Am. J. Trop. Med. Hyg., 77(Suppl 6), 2007, pp. 99–105
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Patterns of Age-Specific Mortality in Children in Endemic Areas of Sub-Saharan Africa

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Abstract. Understanding of the age- and season- dependence of malaria mortality is an important prerequisite for epidemiologic models of malaria immunity. However, most studies of malaria mortality have aggregated their results into broad age groups and across seasons, making it hard to predict the likely impact of interventions targeted at specific age groups of children. We present age-specific mortality rates for children aged < 15 years for the period of 2001–2005 in 7 demographic surveillance sites in areas of sub-Saharan Africa with stable endemic *Plasmodium falciparum* malaria. We use verbal autopsies (VAs) to estimate the proportion of deaths by age group due to malaria, and thus calculate malaria-specific mortality rates for each site, age-group, and month of the year. In all sites a substantial proportion of deaths (ranging from 20.1% in a Mozambican site to 46.2% in a site in Burkina Faso) were attributed to malaria. The overall age patterns of malaria mortality were similar in the different sites. Deaths in the youngest children (< 3 months old) were only rarely attributed to malaria, but in children over 1 year of age the proportion of deaths attributed to malaria was only weakly age-dependent. In most of the sites all-cause mortality rates peaked during the rainy season, but the strong seasonality in malaria transmission in these sites was not reflected in strong seasonality in the proportion of deaths attributed to malaria, except in the two sites in Burkina Faso. Improvement in the specificity of malaria verbal autopsies would make it easier to interpret the age and season patterns in such data.

INTRODUCTION

In endemic areas, severe *Plasmodium falciparum* malaria is primarily a disease of young children, and children under 5 years of age are the focus of most strategies for control of the disease in endemic areas of Africa. Several new strategies for intervening to reduce this burden, such as intermittent preventative treatment (IPT) and distribution of insecticide treated nets (ITNs), propose to make use of the Expanded Program of Immunization, which focuses on the youngest of these children. The likely impact of such interventions thus depends very much on the distribution of morbidity and mortality between children of different ages. Moreover, successful intervention programs are likely to lead to changes in the age distribution of the disease, so it is important to have baseline information from which to evaluate such changes.

Most reports of pediatric malaria mortality have presented rates for broad multi-year age groups, making it hard to predict the likely impact of interventions targeted at specific age groups of children; moreover, inclusion criteria, diagnostic algorithms, and methods for estimating all-cause mortality rates vary.

We now present estimates of malaria-specific mortality rates for 3-month age groups up to 2 years of age and single-year age groups up to 15 years of age from 7 sites in sub-Saharan Africa. These sites all conduct prospective demographic surveillance using standardized procedures[1] and use verbal autopsy (VA) methodologies to assign causes of death. This involves interviewing the family of the deceased concerning the circumstances leading to death and the symptoms and signs during the terminal illness.[2–5] We use these VA data to estimate the age-specific malaria mortality rates for rural populations in Tanzania, Mozambique, Ghana, Kenya, and Burkina Faso.

METHODS

Contributing sites. INDEPTH currently (November 2006) embraces a total of 37 sites conducting prospective demographic surveillance of populations in developing countries across the world. Seven of these sites, each in a malaria endemic part of sub-Saharan Africa, contributed disaggregated VA data and mortality rates that could be used for the present analyses (Table 1). These sites were also participants in the INDEPTH Malaria Transmission Intensity and Mortality Burden Across Africa (MTIMBA) initiative.

There are considerable year-to-year variations in the transmission intensity in any single site, but the Ifakara,[6] Kourweogo, Oubritenga,[7] Navrongo,[8] and Rufiji sites all have high levels of *P. falciparum*, with average EIR of several hundred infectious bites per annum. Malaria transmission in the Kisumu site was much lower than in these sites at the time of the study, because a trial of insecticide treated bed nets led to high coverage in the study area.[9] Manhiça is also known to be a site with lower transmission intensity than the other sites.[10]

Demographic surveillance and all-cause mortality rates. Demographic surveillance, including continuous recording of births, deaths, and migrations, was conducted in all sites as described previously.[1] For each site the period of analysis comprised as much of the period from 1999–2003 as data were available.

