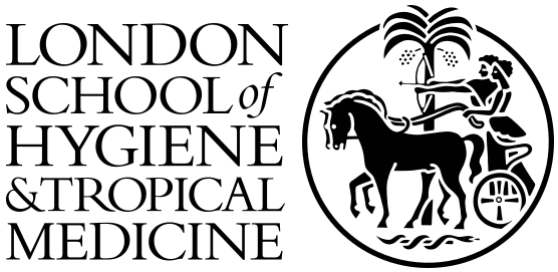

Observational Study: Twenty-Seven Years of Severe Malaria Surveillance in Kilifi, Kenya

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Abstract

Background

Many parts of Africa have witnessed reductions in *Plasmodium falciparum* transmission and associated mortality over the last 15 years. Since immunity to malaria is acquired more rapidly at higher transmission, the slower acquisition of immunity at lower transmission may partially offset the benefits of reductions in transmission. We examined the clinical spectrum of disease and predictors of mortality after sustained changes in transmission intensity, using data from 1989 to 2016.

Methods

We conducted a temporal observational analysis of 18,000 children, aged 14 days to 14 years old, who were admitted to Kilifi County Hospital, Kenya from 1989 to 2016 with malaria. We describe the trends over time of the clinical and laboratory criteria for severe malaria and associated risk of mortality.

Results

During the time periods 1989-2003; 2004-2008; and 2009-2016, Kilifi County Hospital admitted averages of 657, 310 and 174 cases of severe malaria per year including averages of 48, 14 and 12 malaria-associated deaths per year, respectively. The median ages in years of children

admitted with cerebral malaria, severe anaemia and malaria-associated mortality were 3.0 (95% confidence interval (CI) 2.2-3.9), 1.1 (95% CI 0.9-1.4), and 1.1 (95% CI 0.3-2.2) in the year 1989, rising to 4.9 (95% CI 3.9-5.9), 3.8 (95% CI 2.5-7.1) and 5 (95% CI 3.3-6.3) in the year 2016. The ratio of children with cerebral malaria to severe anaemia rose from 1:2 before 2004 to 3:2 after 2009. Hyperparasitaemia was a risk factor for death after 2009 but not in earlier time periods.

Conclusion

Despite the evidence of slower acquisition of immunity, continued reductions in the numbers of cases of severe malaria resulted in lower overall mortality. Our temporal data are limited to a single site, albeit potentially applicable to a secular trend present in many parts of Africa.

Keywords

Severe malaria, secular trend, mortality, Africa, longitudinal surveillance

Introduction

Plasmodium falciparum malaria is an important cause of childhood morbidity and mortality in sub-Saharan Africa (sSA), which accounts for 90% of the world's malaria deaths [1]. Most malaria episodes are successfully treated without hospital admission, but a small proportion of children are admitted to hospital for severe complications which may include coma (i.e. cerebral malaria), severe anaemia (necessitating urgent blood transfusion) or deep breathing (due to severe metabolic acidosis) [2, 3]. Globally, unprecedented reductions in *Plasmodium falciparum* transmission were observed from 2000 to 2010, but progress has stalled since 2010 [4] and the global mortality from malaria may now be increasing [1].

Immunity to clinical malaria is acquired following repeated exposure to malaria parasites. In high transmission areas significant clinical malaria is rare after 5 years of age, owing to acquisition of immunity in early childhood. In low transmission areas clinical malaria continues to occur at older ages [5], and case fatality may be higher at older age [6]. The dominant severe malaria phenotype in areas of low transmission is cerebral malaria rather than severe anaemia [5]. Cerebral malaria is associated with higher case fatality than severe anaemia, even when the most effective anti-malarial treatment artesunate is used [7, 8]. As many parts of sSA approach lower transmission intensities, the changing clinical spectrum of severe malaria could potentially offset some of the gains in mortality that would otherwise be expected by improved malaria control [9].

In this paper we report the trends of severe malaria in Kilifi County Hospital. We relate the trends to trends in transmission intensity previously observed using parasite prevalence surveys in the community. A decline in transmission is evidenced 2000 and 2010 in many parts of Africa [4]. Detailed analysis of community surveys on the Kenyan Coast show that this recent decline began in the mid-1990s, and that transmission increased again after 2010 [10]. In Kilifi County

a consistent trend was seen using yearly parasite prevalences from children admitted with trauma (as a proxy for community parasite prevalence) [11].

