Research

Estimating mortality, morbidity and disability due to malaria among Africa’s non-pregnant population

R.W. Snow,1,2 M. Craig,3 U. Deichmann,4 & K. Marsh2,5

The contribution of malaria to morbidity and mortality among people in Africa has been a subject of academic interest, political advocacy, and speculation. National statistics for much of sub-Saharan Africa have proved to be an unreliable source of disease-specific morbidity and mortality data. Credible estimates of disease-specific burdens are required for setting global and national priorities for health in order to rationalize the use of limited resources and lobby for financial support. We have taken an empirical approach to defining the limits of Plasmodium falciparum transmission across the continent and interpolated the distributions of projected populations in 1995. By combining a review of the literature on malaria in Africa and models of acquired functional immunity, we have estimated the age-structured rates of the fatal, morbid and disabling sequelae following exposure to malaria infection under different epidemiological conditions.

Voir page 636 le résumé en français. En la página 636 figura un resumen en español

Introduction

The available health information for much of sub-Saharan Africa is of very poor quality. As a result, estimates of the health impact of diseases such as malaria have swung between semi-informed guesses and wild speculation. Previous estimates of 0.5–2 million deaths from malaria in Africa each year (1–5) have proved to be a useful advocacy tool, but there has been scepticism about their origin and validity. Evidence-based approaches provide greater credibility to disease control initiatives. Following 20 years of disillusionment on the part of the public health sector towards malaria control there is an urgent need to improve credibility for the new era of “roll back” malaria (6).

Recognizing the limitations of national statistics, we have focused on the epidemiological associations between climate and the likelihood of stable Plasmodium falciparum transmission, empirical survey-derived estimates of disease risks linked to epidemiological features of acquired immunity, and interpolated models of population distribution in Africa. This work is an extension of previous efforts to combine transmission risks, malaria mortality data, and population data for 1990 (7) with a refined effort at disease-risk and population stratification, a wider range of empirical data, and a consideration of burdens other than mortality among the 1995 non-pregnant population of Africa.

Data and methods

Climate suitability for P. falciparum transmission

Malaria is governed by a large number of environmental factors, which affect its distribution, seasonality, and transmission intensity. The Anopheles gambiae complex is the major vector system in Africa and exists only in frost-free regions (8), or where the minimum temperature in winter remains above 5 °C (9). Temperature affects the transmission cycle of P. falciparum in many different ways, but the effects on the duration of the sporogonic cycle of the parasite and vector survival are particularly important. At temperatures below about 22 °C the determining factor is the number of mosquitoes surviving the parasite’s incubation period, which takes 55 days at 18 °C (10) and ceases at around 16 °C. After 55 days the proportion of a cohort of mosquitoes that survives is only 0.003 (11).

1 Kenya Medical Research Institute (KEMRI)/Wellcome Trust, Collaborative Programme, P.O.Box 43460, Nairobi, Kenya (e-mail: bob.snow@wtrl.or.ke). Correspondence should be sent to Dr R.W. Snow at this address.
2 Department of Tropical Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, England.
3 National Malaria Research Programme, South African Medical Research Council, Congella, Durban, South Africa.
4 National Center for Geographic Information and Analysis, University of California, Santa Barbara, CA, USA.
5 Centre for Geographic Medicine, KEMRI, Kilifi, Kenya.
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Rainfall provides breeding sites for mosquitos and increases the humidity, which enhances their survival; the overall relationship between mosquito abundance and rainfall has been illustrated repeatedly (12, 13). We have examined rainfall patterns in known malaria and non-malarious areas; an average of 80 mm per month, for at least 3–5 months, is a minimum for stable malaria transmission (14).

In our work, a combination of temperature and rainfall has been used to define the vector and parasite viability for transmission within fixed seasonal windows of time. Fuzzy logic models (15) have been used to define the suitability for stable malaria transmission across the continent at approximately a 5 x 5 km resolution (14). In our model, climate data were derived from weather station data for the period 1920 to 1980 (16) and were interpolated into mean monthly temperature and rainfall surfaces. The model was structured to define distribution by setting the lower temperature cut-off at 18 °C and assuming a saturation of the temperature effect by 22 °C; similarly, rainfall values of 0–80 mm demarcate the range within which transmission is limited. When combined, these features must coincide on a month-to-month basis for five consecutive months, and a frost factor (minimum temperature, <5 °C) would eliminate transmission at any point in a contiguous period. In North Africa, a combination of high temperatures with a rapid onset of a short duration of rainfall allows for a limited transmission period of <3 months. The model was modified to allow for 3-month conditions for North African areas. The model (Fig. 1) accommodates “fuzzy” membership, or climate suitability values, ranging from 0 (unsuitable) to 1 (very suitable). Overall, the model compares well with both expert opinion maps developed between 1930 and 1960 for southern and East Africa and empirical parasitological survey data (MARA/ARMA Collaboration, unpublished observations, 1999). Because the model is based upon long-term climatic averages, it provides a conservative estimate of stable transmission distribution and does not allow for epidemic potentials among areas where transmission is traditionally limited by either rainfall or temperature. Furthermore, comparisons with expert-opinion maps indicate that discrepancies in major river valleys result because the model uses only rainfall to predict water availability, while mosquitos do survive along major river banks and flood plains.

**Epidemiological stratification**

**North Africa**

North Africa is densely populated along the Mediterranean and Moroccan coast; however, the majority of these areas do not support stable *Plasmodium falciparum* transmission as defined through the fuzzy climate suitability model (Fig. 1). In addition, the WHO regional offices covering these areas reported no cases of malaria mortality during the 1995 period. These countries (Algeria, Egypt, Libyan Arab Jamahiriya, Morocco, and Tunisia) have been excluded from the analysis of malaria disease burden in Africa.