Time at risk was calculated for each individual registered in the demographic surveillance system, subtracting out periods of absence due to migration. All-cause mortality rates were calculated by dividing the numbers of deaths in an age group by the time at risk, and expressed as deaths per 1,000 person-years at risk.

Assignment of cause of death. The procedures used for assignment of death differed in detail between the sites. Each of

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TABLE 1
Summary of mortality data

Site	Country	Period of analysis	Children < 15 years of age*			
			Total child deaths during the surveillance period	Total child-years at risk	Crude child death rate (/1000 person – years)	Total verbal autopsies specifying a cause of death
Ifakara	Tanzania	Oct 2001–Sep 2004	1138	91493.2	12.4	554
Kisumu	Kenya	Aug 2001–Sep 2005	3602	75566.9	*	1046
Kourweogo	Burkina Faso	Jan 2002–Dec 2003	1229	68871.2	17.8	1013
Manhiça	Mozambique	Oct 2001–Sep 2004	844	50874.4	16.6	716
Navrongo	Ghana	Nov 2001–Oct 2004	1847	164065.3	11.3	1161
Oubritenga	Burkina Faso	Jan 2002–Dec 2003	1783	101072.0	17.6	1491
Rufiji	Tanzania	Oct 2001–Sep 2004	953	116663.5	8.2	837

* Children < 5 years of age in the Kisumu site.
† Number obtained by summing fractions where malaria was assigned or where multiple causes including malaria were coded.
‡ The total obtained by summing fractions where malaria was assigned or where multiple causes including malaria or acute febrile illness of unknown origin were coded.
§ Un-weighted estimate calculated as the product of the crude death rate and the proportion of deaths assigned as malaria or acute febrile illness.

the codes used by the sites was mapped onto the standard ICD10 codes before further analyses. Where a death may have been assigned to different causes by different VA coders, we assigned deaths proportionately to the different codes assigned to them, as described previously.[11] We thus computed the proportion of deaths coded as malaria within each age group and site. To compute malaria-specific mortality rates we multiplied this proportion by the corresponding all-cause mortality rate. A death for which there was no VA or where the VA coders indicated that the cause of death was uncertain, was thus redistributed in proportion to the frequencies of diagnoses for the other deaths.

In most of the sites, deaths due to acute febrile illnesses where there is no indication of any other etiology are generally coded as malaria. In several sites, deaths with additional evidence of malaria causality were distinguished from fevers of unknown origin, but the ways in which this was done differed between sites, leading to different ratios of malaria deaths (using local definitions) to fevers of unknown origin (Table 1). Consequently it is not possible to carry out meaningful cross-site analyses using the stricter definitions. To harmonize coding across sites we have grouped deaths coded as fevers of unknown origin under malaria in the analyses of age- and season- dependence of the malaria mortality rates. Analyses were conducted for children < 15 years of age except for one site (Kisumu), where the VAs referred only to deaths in children less than 5 years of age.

RESULTS

Each site exhibits a steep decline in all-cause mortality rate with age (Figure 1), and a less steep decline in malaria-specific mortality. In all sites, malaria (or fever of uncertain etiology) was the most frequent cause of pediatric mortality identified by the coders (Table 1[12]). In all sites, the vast majority of the deaths before the age of 15 years occurred before the age of 5 years, so the curves of cumulative probability of dying by age were similar in shape (Figure 2A). Therefore, differences between sites in the overall pediatric death rates, and hence the maximum of this cumulative probability, were substantial (Table 1), with the percentage of deaths attributable to malaria varying from 20.1% (Manhiça) to 46.2% (Oubritenga). In every site all-cause mortality rates in children decreased with age. The maximum malaria mortality rate (deaths per person-year at risk) was everywhere reached at some time during the first year of life (Figure 1). In all sites, the proportion of deaths attributed to malaria was relatively low in the youngest age group (< 3 months, Figure 3) but did not show clear patterns with age after that, especially in the older age groups where the number of deaths was relatively low and hence the estimates of rates rather unstable (Figure 3). In some sites (Navrongo, Oubritenga) there was a clear decline in this proportion at ages above 5 years. In other sites, especially when the total number of deaths analyzed was rather low, this trend was less pronounced.