We previously reported reduced mortality and morbidity during the period of declining malaria transmission in Kilifi County Hospital (KCH) in Coastal Kenya from 1989-2008 [12]. Subsequently we reported increases in the proportion of children admitted to hospital with malaria infection from 2009 to 2014, with older children accounting for much of this increase [11]. We now report outcomes to 2016 including detailed data on mortality, clinical features and predictors of case fatality.

Methods

Since May 1989 there has been continuous surveillance of hospital admissions at KCH as a partnership between the Research Programme and Kilifi County Department of Health. Consent for the use of data is sought from the parents or legal guardians of admitted children, and wider community engagement to explain research activity was undertaken [13]. Linkage to the Kilifi Health and Demographic Surveillance System (KHDSS) was established in 2002[14]. At the midpoint of the surveillance period, the KHDSS comprised 250,000 residents, including 46,000 children below 5 years of age and 110,000 children below 14 years of age. Malaria control activities include distributions of insecticide treated bed nets [15], but no indoor residual spraying. The malaria vaccine RTS,S was tested in clinical trials but has not been used routinely [16, 17].

Clinical Surveillance

The pediatric service at KCH includes two wards; a 70-bed general ward and a 15-bed high dependency unit (HDU) staffed by research clinicians and nurses. The HDU admits children with serious illness requiring more intensive monitoring and management (albeit without mechanical ventilation facilities). Structured case record are completed electronically on all admissions, capturing age, residence, vital signs, clinical history and examination, and the Blantyre coma score [18]. Data are linked to the KHDSS database. All admissions routinely have a malaria blood slide, full blood count, blood glucose, blood culture investigations. An extended biochemical screen, including blood gases, is included for children with severe illness. Ward clinicians review the hospital notes on discharge and assign one or two diagnostic terms. Inpatient treatment for malaria was parenteral quinine between 1989 and 2010. In 2010 parenteral treatment was changed to artesunate [7]. When children were able to take oral medication, this was chloroquine until 1998, then sulfadoxine/ pyramethamine until 2003, amodiaquine until 2005, and then artemether/ lumefantrine to date.

Definitions

Severe *P. falciparum* malaria was defined as per the WHO definition [19] as a positive malaria slide with parasitaemia above 2,500 parasites/µl with any one of the following: a) cerebral malaria (defined as Blantyre coma score of < 3); b) severe malaria anaemia (defined as

hemoglobin concentration less than 5 g/dL); c) respiratory distress (defined as deep breathing); d) prostration (defined as inability to stand in children who can usually stand, inability to sit in children who cannot usually stand but can sit, or inability to breastfeed in children who cannot usually do sit or stand); e) multiple convulsions (defined as two or more convulsions in the 24-hour period prior to admission) f) jaundice (defined clinically); g) compensated shock (defined by age-specific increases in heart rate (in beats per minute (bpm) >180 for children <12 months of age; bpm>160 for 12 months to 5 years of age; and bpm>140 for children >5 years of age) plus a capillary refill time of >2 seconds; h) decompensated shock (defined as systolic blood pressure < 50 mmHg); i) kidney injury (defined according to age-specific pRIFLE criteria to calculate estimated glomerular filtration rates[20], using actual height and weight where available, and imputing an age-specific average height and weight for where these were not measured); j) hypoglycemia (defined as glucose<2.2 mmol/l in accordance with WHO guidelines, although a threshold of 3 mmol/l was used for clinical management); k) hyperparasitaemia (defined as parasite density >250,000 parasites per µl).

In this analysis malaria parasite status was retrospectively defined as positive if any of three slides taken over the first 3 days of admission were positive for *P. falciparum*, and the highest parasite density of these was used in analysis. Malaria mortality was defined as inpatient death in association with a positive malaria slide. We refer to mortality when describing absolute numbers of children dying with malaria, and case fatality when describing the proportion of deaths among those admitted.