**Areas of sub-Saharan Africa unsuitable for stable transmission**

The climate model described above provides a range of suitability estimates for stable transmission (transmission and/or new clinical cases every year). Areas classified as zero suitability are extremely unlikely to support transmission of *Plasmodium falciparum* on an average year either on the basis of low ambient temperatures or inadequate rainfall. Many of these areas are located at high altitude (serving as a proxy for low temperature) in East Africa and the Horn of Africa and among the arid deserts at the juncture of Kenya, Ethiopia and Somalia. It must be recognized, however, that chance epidemics could occur in these areas although they are unlikely. In addition, Africa’s population is incredibly mobile constituting a risk among migrants from these areas to areas of stable or epidemic transmission.

**Areas of unstable, epidemic or fringe malaria transmission**

Previously we have used a 0.5 climate suitability index to define the limits of stable malaria transmission in Africa (7). While this corresponds well to historically...
defined boundaries of transmission in southern Africa (14), it is too exclusive for areas in East Africa. For the present analysis we selected 0.5 as the boundary for stable transmission in southern Africa and 0.2 for the rest of Africa. This arbitrary classification is supported by empirical observations and historical “expert” opinion maps from South Africa, Kenya and the United Republic of Tanzania. Among areas located within the climate suitability classification of greater than zero but less than 0.5 for southern Africa and less than 0.2 for the rest of sub-Saharan Africa, the overall risks of disease and death are dependent upon large between-year changes in climate providing an unusual window of transmission suitability. The typology of these areas varies according to whether the transmission potential is reached due to exceptional rainfall and flooding among traditionally hot, arid areas or whether small variations in temperature in traditionally wet areas permit transmission. Epidemiological definitions of unstable or epidemic malaria do not reflect the public health significance of the disease for these regions of Africa. An underlying principle for the clinical patterns of disease and mortality among these “fringe” populations is that risks are equivalent among all age groups owing to a lack of functional immunity acquired through repeated parasite exposure. A recent analysis of the ratio adult:childhood malaria admissions to over 50 hospital settings in Kenya indicates that, among communities located within the fuzzy climate suitability regions of less than 0.2, over 90% of the adult:child admission ratios exceed 1 (Snow et al., in preparation). This provides a justification for the selection of this climate suitability index as defining a special epidemiological situation for these “fringe” areas.

**Areas of stable *P. falciparum* transmission**

The sub-Saharan areas (excluding North Africa and southern Africa), which lie within the arbitrary limits of climate suitability greater than or equal to 0.2, have been defined as able to support stable *P. falciparum* transmission. This area encompasses a wide range of endemicities. For the present analysis we have assumed an equivalent disease and mortality risk across the wide range of stable endemicities supported in Africa. Clearly this will lead to an overestimate of disease burden where low, stable endemic areas are treated equally with more intense transmission areas. The disease risks among the populations located under low, stable endemic conditions, including large urban settlements in Africa, will be low and result from the host’s chance encounters with the parasite. Conversely, disease risks among populations exposed to intense stable transmission will be modified by acquired immune responses and the intensity of transmission will define the speed with which the population develops functional immunity to the severe and fatal consequences of infection. Recent epidemiological studies (17) have demonstrated that the burden of morbidity and mortality is concentrated among the youngest age groups under conditions of intense, perennial, stable transmission and that while life-threatening pathologies such as cerebral malaria are rare, the incidence of severe anaemia is high. As transmission becomes less intense, more seasonal and ultimately unstable or epidemic, the clinical patterns of disease increasingly include cerebral malaria and overall life-threatening disease risk is spread across a much wider age range. The precise relationship between frequency of parasite exposure, functional immunity and disease risk remains ill defined. However, under conditions of moderate-to-high intensity there is evidence that the cumulative risks of severe, life-threatening disease do not vary despite marked differences in the age patterns of disease (17).

**Southern Africa**

The southern African region has historically supported transmission of malaria within well-defined ecological boundaries. These boundaries are best defined from the fuzzy climate model among areas with a suitability index of \( \geq 0.5 \) (14). For many years countries located in southern Africa have mounted rigorous malaria control strategies, involving active case detection, mass drug administration and, most significantly, aggressive vector control through residual house spraying. These combined strategies have been successful in reducing the basic reproduction rate of infection and disease incidence. Consequently, on the basis of this unique disease ecology, these areas have been identified separately from the rest of sub-Saharan Africa and comprise Botswana, Lesotho, Namibia, South Africa, Swaziland, and Zimbabwe.

**Population distributions in Africa**

A GIS (geographic information system) population database for Africa was used to define at-risk populations. Full details of this database are presented elsewhere (18). The data were constructed using population totals from the last available censuses for more than 4000 administrative units in Africa. To improve the spatial resolution of the population information further, the data by administrative units were converted into a regular raster grid of population totals that was compatible with the climate suitability surfaces. For this purpose auxiliary information was used to distribute the population total recorded for the administrative unit across the raster grid cells that fall within this unit. This process incorporated information on where people tend to live: in or close to towns and cities, close to transport infrastructure, outside protected areas and water bodies, or very high elevations. Using GIS-based information on the location and size of towns and cities, roads, railroads, navigable rivers and uninhabitable areas, a weighting surface was constructed, where a high value implies a high
likelihood of high population density and a low or zero value implies low or no population. These weights were then used to proportionately distribute population to grid cells. The digital map (Fig. 2) shows population totals for each cell in a regular raster grid (the resolution of these cells is 2.5 arc minutes or approximately 5 km at the equator).