The curves for the cumulative probability of a malaria death by age (Figure 2B) were broadly the same shape as those for all-cause mortality (Figure 2A), with the main difference between the sites being in the level at which the curves plateau. Oubritenga and Kourweogo not only featured among the sites with the highest all-cause mortality but also stood out with distinctly higher malaria mortality than the others. There is no obvious relationship between the overall level of this plateau and the age at which malaria deaths occur. Severe disease occurs more often in older children in areas of low malaria transmission, than in areas of higher transmission.[13] It might therefore be expected that in the sites with lower malaria mortality rates, the malaria deaths would be shifted to older ages. Only the Manhiça data seemed to fit in with this pattern, combining the lowest malaria mortality rate with the highest median age of malaria deaths (Table 1). In the other sites, the median age of malaria deaths fell between 1 year and 15 months, irrespective of the malaria mortality rate.

All the sites showed seasonality in mortality, with most of them showing peak mortality during the rainy season, though in all these sites there is much more seasonality in malaria transmission indices than in mortality (data not shown). In sites in the southern hemisphere (Manhiça, Rufiji) and in Kisumu (equatorial) this led to peak mortality in the first half of the year (Figure 4), while in those in the northern hemisphere (Kourweogo, Navrongo, and Oubritenga) the peak in both rainfall and mortality is in the second half of the year. The mortality pattern for Ifakara during the study period differed from this, with peak mortality in October, despite a rainy season during the first half of the year. This is at least partly a consequence of seasonality in births, and hence in the number of neonatal deaths (data not shown). In most of the sites, the seasonal pattern of malaria-diagnosed mortality followed closely that of all-cause mortality (Figures 4 and 5), but

TABLE 1
Continued

Children < 15 years of age*				
Verbal autopsies assigned malaria as cause of death†	Total verbal autopsies assigned malaria or acute febrile illness§	Overall malaria mortality rate (/1000 person – years§)	% of child deaths assigned malaria or acute febrile illness‡	Median age of deaths assigned malaria or acute febrile illness (years)‡
161.6	241.0	5.4	43.5	1.20
234.0	234.0	*	22.4	1.01
446.1	446.1	7.9	44.0	1.01
142.2	144.0	3.3	20.1	1.65
254.3	259.1	2.5	22.3	1.25
689.0	689.0	8.2	46.2	1.18
203.1	359.6	3.5	43.0	1.02

with a small wet season increase in the proportion of deaths attributed to malaria. In the two Burkinabé sites of Kourweogo and Oubritenga, where malaria transmission is highly seasonal, there were clear peaks during the rainy season in the proportion of deaths assigned to malaria.

DISCUSSION

Statistics on causes of death are invaluable for use in prioritizing public health interventions,[14] but are difficult to obtain for those rural areas in Africa where malaria endemicity is highest. Few deaths in these areas are attended by medically qualified personnel, and information on the proportions of deaths with specific causes is usually of poor quality.[15] Often the overall numbers of deaths and consequently the all-cause mortality rates are also highly uncertain.

Prospective demographic surveillance provides reliable all-cause mortality rates and VAs remain our best tool for assigning etiologies to individual deaths in the absence of medical certification.[16] However, there are surprisingly large differences between the sites studied in levels of malaria mortality determined by VA. One possible set of explanations is differences in health systems and in histories of intervention in the sites. Navrongo,[17] Kisumu,[18] and Ifakara[19] DSS sites have hosted trials of ITNs; Oubritenga was the site of a large-scale trial of insecticide treated curtains[20]; and Rufiji was the site of a successful trial of Integrated Management of Childhood Illness (IMCI).[21] Some of the inter-site differences presumably result from these trials, and the extent to which the interventions were effective during the study period.