Analysis

The analysis in this study runs from May 1989 to December 2016 and was restricted to children aged 14 days to 14 years of age. STATA software was used (Version 15.0, College Station, TX: StataCorp; 2017). The binomial method was used to calculate 95% confidence intervals for median ages, Kruskal-wallis to compare median ages by year restricted to subgroups of children with severe malaria. Logistic regression was used to examine risk of death, including all children admitted with a positive malaria slide. Three time-periods were defined: 1989-2003; 2004-2008; and 2009-2016; covering before, during, and after the reduction in malaria cases, respectively [11]. In community surveys declining transmission was documented beginning in the mid-90s {Snow, 2015 #2303}, and hence preceded the declines observed in clinical cases. We justify these three time periods as corresponding to the clinical manifestations, which have a non-linear relationship with transmission intensity{Snow, 1997 #641}{Okiro, 2009 #857}. Models were developed as follows: univariable analyses; multivariable analysis of all covariates; backwards exclusion of non-significant associations (i.e. p>0.05) excepting the three major grouping of severe malaria, age and time-period which were maintained regardless of significance; then adding interactions between covariates and time (excluding those for which p>0.05).

Asymptomatic parasitaemia is frequent in malaria endemic regions and clinical features of severe malaria overlap with other common causes of admission. This is countered by

restricting analysis to parasitaemia above 2,500 parasites/µl, as described above [21]. As a sensitivity analysis we re-ran all analyses including malaria parasitaemia at any density, but restricting to children where "malaria" was used among the top two clinical diagnostic terms assigned by clinicians reviewing the clinical records after discharge (supplementary material only). We also conducted a sub-analysis included only children resident in the KHDSS, which provided denominators in order to calculate incidences.

Results

Between 6th May 1989 and 31st December 2016 there were 116,056 pediatric admissions, of whom 99,126 (85.4%) children were aged 14 days to 14 years of age. Of these children, 17,691 (17.8%) showed one or more criteria for severe malaria, of whom 12,805 (72.3%) had a parasite count of >2,500/µl. Annual pediatric admissions to KCH varied, from 3,886 in the mid-1990s to a high of 4700 in the year 2000 before falling to 2,986 in 2014 (Supplementary Figure 1).

Trends in Severe Malaria Cases

The number of severe malaria cases peaked in 1999. However, this apparent peak coincides with improved data collection on the full range of signs and symptoms of severe malaria in 1999 (panels d, e of Figure 1 and Supplementary Figure 1). Data collection was consistent from 2000 onwards, hence the declining trend after 2000 to a nadir in 2009 and then the subsequent slight increase through to 2016 are not associated with changing patterns in data collection (Supplementary Figure 2).

The period 1989 to 2003 included averages of 657 cases of severe malaria per year and 48 malaria-associated deaths per year. From 2004 to 2008 there were averages of 310 cases and 14 deaths per year, and from 2009 to 2016 there were 174 cases and 12 deaths per year. The absolute numbers of non-severe malaria admissions fell more year-on-year than the absolute numbers of severe malaria admissions, hence there was a general trend for an increasing proportion of all admissions with one or more criteria for severe malaria increased year-on-year.

Criteria for Severe Malaria

There were averages of 85, 62 and 44 cases of cerebral malaria per year with 14 (16%), 10 (16%) and 8 (18%) deaths in the periods 1989-2003; 2004-2008; and 2009-2016, respectively. The ratio of children with cerebral malaria to severe anaemia gradually changed from 1:2 before 2004 to 3:2 after 2009 (Figure 1). Respiratory distress, hypoglycaemia, hyperparasitaemia and multiple convulsions were experienced by >10% of children, but jaundice, kidney injury and compensated shock were uncommon (i.e. <5%), with almost no cases of decompensated shock. There was no observed variation in the proportion of children with malaria showing these additional signs over time excepting the increase since in 1999 which coincided with improved data collection (Supplementary Figure 2).

Incidence among Residents of KHDSS Area

Similar trends in clinical features and mortality were seen when data were restricted to children resident within the KHDSS area, allowing incidence rates to be computed. The incidence of severe disease fell from 7.9 per 1,000 in 2003 to 1.6 per 1,000 in 2015. Cerebral disease fell from 1.3 per 1,000 in 2003 to a low of 0.1 per 1000 in 2008, but then increased to 0.5 per 1,000 in 2015 (Supplementary Figure 3).