The population totals were brought to a common base year (1995) using simple interpolation and trend forecasts based on available census results and official estimates for different years (18). We assumed a continuation of population trends that prevailed in the 1980s and early 1990s to define populations in 1995. However, we subsequently adjusted uniformly the resulting population totals in the cells within each country so that the total estimated national populations equal those reported by the United Nations (19). Since the UN Population Division’s figures are based on estimations incorporating assumptions about fertility and mortality in a country, these totals may differ (sometimes significantly) from the total of administrative unit populations reported by the country. Nevertheless, we believe that the UN figures provide an appropriate benchmark for this study since they are consistent and widely used in international comparisons. The age composition of all African countries at the national level was available from the UN World population prospects, 1996 revision (19). For each country, the proportions of the population within the age groups 0–4, 5–9, 10–14 and >15 years were calculated. These proportions were then applied to the raster grid map of total population to obtain a surface of population counts for each relevant age group. This assumes that there is no subnational variation of demographic characteristics within a country. This simplifying assumption is unavoidable owing to the lack of detailed and consistent subnational data on age distribution, births and other relevant indicators.

Overall, the uncertainty in these population estimates is likely to be significant but remains within the usual error bounds associated with census figures for developing countries. The combined GIS climate and population models were used to identify populations by age who are exposed to the risks of disease ecologies. The 1995 populations, according to different disease risk categories, are summarized in Table 1 and Fig. 3.

Empirical data sources
A combination of electronic database searches (MEDLINE and EMBASE), manual searches of pre-1960 peer-reviewed journals, national malaria control programme reports (for southern Africa), and correspondence with malarologists working in Africa were used to identify the available mortality and morbidity data. Where possible, data were selected only if they represented control populations used during randomized controlled intervention trials or descriptive data without targeted intervention. Estimates reported over wide geographic areas or several years of observation were disaggregated to enable a more precise estimate of variation between years and between higher resolution geographic areas. Data from reports and direct communication with authors enabled the reconstruction of data according to age but not sex.

Mortality under stable endemic conditions in Africa
A total of 76 independent estimates of annual malaria mortality in childhood, conducted between 1931 and 1997, were identified (20–56; unpublished data from Kenya; Snow et al., personal communication, 1997); 66% had been conducted after 1980. The mortality studies undertaken between 1930 and the 1950s used civil registration data from colonial protectorates where death certification (including cause-of-death) was obligatory (21 reports). There is no estimate of the completeness of registration or the criteria used to define malaria deaths occurring outside clinical settings. Several studies in the 1980s used retrospective methods, enquiring after survival of live births during the preceding 3 years (2 reports). These are likely to differ significantly in terms of completeness of coverage compared with the majority of studies in the series which employed prospective mortality surveillance (53 reports). Most studies since 1980 undertook verbal autopsy investigations to
establish causes of death. These survey tools have been shown to lack precision for malaria diagnosis \((57, 58)\). Many of the studies do not provide details of how malaria was attributed as a cause of death, although it was often through a process of a consensus agreement from independent review by three physicians of reports recorded from bereaved relatives. Despite variations in mortality detection methods, completeness of registration, and precision of verbal-autopsy-diagnosed causes of death, these studies represent our only empirical sources of malaria-specific mortality among African children.

Five reports presented data among age groups not consistent with a childhood age range of 0–4 years \((20, 40)\) and were excluded from the analysis of mortality risks among children aged 0–4 years. The remaining 71 studies cover 16 countries. Estimates of endemicity (cross-sectional parasite ratio surveys among childhood populations) were independently identified for 54 of the mortality survey locations. A total of 50% of this series was undertaken in areas exposed to intense transmission (childhood parasite ratios \(\geq 70\%\)). The range in mortality estimates encompasses zero \((29)\), an unlikely estimate. Nevertheless, the underlying principle behind this analysis has been not to make any value judgements on quality and precision of the estimates provided. To this end, all data have been included and medians and interquartile ranges (IQR) have been used to summarize the data. The median estimate of malaria-specific mortality among children aged 0–4 years was 9.4 per 1000 per annum (IQR: 7.1, 12.4).

Most studies of the causal structure of mortality in Africa have focused on childhood. Consequently, we know surprisingly little about malaria mortality among older children and non-pregnant adults under endemic conditions in Africa. We have approached this paucity of data by modelling the declining mortality risk with age in accordance with our present knowledge on the development of functional immunity to severe, life-threatening malaria. To model declining mortality risks with age we have used age-specific data derived from proportional, severe malaria admission rates among children aged 0–9 years for 14 hospital

### Table 1. Population and mortality estimates for the interpolated distribution of people according to classifications of transmission risk\(^a\)

<table>
<thead>
<tr>
<th>African population exposed</th>
<th>Median mortality rate per 1000 population</th>
<th>Estimated numbers of deaths in 1995</th>
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</table>
| to different malaria risks | *0 climate suitability:* No malaria risk | *
| (excluding southern and northern Africa) | *>0 and <0.2 climate suitability:* Epidemic malaria risk\(^b\) | *≥0.2 climate suitability:* Stable transmission |
| Population aged 0–4 years | 4 609 524 | 9 850 391 |
| Median mortality rate per 1000 population | – | 9.4 (7.1, 12.4)\(^b\) |
| Estimated numbers of deaths in 1995 | 0 | NA |
| Population aged 5–9 years | 3 770 381 | 8 174 807 |
| Median mortality rate per 1000 population | – | NA |
| Estimated numbers of deaths in 1995 | 0 | NA |
| Population aged 10–14 years | 3 097 257 | 6 906 370 |
| Median mortality rate per 1000 population | – | NA |
| Estimated numbers of deaths in 1995 | 0 | NA |
| Population aged >15 years | 13 329 952 | 29 639 097 |
| Median mortality rate per 1000 population | – | NA |
| Estimated numbers of deaths in 1995 | 0 | NA |
| Total population in 1995 | 24 807 114 | 54 570 668 |
| Total deaths in 1995 [non-epidemic year] | 2 422 110 | 24 779 130 |

\(^a\) No reliable estimates of age-specific malaria mortality during malaria epidemics are available.