A note of caution is needed in interpreting the VAs. The VA technique assumes that deaths can be classified into useful categories of etiology on the basis of distinct symptom complexes that can be recognized, remembered, and reported by lay respondents. Validations of pediatric VAs have, however, suggested that they have rather poor sensitivity and specificity for malaria.[22,23] In most sites with endemic malaria, the practice has been to assign as malaria those deaths with acute febrile illness where there is no other cause evident. Although this procedure necessarily leads to inclusion of some deaths due to other causes, comparison with other sites in rural areas of Africa where malaria is a relatively minor cause of death suggested that the overestimation of malaria mortality rates as a result of including fevers of unknown origin is modest.[12]

Verbal autopsy results can be adjusted to allow for some of the misclassification biases[16,24] but this requires quantitation of the transmission intensity and it may be that different correction algorithms will be needed for sites with different patterns of competing causes of death.[25] Community-based estimates of malaria-specific mortality rates in children have previously been estimated using VAs for a number of endemic areas, but have generally been calculated for single under 5 years, or 1–4-year age groups.[16]

Given these problems of comparison between sites, VA might appear most useful as a tool for studying variations in malaria mortality within a site. Information about age- and season- dependence of malaria mortality is not readily available from other sources, and most data refer to hospital cases. Cases that reach a hospital are likely to be unrepresentative of those occurring in the community. Hospital-diagnosed severe malaria in children is most frequent at intermediate transmission intensities.[26,27] Malaria case fatality rates in hospitals are age-dependent, with the highest rates in young infants and older children and a minimum in between.[27,28]

These patterns are not evident in the community-based mortality data that we have assembled.

Malaria-specific mortality rates might be expected to show different relationships with age than do severe morbidity rates because of the age-dependence in case fatality[29]; however, it is to be expected that, whatever the detailed pattern, malaria deaths would occur in younger children in areas of high transmission than those of lower transmission. The sites vary, not only in the underlying transmission rates, but also in the characteristics of the health systems and the extent of vector control interventions. However, the peak ages of malaria mortality that we observe (Figure 1) are similar across all the sites, despite considerable variations in transmission pattern. Moreover, there is considerable seasonality in malaria transmission in all the sites, and thus if non-malaria deaths were unaffected by malaria incidence, malaria, as a proportion of all deaths, should be highly seasonal. Yet this proportion showed strong seasonality only in the two sites in Burkina Faso, despite peaks in all-cause mortality in the malaria transmission season in 6 of the 7 sites.

A simple proposal to explain the lack of age- or seasonal-variation in the proportions of deaths diagnosed as malaria, is that it results from misclassification of deaths by the VAs, as shown schematically in Figure 6. Misclassification of deaths could account for the low degree of seasonality in malaria VAs in most of the sites. Even if the bias in overall cause-specific death rates is small, misclassification could profoundly affect within site variations in cause-specific mortality.