Trends in Median Age

We studied median ages of children with different clinical features of malaria as an indication of the relative susceptibilities of older vs younger children (Figure 2).

In 1989 the median ages of children in the following groups: a) hospitalized without malaria; b) with severe malaria anaemia; and c) with cerebral malaria were: a) 1.1 years (95% CI 1.0-1.2); b) 1.1 years (95% CI 0.9-1.4) and c) 3.0 years (95% CI 2.2-3.9), respectively. By the year 2016 the median ages were: a) 1.8 years (95% CI 1.7-1.9); b) 3.8 years (95% CI 2.5-7.1) and c) 4.9 years (95% CI 3.9-5.9), respectively. Hence there were slight increases in median ages among children hospitalized without malaria, but marked increases among children hospitalized with severe anaemia and cerebral malaria ($p<0.0001$ for comparison of 1989 with 2016).

Among children dying with and without malaria, the median ages in 1989 were 1.1 years (95% CI 0.3-2.2) and 1.4 years (95% CI 0.9-1.8), respectively rising by 2016 to 5 years (95% CI 3.3-6.3) and 1.2 years (95% CI 1-1.3). Similar results were seen using the alternate case definition (Supplementary Figure 4).

Case Fatality

Univariable analysis demonstrated that all the criteria tested for severe malaria were associated with increased risk of mortality excepting prostration (Table 1). On multivariable analysis including all factors the independent predictors of case fatality were cerebral malaria, respiratory distress, severe anaemia, acidosis, kidney injury and hypoglycaemia ("Multivariable (all variables)" in Table 1). We therefore restricted further multivariable analysis to the statistically significant criteria for clinical malaria, also retaining time period, age and cerebral/respiratory distress/severe anaemia as predictors ("Multivariable (restricted) in Table 1).

We selected interactions to consider for the final model by examined the unadjusted interactions between criteria for severe malaria and time period (Supplementary Table 2). Adjusted interactions were not significant between time and acidosis ($p=0.8$), cerebral malaria ($p=0.7$), age ($p=0.6$), compensated shock ($p=0.7$) and hypoglycaemia ($p=0.5$) and respiratory distress ($p=0.7$), and therefore not included in the final model. The adjusted interaction was statistically significant for hyperparasitaemia ($p=0.001$), which was retained for the final interaction model. Age and time-period did not show a significant interaction ($p=0.7$), indicating that the case fatality for a given age and phenotype was consistent over time.

Akaike's Information Criteria scores were 812.2 for the multivariable (all variables) model, 804.7 for the multivariable (restricted) model and 803.6 for the interaction model with 13, 9 and 11 degrees of freedom, respectively.

Increasing age was associated reduced mortality on univariable analysis but not after adjusting. Within time period, there was reduced mortality during the decline in univariable and restricted multivariable analysis, but not after adjusting in the interaction model. After the decline (i.e. 2009-16) there was a slight, but statistically non-significant increase in mortality on unadjusted analysis which was not evident after adjusting. Using the alternate case definition based on clinical judgement (Supplementary Table 3,4) the post-decline increase in mortality was significant when unadjusted, but again was not significant after adjusting (Supplementary Table 4).

Discussion

Over 27 years of continuous longitudinal surveillance we show substantial changes in the numbers of admissions to hospital with severe malaria and in mortality. We previously reported detailed the epidemiological transition to the nadir of severe malaria cases in 2009 [12], and reported spatial and temporal distributions of malaria slide positivity through to 2014{Mogeni, 2016 #2682}. These updated data show the longer-term outcomes with more detailed clinical categorization through to 2016 [4, 24].

The increasing median ages among children with severe anaemia, with cerebral malaria, and with malaria-associated mortality suggest that children at later time periods had less immunity than would have been the case at earlier time periods, and hence a population of older children had emerged with susceptibility to severe malaria. In 1989 severe malaria was largely limited to children under 5 years of age. In 2016 half of all children with severe malaria were above 5 years of age. Immunological studies in Kilifi report reduced titres of anti-malaria antibodies as transmission declines [25].