\(^b\) Figures in parentheses are the interquartile range.

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Research

628

settings in Africa (17, 59–63). While there is a wide range of age-specific patterns, these 14 studies encompass the ranges of endemicity covered by the identified mortality data. The hospital data were aggregated to provide an age-risk function curve using a reciprocal quadratic function to model risks through childhood into adulthood (Fig. 4). This function was applied to the median and IQR base-estimate in the 0–4-year group to derive estimates at older age groups (Table 1).

**Morbidity under conditions of stable endemicity in Africa**

The mild clinical consequences of *P. falciparum* infection often present as fever and a variety of associated symptoms including rigors, headache, body pains, cough and diarrhoea. The age-specific patterns of clinical manifestations of *P. falciparum* for mild, acute malaria disease in endemic Africa are provided by Rogier et al. (64). For most individuals in endemic settings these clinical events will be either effectively treated or treated with only partial success due to inappropriate drugs or dosages, or the patient will spontaneously recover in the absence of any intervention. A minority of these events will progress to severe pathological complications, which may result in death.

Field-based epidemiological studies of mild morbidity frequently use fever and accompanying high parasite densities as characterizing a clinical event. These events are either detected through active surveillance or passively detected at referral centres among well-defined cohorts of children. Of these, passive detection best reflects what the local community perceives as ill health, but it will not detect all mild, transitory clinical events. Active surveillance relies heavily on the attribution of a febrile event to the associated parasitaemia, which in many endemic settings will be present among the majority of asymptomatic hosts; statistical methods have been developed to attribute risk for specific parasite density cut-offs (65).

A total of 51 studies of febrile clinical episodes of malaria in childhood were identified through the literature and unpublished data-sets in areas of stable endemicity (22–24, 27, 32, 36–38, 40, 56, 66–92; unpublished data from Kenya: Snow et al., personal communication, 1997). These surveys had actively or passively surveyed for febrile malaria episodes in childhood. The frequency of surveillance determines the likely chances of detecting events. For example in the Gambia, weekly surveillance detected 75% of events identified by daily surveillance and monthly surveillance detected 25% of weekly surveillance events (93). Data reported from active surveillance studies have been corrected to annualized (or transmission season) risks as would have been defined through weekly surveillance, according to whether they made single, cross-sectional, weekly or monthly observations. Five studies did not include parasitological examinations of detected febrile events and these were excluded from subsequent analysis. The remaining studies were conducted in 13 countries; 18 were undertaken in areas with a childhood cross-sectional parasite ratio of <50%, 7 in areas where childhood prevalence of infection was 50–69%, and 21 studies in areas where the prevalence of infection was ≥70%.

Case definitions for clinical episodes of malaria are complex. Many of the studies reported the number of children seen, the number with a raised
temperature or reported fever, and the number with detectable \textit{P. falciparum} infection in the peripheral blood (and sometimes those with elevated parasite densities). It is not possible to provide a uniform case definition under every setting since etiological fractions of fever and parasite density will be a function of the risks of super-infection and immunity by age. Consequently the data have been presented initially according to “any” level of infection as the most basic common denominator between the studies. Ten studies (37, 55, 76–77, 88–90; unpublished data from Kenya; Snow et al., personal communication, 1997) reported both rates for any level of infection and a qualifying parasite density consistent with the background levels of parasite density in that population. The relative differences between the two definitions (any versus an elevated parasite density) ranged from 1.2 to 2.5 and the average difference was 1.84. Studies were therefore categorized as: 1) those providing a corrected parasite density qualification for a case; and 2) those where any level of infection was used. The latter were corrected according to a 1.84 lower incidence derived from the 10 studies providing both estimates. These 46 clinical attack rate estimates provide a median estimate for attack rate for malaria of 998.5 per 1000 children per annum (IQR: 462.0, 1720.0).

Only four studies provided rates of disease by age throughout childhood (23, 78, 82, 85) and there are no published single-year age-group estimates of morbidity risk to define a risk-function curve as was calculated for mortality. The four studies combined suggest an average decline in attack rates of 4.19 between the two age groups 0–4 years and 5–9 years. When applied to our base estimate of 998.5 per 1000 children aged 0–4 years per annum, one would expect an attack rate of 238.5 per 1000 per annum among children aged 5–9 years.

Fewer studies exist for adults and only 10 estimates could be identified (64, 66, 94–97). The median attack rate for clinical malaria, as defined by this series, was 939 per 1000 adults per annum (IQR 400, 1400). These combined empirical observations suggest that morbidity risks would be similar to those of early childhood; however, we know little about changing patterns of severity or debilitation with increasing age. While it is generally accepted that the nature of immunity to malaria is complex, with important differences between immune mechanisms targeted at reducing fatal outcomes and those targeted at fever modulation, immunity to mild clinical attacks is acquired with age. One possible explanation for this discrepancy is that malaria case definitions for adult attacks have not been well defined and we have not employed correction factors in accordance with parasite density criteria. The most rigorous contemporary study conducted among African adults living in a highly endemic area was that undertaken among the residents of Dielmo village in Senegal, who participated in daily parasitological and clinical observations over 3 years (64). The authors defined a malaria attack rate of 400 per 1000 adults per annum. It seems plausible that morbidity risks increase in old age and among pregnant women through a weakening of overall immune responses. While there is evidence to support this weakening (98), there is a paucity of clinical epidemiological evidence among non-pregnant adults living in endemic areas of Africa. In our analysis we have assumed approximately 1 clinical attack of malaria per child aged 0–4 years, 0.25 per child aged 5–14 years, and 0.4 per adult per annum.