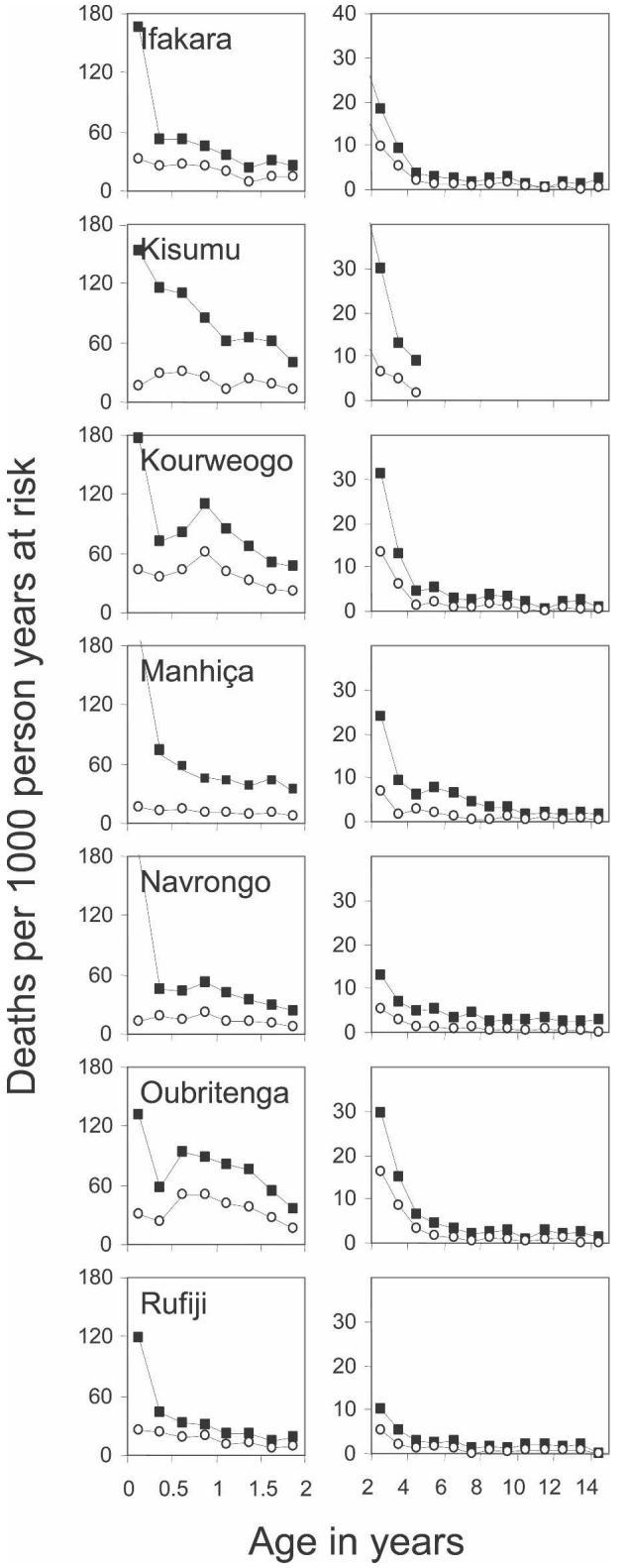

FIGURE 1. Age-specific mortality rates. ■——■, all cause; ○——○, malaria specific.

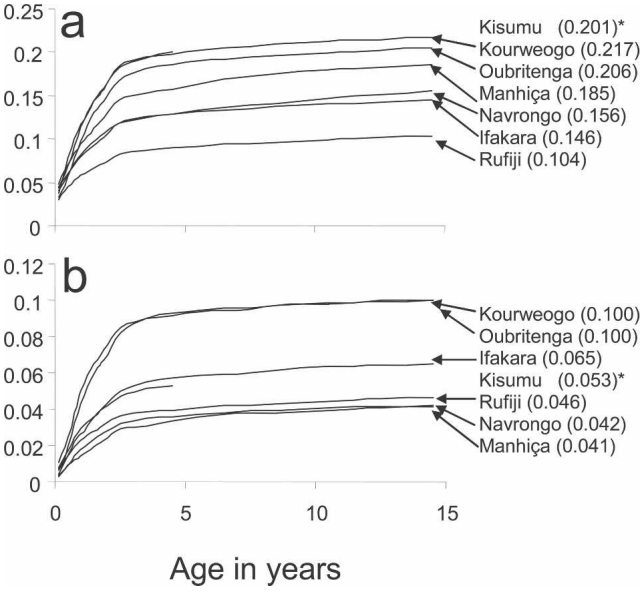

FIGURE 2. Cumulative probability of dying by given age. a: all cause mortality; b: malaria specific mortality (broad definition). Figures in parenthesis are the overall probability of dying by age 15 years. *For Kisumu the data analysed refer only to ages 0–5 years, and the figures in parenthesis are the probability of dying by age 5 years.

The concept of misclassification implies that it is possible to define a subset of deaths with an underlying cause of malaria (the union of A and D in Figure 6). The underlying cause is defined as the disease or injury that initiated the train of events leading directly to death. But many African children are exposed continually to multiple infectious agents and other hazards. In this context it is not unusual for a child to be born of an anemic mother with placental malaria, to subsequently receive a meager diet, to experience multiple episodes of diarrhea and pneumonia, and to be chronically infected with *P. falciparum* from the middle of the first year of life, with frequent acute episodes of the disease. If this child dies, where is it to be placed on Figure 6? Whether it is diagnosed as malaria in VA is almost serendipitous. The timing of the identifiable terminal illness depends on many factors in addition to the timing of the malaria infections. Whether the true underlying cause is malaria is debatable, as is the question of whether, indeed, it makes sense to refer to a single etiology underlying such a complex causal web. However, it does seem likely that the event would have been averted by eliminating malaria. In considering where to place such a characteristic case on Figure 6 we can therefore exclude the possibility that it falls within area B, but it is unclear which of categories A, C, D, or E applies.