What impact does lowered immunity have on case fatality? Predictors of case fatality remained constant over time, with the exception of hyperparasitaemia which emerged as a risk factor for case fatality after 2009. Cerebral malaria carries a high case fatality [8]. The increasing proportion of children with cerebral malaria and the emergence of hyperparasitaemia as a risk factor will lead to an increase in overall case fatality, and therefore could be expected to lead to increased mortality. However, although numbers of cerebral malaria cases increased, overall numbers of admissions with severe malaria fell, hence there was no increase in absolute mortality.

There was a statistically non-significant increase in case fatality after 2009 in primary analysis (Table 1), although this was statistically significant using the alternate case definition on clinical criteria (Supplementary Table 4). In both cases this increase was accounted for by adjusting for other factors, and likely relates to the increased case fatality seen in cerebral malaria. There was no indication that case fatality among specific sub-groups increased after 2009 with the

exception of hyperparasitaemia. This finding was the only evidence that waning immunity might have a detrimental impact on case fatality. It is possible that other trends countered the potential impact on case fatality such as improved medical care with intravenous artesunate in 2010 [7] or improved fluid management [27].

The study has limitations. Data were incomplete, particularly for the presence of multiple convulsions, although this was not an independent predictor of mortality. Secular trends may confound our analysis. Improved medical management has already been mentioned, and improved access to community and/or hospital healthcare is likely to impact the frequency and/or severity of presentation with malaria. The population has increased over time. While fertility rates are falling, increasing child survival and changes in hospital usage might have impacts on the median age of children coming to the hospital. There was a trend of increasing age among children without malaria, but not among children admitted whose admission ended in death (Figure 2), suggesting that the increases in median age among children with malaria are not due to a general trend impacting the wider population.

The definition of severe malaria is non-specific when asymptomatic parasitaemia coincides with severe illness of non-malarial etiology [21]. This was mitigated by two different case definitions: a) including a parasite density threshold b) restricting analysis to those children in whom clinicians had confirmed a discharge diagnosis of malaria. Our definitions of severe malarial anaemia and cerebral malaria followed the WHO definition [23], but could have been refined using additional clinical criteria [8, 28] and retinal examination [29], which we did not conduct.

Conclusion

Our data indicate one possible outcome of a secular trend of reducing malaria transmission followed by stagnation, and this secular trend seems to be widespread in many parts of Africa [4]. Investment in data collection in routine settings is essential to more widely describe the outcomes of changes in malaria transmission and access to care, and offers a cost-effective and scalable solution to malaria monitoring.

Declarations

Ethical approval was granted by KEMRI SSC/ERC committees prior to 2010, then subsequenctly by KEMRI SERU. Written informed consent was taken from guardians with verbal explanations and forms in local languages.

Data are available in Harvard Dataverse under managed access given the joint ownership of data with the County Hospital. Applications for access can be made through the Data Governance Committee with details available on www.kemri-wellcome.org.

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The original concept for the analysis was developed by Patricia Njuguna and Philip Bejon. Data collection was contributed to by Patricia Njuguna, Kathryn Maitland, Amek Nyaguara, Neema Mturi, Shebe Mohammed, Ifedayo Adetifa, J Anthony G Scott, Thomas N Williams, Sarah Atkinson, Kevin Marsh, Benjamin Tsofa, Norbert Peshu, Mainga Hamaluba, James A Berkley, Charles RJ Newton, John Fondo, Anisa Omar, Philip Bejon. Laboratory work was conducted by Gabriel Mwambingu, Caroline Ngetsa, Kenedy Awuondo and Brett Lowe. Data management and analysis were done by Patricia Njuguna, Amek Nyaguara, Daniel Mwanga and Philip Bejon. The first manuscript was drafted by Patricia Njuguna and redrafted by Philip Bejon, Kath Maitland, Ifedayo Adetifa, Kevin Marsh, James Berkley and Charles Newton. All authors commented on and approved the final manuscript.

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Table 1: Univariable and Multivariable Logistic Regression Models for Risk of Mortality in Severe Malaria (Case Definition Includes the >2,500 parasites per µl Threshold.)