Mortality and morbidity in southern Africa

Data for southern Africa were derived from national surveillance reports which reported on combinations of active surveillance, case reporting of malaria (malaria is a notifiable disease in all these countries), and civil registration data. While there can be no claims to completeness of notification, the southern African countries have invested heavily in malaria surveillance to support control operations. Estimates of mortality were available from Botswana, Namibia, South Africa, and Zimbabwe (99–106). Only provinces, districts or regions within the ≥0.5 climate suitability limits were included. Reports presenting data by age indicated very little variation in risks by age, consistent with a population with little functional immunity. In South Africa several fatalities will have been included among migrants from Mozambique and it was not possible to separate out these events. The median mortality rate from 15 reports was 0.104 per 1000 total population per annum (IQR: 0.02, 0.20). From similar areas we identified 35 estimates of malaria morbidity from malaria control programme reports (99–107). These reports, covering the last 10 years, provide a median estimate of 11 episodes per 1000 total population per annum (IQR = 4.4, 29.4), representing an average of one episode per person every 10 years.

Mortality and morbidity among populations exposed to epidemics

A significant proportion of the population in southern and East Africa and in the Horn of Africa are exposed to unstable malaria, giving rise to epidemics. A total of 15 published and unpublished reports on morbidity and mortality risks among populations exposed to unnatural epidemics were identified (108–114). These data have been reported as risks per day and, in the majority of mortality reports, relate to all-cause mortality. Mortality estimates for malaria alone are only available for four areas recorded during the 1958 malaria epidemic in Ethiopia (ranging from 59.64 to 350 per 1000 population per annum) (109); the median was 235.13 per 1000 total population per annum (IQR = 103, 350). These risks demonstrate the devastating effects of malaria epidemics; however, they derive from a single crisis situation among a
population with virtually no immunity and no access to curative services. Such epidemic scenarios are likely to be uncommon, occurring perhaps every 30 years. More typical are the effects among partially immune populations located in the highlands of East Africa and the Horn of Africa. The periodicity and clinical-epidemiological descriptions of malaria in these altitude-epidemic-prone areas are poorly defined. Indeed, we have no empirical basis on which to define the risks of fatal outcomes among these populations and these have therefore been omitted from Table 1.

Seven reports of clinical attack rates per 1000 total population per day during epidemics in arid and altitude areas were identified (108, 109, 111, 113, 114). The median annualized estimate for these studies is 976 per 1000 population (IQR 149, 1176). Despite the paucity of data, this would appear to be a reasonable estimate as all new infections will probably lead to clinical disease and this rate is consistent with semi-immune young children exposed to stable endemic malaria. We have assumed these epidemic risks last for approximately 3 months and occur on average every 3–5 years affecting all age groups equally.

Sequelae from cerebral malaria among children living under stable endemic conditions

Cerebral malaria is defined in clinical terms as the presence of coma due to malaria (115). Its pathology stems from a series of complex mechanisms which may operate independently, but all result in a brain insult. Several factors may increase the risk of neurological sequelae following cerebral malaria, including hypoglycaemia, multiple seizures, reduced cerebral perfusion pressure associated with raised intracranial pressure, hypoxia associated with microvascular obstruction, and tissue damage following induction of cytokine cascades (116).

Waller et al. (117) identified 29 studies of cerebral malaria in African children published between 1956 and 1994, which included reports on the incidence of neurological sequelae. A total of 206 of 2612 (7.8%) children were reported to have sequelae. However, there were major differences in the methodologies and definitions of cerebral malaria used, and this is reflected in the wide range of reported incidence (0–25%). We have therefore concentrated on six more recent studies (118–122;}

<table>
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<tr>
<th>Table 2. Morbidity estimates for the interpolated distribution of people according to classifications of transmission risk</th>
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<tr>
<td>Median morbidity rate per 1000 population aged 0–4 years population</td>
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<tr>
<td>Estimated numbers of clinical attacks among 0–4-year-olds in 1995</td>
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<tr>
<td>Median morbidity rate per 1000 population aged 5–9 years</td>
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<tr>
<td>Estimated numbers of clinical attacks among 5–9-year-olds in 1995</td>
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<td>Median morbidity rate per 1000 population aged 10–14 years</td>
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<td>Estimated numbers of clinical attacks among 10–14-year-olds in 1995</td>
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<td>Median morbidity rate per 1000 population aged &gt;15 years</td>
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<td>Estimated numbers of clinical attacks among &gt;15-year-olds in 1995</td>
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<tr>
<td>Total numbers of clinical attacks in 1995 (non-epidemic year)</td>
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a Epidemic estimates assume 3 months of risk and that rates and burden occur every 3–5 years.

b Figures in parentheses are the interquartile range.

c Figures in italics are the range.

d Estimates for non-epidemic year provided for the entire population in parentheses and are based upon risks associated with conditions in southern Africa.
unpublished data from Kenya, Peshu et al., personal communication, 1998), which used comparable diagnostic criteria. These studies report on a total of 1854 children with cerebral malaria, 302 (16.3%) of whom died, while 248 (16% of survivors) were reported to have neurological sequelae at discharge. Even using standardized criteria for the definition of cerebral malaria, the reported incidence varied from 9% (118) to 23% (122). Most of this variation probably stems from differences in what is taken to constitute a significant deficit on discharge; many children examined within a few days of an encephalopathic illness will have residual problems such as ataxia which resolve rapidly over the next few weeks or months. More significant are those neurological sequelae that are persistent. Five studies differed in follow-up schedules and completeness of follow-up, but four of the studies (119, 120, 122, unpublished data from Kenya, Peshu et al., personal communication, 1998) covering 1258 children had follow-up periods of at least 6 months; among this series the overall rate for persisting neurological sequelae was 5.6%. Although there may continue to be improvement beyond 6 months, we have used this rate in the calculations of the risks of long-term sequelae given below.