It has long been agreed that there is considerable indirect mortality due to malaria, with the local elimination of malaria, notably in Sri Lanka[30] and in the sugar plantations of Guyana[31] reducing all-cause mortality by much more than the number of deaths diagnosed pre-intervention as malaria. Several studies in Africa have found the same thing.[32,33] The results in the present article suggest that the events diagnosed as malaria in VA (Figures 6A–C) show quite different epidemiologic patterns to those that we expect for events in sets D or E. The present analyses imply that it makes more sense to consider malaria as a risk factor (in which case the set of events assigned to it comprises the union of A, C, D, and E), rather than as an etiology. Recent global burden of disease studies have included estimates of the impact of different risk

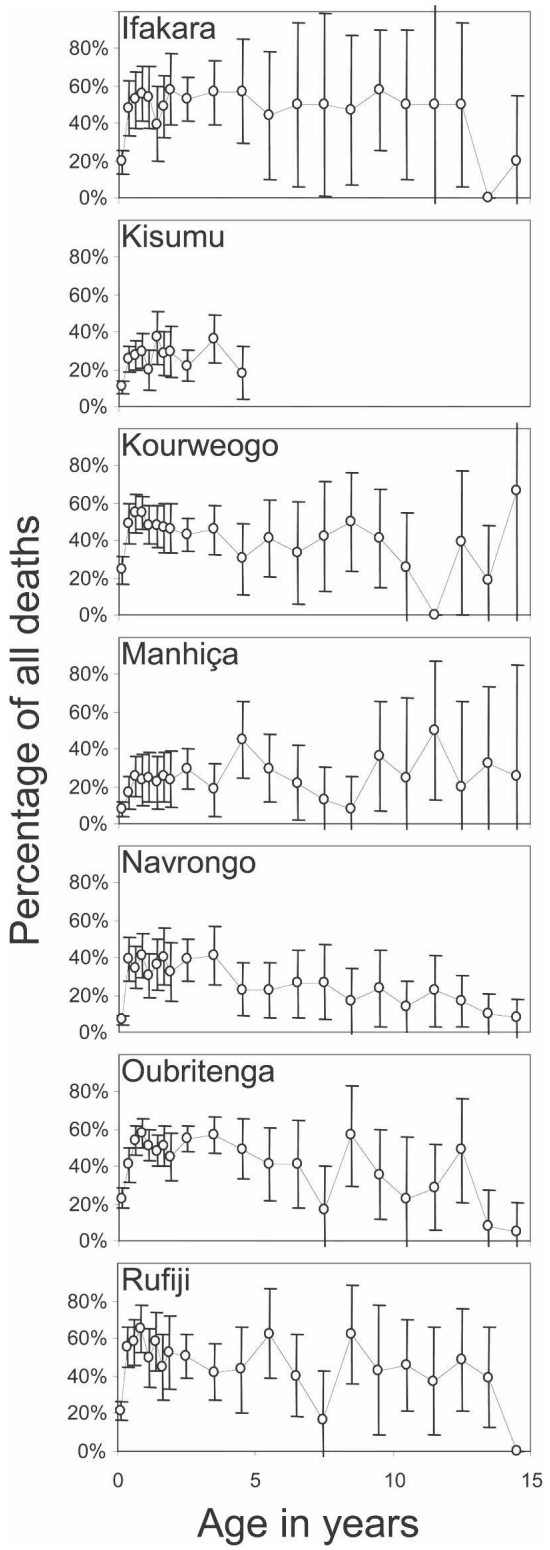

FIGURE 3. Percentage of deaths attributed to malaria. Error bars are 95% confidence intervals constructed using a normal approximation to the binomial distribution.