Predictors	Univariable		Multivariable (all variables)		Multivariable (restricted)		Interaction model	
	Odds Ratio	P value	Odds Ratio	P value	Odds Ratio	P value	Odds Ratio	P value
Time (1989-1999)	Reference							
Time (2004-2008)	.7 (.55 to .9)	0.005	NA	NA	.68 (.48 to .97)	0.03	.8 (.53 to 1.2)	0.28
Time (2009-2016)	1.09 (.88 to 1.37)	0.43	.75 (.46 to 1.24)	0.26	1.05 (.68 to 1.6)	0.83	.8 (.48 to 1.32)	0.38
Acidosis	7.07 (5.77 to 8.67)	<0.0001	3.31 (2.09 to 5.25)	<0.0001	2.75 (2.01 to 3.76)	<0.0001	2.83 (2.06 to 3.89)	<0.0001
Age (years)	.96 (.93 to .99)	0.02	1.08 (.98 to 1.18)	0.11	1.05 (.98 to 1.12)	0.19	1.05 (.98 to 1.13)	0.16
Cerebral	7.63 (6.59 to 8.83)	<0.0001	3.81 (2.54 to 5.74)	<0.0001	4.21 (3.17 to 5.57)	<0.0001	4.38 (3.3 to 5.82)	<0.0001
Compensated Shock	4.76 (3.4 to 6.66)	<0.0001	1.03 (.47 to 2.23)	0.94	NA	NA	NA	NA
Hyperparasitaemia	1.19 (1.02 to 1.38)	0.03	.89 (.58 to 1.37)	0.6	NA	NA	.75 (.51 to 1.09)	0.13
Hypoglycaemia	8.81 (6.98 to 11.1)	<0.0001	1.93 (1.17 to 3.2)	0.01	3 (2.17 to 4.14)	<0.0001	3.2 (2.3 to 4.45)	<0.0001
Kidney Injury	6.09 (4.43 to 8.37)	<0.0001	2.45 (1.29 to 4.63)	0.006	2.76 (1.79 to 4.25)	<0.0001	2.64 (1.71 to 4.09)	<0.0001
Mx Convulsions	2.21 (1.67 to 2.92)	<0.0001	.92 (.56 to 1.51)	0.75	NA	NA	NA	NA
Jaundice	2.43 (1.49 to 3.98)	0.0004	.87 (.31 to 2.49)	0.8	NA	NA	NA	NA
Prostration	1.05 (.71 to 1.56)	0.81	NA	NA	NA	NA	NA	NA
Resp. Distress	9.41 (7.69 to 11.5)	<0.0001	2.23 (1.45 to 3.42)	0.0002	1.92 (1.42 to 2.6)	<0.0001	1.95 (1.44 to 2.65)	<0.0001
Severe Anaemia	2.24 (1.93 to 2.6)	<0.0001	1.25 (.78 to 1.99)	0.35	1.1 (.78 to 1.54)	0.59	1.08 (.77 to 1.52)	0.66
Time (2004-2008) * Hyperparasitaemia			NA	NA	NA	NA	.63 (.29 to 1.34)	0.23
Time (2009-2016) * Hyperparasitaemia			NA	NA	NA	NA	2.53 (1.07 to 5.97)	0.03

Footnote: Odds Ratios (ORs) are shown with 95% confidence intervals in brackets. Interaction terms are not relevant to univariable models. "NA" is shown for cells where the model was not applicable, and "-" is shown for cells with insufficient data (occurring where multiple seizures and other covariates were not collected between 2004 to 2009). Multivariable (restricted) refers to a model where non-significant predictors were excluded from the model.

Figure 1: Trends in Mortality and Clinical Features of Severe Malaria over Time.