The sequelae reported (in approximate order of frequency) included the following: hemiplegia/hemiparesis (weakness in one or both limbs on one side of the body), speech disorders, behavioural disorders, blindness, hearing impairment, cerebral palsy (also called spastic paresis in some studies — these children have a generalized increase in muscle tone and are very severely disabled, requiring constant attention from a caretaker) and epilepsy. Children often have multiple sequelae and it is not possible to disaggregate the data from the published studies to give absolute rates for each type of sequelae.

To define the annual risks of cerebral malaria presenting to hospital, we selected 10 demographically and geographically defined communities within 15 km of a hospital setting with upgraded diagnostic facilities and a prospective epidemiological surveillance system (17, 60). These clinical sites were situated among a wide range of endemicities ranging from cross-sectional, prevalence infection rates among children aged 0–9 years of 2% in the Gambia to >80% in Kenya and the United Republic of Tanzania. Median estimates described through these studies have been used to define the risks of cerebral malaria among children aged 0–4 years and 5–9 years for communities with easy access to tertiary-level care. These estimates were 1.82 per 1000 children aged 0–4 years per annum (IQR: 0.26, 2.60) and 0.35 per 1000 children aged 5–9 years per annum (IQR: 0.13, 0.61). Not all of these children will survive admission because cerebral malaria has a poor prognosis even under optimal care. Application of the case-fatality estimate (16.3%) defined above indicated that only 83.7% survive admission and are subject to the risks of neurological sequelae. We have assumed these survival risks are similar across both age groups.

Also we have assumed that children who experience cerebral malaria and do not reach hospital do not spontaneously recover and would probably be included in mortality estimates. To derive an estimate of the proportions of children living in stable endemic areas of Africa within similar reach of essential clinical services capable of managing cerebral malaria cases, we used seven national demographic and health survey reports (Uganda, 1995; Kenya, 1995; United Republic of Tanzania, 1991–92; Mali, 1995–96; Central African Republic, 1994–95; Chad, 1996–97; and Cameroon, 1991) which describe the proportions of randomly selected households within 15 km of hospital care. The average estimate from these community-based surveys was 35.9% (range, 22–65%).

By combining the rates of cerebral malaria per 1000 children exposed to stable transmission with (i) correction factors for access to hospital and case-fatality and (ii) risks of persistent sequelae, we estimated the numbers of events likely to occur among children living under these conditions in 1995 (Table 3). These estimates do not allow for multiple syndromes within the same child and therefore correspond to numbers of events. No data are available on the risks of residual sequelae among adults exposed to cerebral malaria in Africa. Several conservative assumptions were made in deriving these figures: for example, in practice many children are brought to hospital from communities that lie much further than 15 km from hospitals; a proportion of children treated inadequately outside hospital will not survive; and the figures are derived from settings with a level of clinical management considerably higher than that which may apply in many ordinary hospitals. These figures should therefore be viewed as minimum estimates and the true impact is likely to be considerably higher.

Severe anaemia, blood transfusion and HIV risks among children living under stable endemic conditions

Severe anaemia is a feature of life-threatening malaria with a complex etiology combining a rapid haemolysis during acute infection and/or a slow insidious process compounded by antimalarial drug resistance. Severe anaemia is a life-threatening condition in young children and often warrants blood transfusion at a hospital setting. Greenberg et al. examined the human immunodeficiency virus (HIV) and malaria serostatus of 167 paediatric admissions to an emergency ward at the Mama Yemo Hospital, Kinshasa, Zaire (now called Democratic Republic of the Congo) (123). Of 112 malaria diagnoses, 68 had received blood transfusions and 44 had not. HIV infection rates on discharge were 15% among
the transfused group compared with 2% among the nontransfused group. An unadjusted odds ratio for acquired HIV infection of 3.5 was proposed for malaria patients transfused once, rising to 21.5 and 43.0, respectively, for those transfused twice and three times during a single admission. HIV infection rates at the blood bank in Kinshasa were 6.3%. This single observation increases the significance of sequelae of severe malaria. Transfusion is a common paediatric practice in Africa. Criteria for its use vary between clinical settings, but we identified ten studies (123–132) where transfusion rates were provided for children who presented at hospital with a haemoglobin level ≤5.0 g/dl; the average transfusion rate among this series was 70%.

Among the 10 hospital community-linked studies described above, 7 settings recorded haemoglobin concentrations on every admission (17, 60). The median annual rate of presentation to hospital with severe malaria anaemia (a primary diagnosis of malaria and an accompanying haemoglobin of <5.1 g/dl) was 7.61 per 1000 children aged 0–4 years (IQR: 3.99, 11.61) and 0.47 per 1000 children aged 5–9 years (IQR: 0.11, 0.72). Similar correction factors were applied to the childhood populations at risk, as defined above, to calculate the number of children living within 15 km of a hospital. The average case-fatality rate for paediatric severe malaria anaemia from 11 reports (17, 60, 126–132) from hospitals located in endemic areas was 7.9% (90.3% survived). Combining these parameter estimates provides a means to calculate the numbers of children who developed severe malaria anaemia, were admitted to hospital, survived, and were treated with blood transfusion, and their subsequent increased risks of developing HIV infection in accordance with the risks described by Greenberg et al. (Table 3).

### Summary of estimates of the malaria burden

The biological basis of transmission and acquired immunity and the application of new GIS technologies using continental-scale databases have driven our approach to defining the malaria burden in Africa. Given the unreliability of national statistics in much of sub-Saharan Africa, we have used empirical, survey-derived data on the risks of mortality, morbidity and disability. We were able to identify over 200 published sources on the health impact of malaria across a wide range of endemcities and disease ecologies common to Africa. In the present analysis we have selected direct estimates or morbid and fatal risks rather than proportional risks attributable to malaria intervention, as defined by randomized controlled trials. Trial data available for such an analysis only cover a small area of Africa (6 studies in total) and none achieved complete coverage or 100% efficacy. We have analysed these studies previously, and the results compared favourably with the direct estimation of malaria mortality in the same areas using verbal autopsies (7).