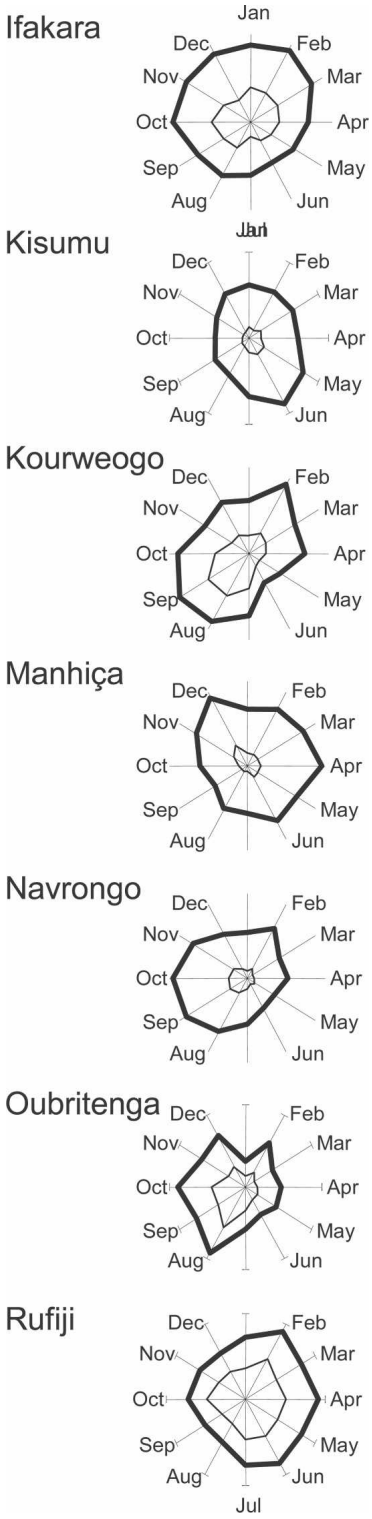

FIGURE 4. Seasonal pattern of mortality. The distance from the center of the figure is proportional to the mortality rate, with the overall circumference adjusted to the maximum monthly rate for the site. The outer (thick) line corresponds to all-cause mortality, the inner (thin) line to malaria-specific mortality.

factors on mortality.[34,35] This perspective makes sense operationally because it measures directly the potential impact of interventions. It also means that the results of randomized trials of interventions (such as those of insecticide treated nets)[17,18,36] can be used to estimate disease burden. In the case of malaria mortality it also sidesteps the conceptual problem involved in defining just what is meant by a malaria death.