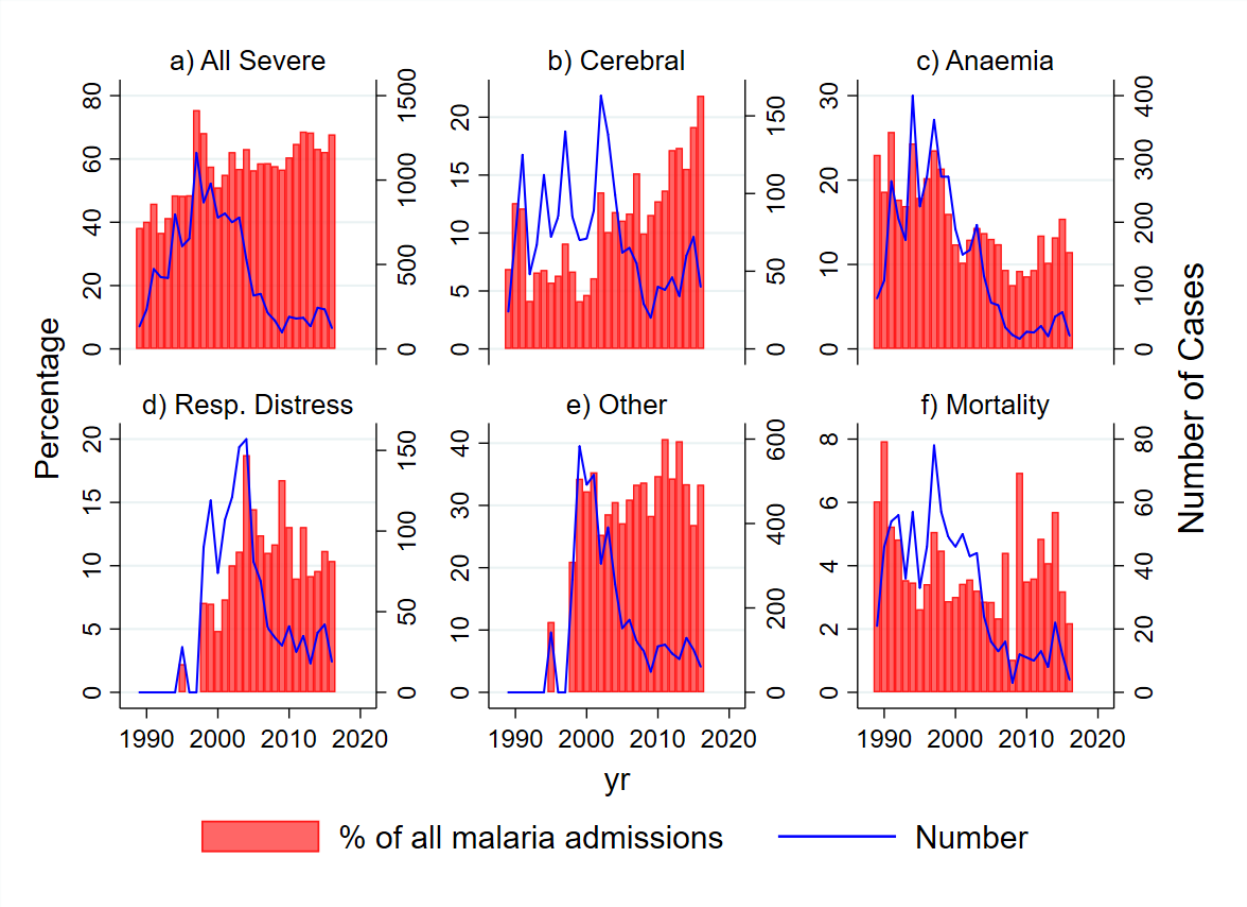

Figure legend 1: The trends over time are shown for clinical features of severe malaria among all children admitted with a parasite threshold of >2500 µl. The % of children with a parasite threshold >2500/µl where the relevant observation was positive is shown in red bars (left y axis); and the absolute number of cases where the observation was positive is shown by the blue line (right y axis).