Through a combination of approaches we have estimated that, among populations exposed to stable endemic malaria in sub-Saharan Africa, approximately 987 466 people may have died in 1995 from direct consequences of *P. falciparum* infection. This would have included 765 442 children below the age of 5 years. We used a combined estimate of mortality risk derived over many years (predominantly since 1980), and there is mounting evidence that mortality risks have increased significantly, coinciding with the rise in failures with chloroquine, the widely used first-line treatment (52, 59). Also, our estimates only consider the direct consequences of infection. We have not considered any indirect consequences of infection with *P. falciparum* upon fatal outcomes from other causes of death, particularly in childhood, and

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**Table 3. Sequelae risks and events following admission to hospital among children living in stable endemic areas of Africa**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age group (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4</td>
</tr>
<tr>
<td>Risk of cerebral malaria admission from communities within 15 km of a hospital (per 1000 population per annum)</td>
<td>1.815 (0.26, 2.60)</td>
</tr>
<tr>
<td>Risk of surviving hospitalization with cerebral malaria</td>
<td>1.472 (0.211, 2.11)</td>
</tr>
<tr>
<td>Risk of surviving hospitalization with cerebral malaria, allowing for the proportion of population within 15 km of hospital</td>
<td>0.528 (0.076, 0.756)</td>
</tr>
<tr>
<td>Neurological sequelae risk of residual effects after six months (per 1000 children per annum)</td>
<td>0.030 (0.004, 0.042)</td>
</tr>
<tr>
<td>No. of neurological sequelae events</td>
<td>2443 (356–3420)</td>
</tr>
<tr>
<td>Risk of SMA admission from communities within 15 km of a hospital (per 1000 population per annum)</td>
<td>7.61 (3.99, 11.61)</td>
</tr>
<tr>
<td>Risk of surviving SMA admission and receiving a blood transfusion (per 1000 population per annum)</td>
<td>6.87 (3.60, 10.49)</td>
</tr>
<tr>
<td>Risk of surviving hospitalization with SMA allowing for proportion of population within 15 km of hospital (per 1000 population per annum)</td>
<td>4.81 (2.52, 7.34)</td>
</tr>
<tr>
<td>Risk of surviving hospitalization with transfused SMA allowing for proportion of population within 15 km of hospital (per 1000 population per annum)</td>
<td>1.73 (0.905, 2.64)</td>
</tr>
<tr>
<td>Risk of survivors with SMA who had a blood transfusion, who acquire HIV when background risks apply to those in Kinshasa in late 1980s (per 1000 population per annum)</td>
<td>0.225 (0.118, 0.343)</td>
</tr>
<tr>
<td>No. of HIV events arising from blood transfusions of severe malaria anaemia</td>
<td>18 322 (9609–27 930)</td>
</tr>
</tbody>
</table>

a Figures in parentheses are the interquartile range.
b Figures in italics are the range.
c SMA = severe malaria anaemia.
the estimates we have provided may be considered a minimum. For morbidity, despite fewer empirical observations and additional problems of precise case-definition, we estimate that over 207.5 million clinical attacks of malaria may have occurred in Africa among people resident under stable endemic conditions in 1995. This estimate relates only to a strictly defined risk of a clinical episode of malaria allowing for the presence of asymptomatic infection. A far greater number of people would have been presumptively diagnosed and/or treated for malaria in 1995.

The definitions used to describe zero-risk, unstable or epidemic-prone areas of Africa are fraught with technical difficulties (14); these “fringe” areas demand further epidemiological research. Nevertheless, we have used arbitrary selection criteria derived from climate suitability models to define two regions of sub-Saharan Africa which either support unstable transmission conditions or where long-term climate data suggest areas are always unsuitable for transmission. Under both conditions, malaria will pose some burden every year where highly mobile, nonimmune populations migrate between their residence and areas of stable endemic transmission. We have no estimates of these “mobility” risks and have no reliable estimates of mortality among populations exposed to epidemics in Africa. However, information was available for morbidity risks among populations exposed to unstable transmission. There was a striking similarity in the clinical attack rate described in the literature among total populations exposed to epidemic malaria (976 per 1000 per annum) and that described for children born under stable endemic conditions (998.5 per 1000 per annum). These observations support the idea that such populations have no acquired functional immune responses. We have assumed that malaria epidemics last for 3 months and occur on average every 3–5 years. During nonepidemic years we have assumed a minimum risk described for southern Africa that would account for 150,000 clinical attacks. It has been argued that the periodicity of epidemics may be changing over time, with decreasing intervals between epidemics (13,3), possibly leading to a change in the estimates of the longer-term, projected malaria burden.

Among the populations located in southern Africa, we were able to identify malaria control surveillance reports for five countries among districts located within a boundary of likely malaria transmission (Fig. 3). Applying the annualized median risks for mortality and morbidity suggests that, in 1995, this population may have experienced 2135 deaths and 213,509 clinical attacks due to chance encounters with infections not prevented by aggressive control and by prompt and effective treatment. Of interest are the derived case-fatality estimates for southern Africa (1.0%) versus those defined for areas of stable transmission in sub-Saharan Africa (0.48%). Both are high, indicating how potent malaria has been in selecting for host polymorphisms such as sickle cell, but they also highlight the potential significance of naturally acquired immunity against the fatal consequences of infection through repeated parasite exposure.