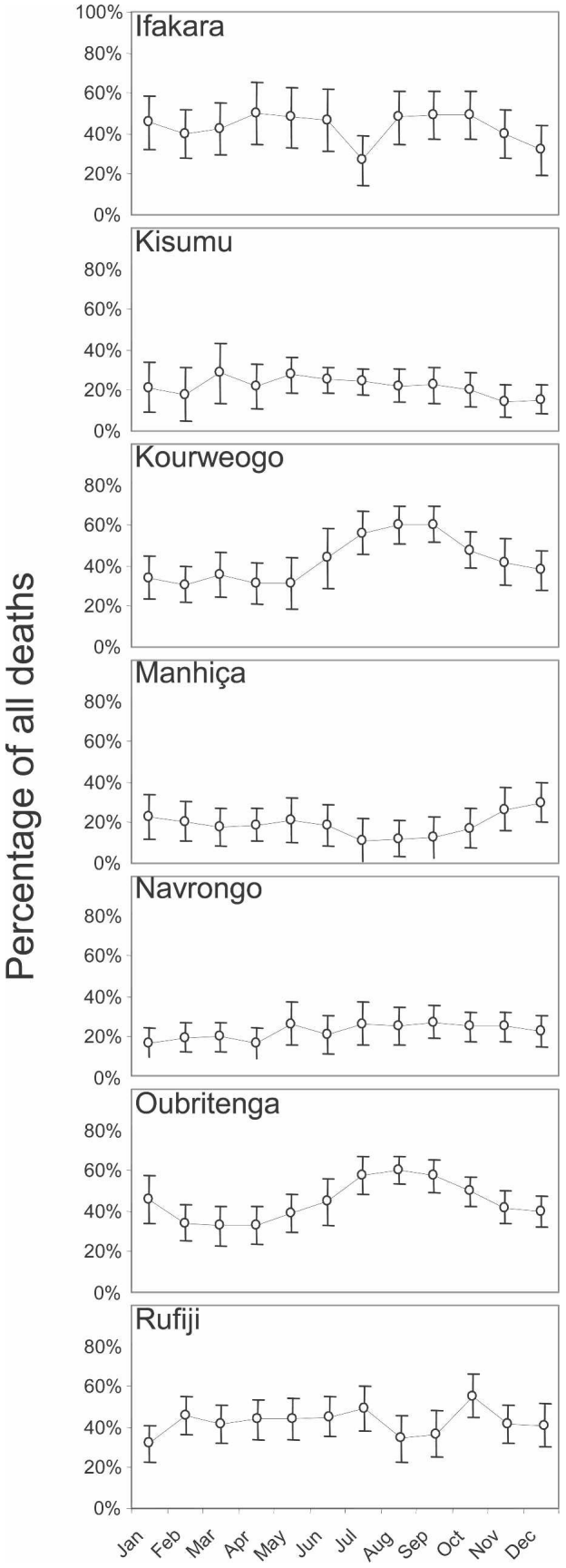

FIGURE 5. Percentage of deaths attributed to malaria (broad definition) by calendar month. Error bars correspond to 95% confidence intervals.

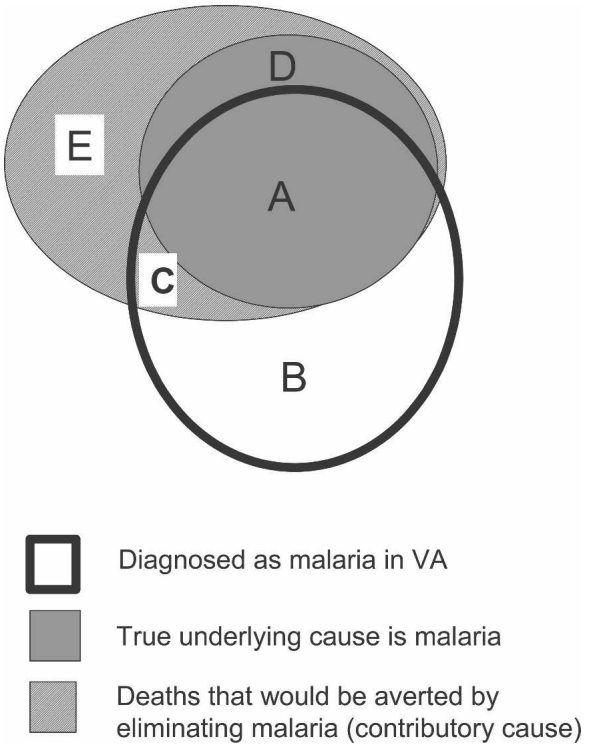

FIGURE 6. Venn diagram illustrating different categories of malaria-related deaths. The labels for the different sub-sets of deaths are explained in the text.

Received August 21, 2006. Accepted for publication April 30, 2007.

Acknowledgments: We thank the contributions of the many fieldworkers, supervisory staff, and data managers in the different sites to the assembly of the database. We particularly want to acknowledge the following DSS sites that contributed data for this article: Kisumu demographic surveillance site, Kourweogo and Oubritenga demographic surveillance sites, Manhiça demographic surveillance site, Navrongo demographic surveillance site, Ifakara demographic surveillance site, and Rufiji demographic surveillance site. The assembly of the cross-site database was coordinated both by the INDEPTH secretariat and by the MTIMBA project.

Financial Support: Main financial support for the vital events registration: Ifakara: Swiss Agency for Development and Co-operation, Swiss National Science Foundation grant number 3270-059541-99; Kisumu: U.S. Centers for Disease Control and Prevention; Manhica: Spanish Agency for International Cooperation; Navrongo: Rockefeller Foundation; Oubritenga and Kourweogo: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the European Commission (INCO-DC, Directorate General XII), the Danish Agency for International Development and the Ministry for University and Scientific Research of Italy. Rufiji: IDRC Canada through the Tanzania Essential Health Interventions Program. Data analysis and interpretation was financed by the Swiss Tropical Institute.

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