Figure 2: Median Ages for Children Admitted to Kilifi County Hospital

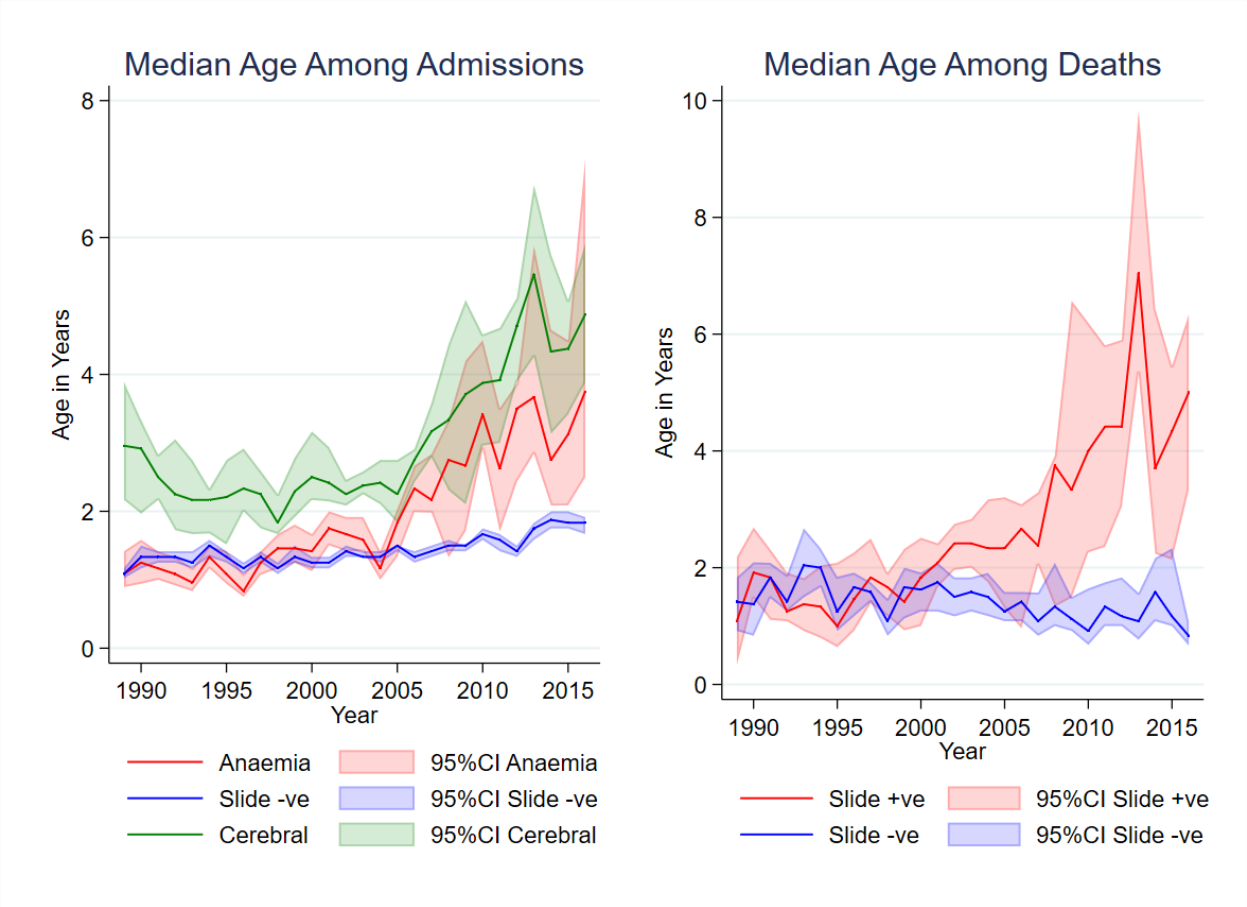

Figure Legend 2: Median ages of presentation to hospital for specific phenotypes (see color legend) are shown over time with 95% confidence intervals calculated by the binomial exact method.

Supplementary Table 1: Frequency of Mortality and Criteria for Severe Malaria by Year

Supplementary Table 2: Unadjusted Logistic Regression for Risk of Death by Time Period. Case Definition Includes Parasite Density threshold (i.e. >2,500 Parasites Per µl).

Supplementary Table 3: Unadjusted Logistic Regression for Risk of Death by Time Period. Case Definition Includes Diagnosis by Clinician.

Supplementary Table 4: Univariate and Multivariate Logistic Regression Models for Risk of Mortality in Severe Malaria. Case Definition Includes Diagnosis by Clinician.

Supplementary Figure 1: Numbers of admissions to Kilifi County Hospital over time.

Supplementary Figure 2: Trends in Mortality, Full Clinical Features of Severe Malaria and Completeness of Data Collection over Time.

Supplementary Figure 3: Trends in Incidence of Mortality and Clinical Features of Severe Malaria over Time for Kilifi Health and Demographic Surveillance System Residents.

Supplementary Figure 4: Median Ages for Children Admitted to Kilifi County Hospital. Case Definition Includes Diagnosis by Clinician.

Supplementary Figure 5: Adjusted Case Fatality Rates in Kilifi and in the AQUAMAT and SMAC studies.