akhwale WS, Snow RW. The challenges of changing national malaria drug policy to artemisinin-based combinations in Kenya. *Malar J* 2007;6:72. [PubMed: 17535417]
27. Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MP, Njenga S, Hart CA, Maitland K, English M, Marsh K, Scott JA. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005;352:39–47. [PubMed: 15635111]

28. Berkley JA, Ross A, Mwangi I, Osier FH, Mohammed M, Shebbe M, Lowe BS, Marsh K, Newton CR. Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study. *BMJ* 2003;326:361. [PubMed: 12586667]
29. Bejon P, Berkley JA, Mwangi T, Ogada E, Mwangi I, Maitland K, Williams T, Scott JA, English M, Lowe BS, Peshu N, Newton CR, Marsh K. Defining childhood severe falciparum malaria for intervention studies. *PLoS Med* 2007;4:e251. [PubMed: 17713980]
30. Macdonald G. The analysis of malaria parasite rates in infants. *Trop Dis Bull* 1950;47:915–938. [PubMed: 14798657]
31. Snow RW, Molyneux CS, Warn PA, Omumbo J, Nevill CG, Gupta S, Marsh K. Infant parasite rates and immunoglobulin in seroprevalence as a measure of exposure to *Plasmodium falciparum* during a randomized controlled trial of insecticide-treated bed nets on the Kenyan coast. *Am J Trop Med Hyg* 1996;55:144–149. [PubMed: 8780451]
32. Pringle G, Draper CC, Clyde DF. A new approach to the measurement of residual transmission in a malaria control scheme in East Africa. *Trans R Soc Trop Med Hyg* 1960;54:434–438. [PubMed: 13738053]
33. Mbogo CNM, Snow RW, Kabiru EW, Ouma JH, Githure JI, Marsh K, Beier JC. Low-level *Plasmodium falciparum* transmission and the incidence of severe malaria infections on the Kenyan coast. *Am J Trop Med Hyg* 1993;49:245–253. [PubMed: 8357087]
34. Rogier C, Tall A, Diagne N, Fontenille D, Spiegel A, Trape JF. *Plasmodium falciparum* clinical malaria: lessons from longitudinal studies in Senegal. *Parassitologia* 1999;41:255–259. [PubMed: 10697865]
35. Schellenberg D, Menendez C, Aponte J, Guinovart C, Mshinda H, Tanner M, Alonso P. The changing epidemiology of malaria in Ifakara Town, southern Tanzania. *Trop Med Int Health* 2004;9:68–76. [PubMed: 14728609]

Figure 1. Annual incidence of clinical malaria (fever plus parasites) per person year at risk (PYAR) with 95% confidence intervals in a longitudinal cohort of children between birth and 8 years old.

Figure 2.

A, Incidence by year of all pediatric hospital admissions (light bars) and slide-positive pediatric admissions (dark bars) per 1,000 children 0–12 years old and residents of Ngerenya. **B,** Fraction of all admissions that were slide positive by year.

Figure 3. Mean age and 95% confidence intervals (dotted lines) of slide-positive pediatric admissions (left) and slide-negative pediatric admissions (right) by year from Ngerenya.

Figure 4. Mean age and incidence of slide-positive hospital admissions plotted versus infant parasite prevalence. Mean age is fit with a linear model and incidence with a power model to facilitate identification of trends.

Table 1
Infant (1–11 months) and childhood (5 years) parasite prevalence in Ngerenya from 1993 to 2005

	1993 [*]	1995 [†]	1998 [‡]	1999	2000	2001	2002 [§]	2003	2004	2005
Infants positive/number sampled	4/21	10/53	4/35	5/45	5/69	5/62	1/54	1/42	0/39	0/22
Parasite prevalence (95% CIs)	19% (5.4, 41.9)	19.7% (9.4, 32.0)	11.4% (3.2, 26.7)	11.1% (3.7, 24.0)	7.2% (2.4, 16.1)	8.1% (2.7, 17.8)	1.9% (0.05, 10.0)	2.4% (0.06, 12.6)	0	0
Age range (months)	3–11	3–11	1–11	1–11	1–11	1–11	1–11	1–11	1–11	1–11
Mean age (years)	0.59	0.64	0.5	0.47	0.51	0.52	0.54	0.51	0.6	0.6
Five-year-olds positive/number sampled [¶]	11/18	4/12	13/33 [¶]	16/45 ^{**}	7/45 ^{**}	17/47 ^{**}	12/49 ^{**}	6/31 ^{**}	0/36 ^{**}	0/24 ^{**}
Parasite prevalence (95% CIs)	61.1% (35.7, 82.7)	33.3% (9.1, 61.4)	39.4% (22.9, 57.9)	35.6% (21.9, 51.2)	15.6% (6.5, 29.5)	36.2% (22.7, 51.5)	24.5% (13.3, 38.9)	19.4% (7.5, 37.5)	0	0

Confidence intervals are exact binomial confidence intervals.

^{*} Personal communications.

[†] Snow and others,¹ August 1994 and March 1995 surveys.

[‡] Mwangi and others¹⁵ 1998–2001.

[§] Personal communications.

[¶] Children 5 years of age (60–71 months) only are included to compare cross-sectional surveys in the lingitudinal cohort. This prevents any child from appearing in more than one PR estimate.

^{**} May cross-sectional surveys only to avoid any child from contributing to the denominator twice.