There are several health outcomes of \textit{P. falciparum} infection which we have not considered, including the potential effects of undernutrition, potentiating effects from other infectious diseases, cognitive impairment and behavioural disturbances (as a consequence of cerebral malaria), possible risks of epilepsy following repeated seizures, and adverse drug reactions to increasingly used second-line antimalarial drugs. Of significance are the effects of malaria infection in pregnancy, which are being considered separately (Guyatt et al., in preparation). However, by way of demonstrating the value of empirical evidence-based approaches, we have selected two sequelae of severe, life-threatening malaria: residual neurological disability following cerebral malaria; and HIV risks consequent upon transfusion for severe malaria anaemia. We have calculated these effects only for children aged <10 years living in areas of stable endemicity in sub-Saharan Africa. Approximately 3000 disabling long-term events may have occurred among survivors of cerebral malaria in this area of Africa in 1995. We have calculated only those events which are likely to be lifelong. Thus, the last decade may have witnessed a cohort of 30,000 children who have been left with residual effects such as “spasticity” and epilepsy attributable to a brain insult caused by malaria. Furthermore, we have estimated that over 19,000 children, aged 0–9 years and residing in the stable endemic areas of Africa, may have survived blood transfusion for their severe malaria anaemia but would have acquired HIV. These estimates stemmed from a single study in Kinshasa where HIV prevalence was 6% in 1986 (123). In the absence of further data on these effects under operational conditions (including screening) in Africa, the significance of these estimates must be judged with caution. On the assumption that these are real threats to paediatric patients with severe malaria anaemia, the next decade may lead to 200,000 children acquiring HIV directly as a consequence of blood transfusions for life-threatening anaemia associated with malaria.

Discussion

The risks of disease and death from malaria are dependent upon a wide range of factors, including the frequency of protective genetic polymorphisms, acquired immunity, access and use of curative services, drug resistance, and the protective behaviours of communities against infection. These factors will vary significantly across the African continent, resulting in significant differences in disease outcomes between areas. Perhaps the most significant of these is acquired functional immunity. There is now good evidence that the intensity of \textit{P. falciparum} transmission determines the age at which functional immunity is acquired in a given
population. Throughout the present analysis of the malaria burden, we have assumed that under stable transmission conditions cumulative disease and mortality risks reach an equilibrium irrespective of their endemicity (17). Such an approach does not reflect reduced risks of mortality and disease under conditions of very low stable transmission. Within the series of reports used in this paper, five were conducted under conditions where point prevalence infection rates among the childhood population aged 0–9 years were below 20% (74, 77, 93), and indicate a 10-fold lower risk of clinical disease relative to the median estimate derived from the studies conducted under conditions of higher endemicity (where mortality risk varied little with increasing intensity of transmission). Of particular relevance is the epidemiology of parasite transmission under urban conditions. There are several examples where transmission intensity is in reality much lower than would be predicted from climate-driven models. For example, among the peri-urban population in Bakau, in the Gambia, infection rates are <5%, while less than 10 km away in a rural area they exceed 30% (17, 77). Urbanization in Africa is a rapidly proliferating demographic change and needs to be captured within the population models for future burden of disease estimates.

One of the principal objectives of the Mapping malaria risk in Africa/Atlas du risque de la malaria en Afrique (MARA/ARMA) collaboration is to provide empirical data and modelled maps showing the high resolution distribution of endemicity risk across Africa (134, 135). This project is in its nascent stages and endemicity risk maps are only available for Kenya (136) and Mali (Magran et al., in preparation). Within the framework of the MARA/ARMA collaboration, these models of spatial heterogeneity of endemicity and risk will provide the basis for a wider and more detailed analysis of burden for the year 2000 and allow for dynamic models which capture changing features such as urbanization and drug resistance.

While we cannot claim to have provided an exhaustive research bibliography of malaria’s impact on mortality and morbidity in Africa, it is striking how little detailed epidemiological work has been undertaken on the clinical consequences of infection. The process of using evidence-based descriptions of disease burden allows us to define both what we do not know and what we do know. To this end, our analysis has highlighted several key weaknesses in the literature, which must be corrected to provide informed approaches to morbidity and mortality risks in Africa. These include the epidemiological patterns and risks of morbidity and mortality across wider age groups, particularly adults, among populations living in urban and epidemic settings, and improved GIS descriptions of unstable malaria, urbanization and higher resolution age-corrected population distributions for the continent. The combined challenge is for epidemiologists, geographers and demographers to redress these deficiencies in our present knowledge by providing more informed estimates of the malaria burden in Africa.

Our estimates of approximately 1 million deaths due to malaria among the African population in 1995 are well within the range described for sub-Saharan Africa by Murray & Lopez (4) for the 1990 population and are consistent with several pre-1990 estimates (2). Some may therefore argue that “back of an envelope” or expert opinions are robust enough methods. We would, however, argue that our approach provides a more rational basis for defining disease burden, which is transparent in its inputs, assumptions, limitations and caveats. Such an approach allows for new evidence, empirically derived confidence limits, and modelled predictions of change. Within the limitations of the evidence and assumptions on disease distribution, we feel confident to claim that P. falciparum causes approximately 1 million deaths and over 200 million clinical events among the people of Africa each year. Our estimates of mortality risk were predominantly derived during an era when first-line therapeutic drugs were effective; as this situation changes, so will the mortality burden. The “roll back” malaria effort has many challenges ahead and will be faced with a disease in Africa that kills thousands of people each day rather than hundreds.

Acknowledgements
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Resumen

Estimación de la mortalidad, la morbilidad y la discapacidad por paludismo entre la población de África, excluyendo a las mujeres embarazadas

El tema de la contribución del paludismo a la morbilidad y la mortalidad entre la población de África ha suscitado interés teórico y ha sido objeto de promoción y especulación. Las estadísticas nacionales de gran parte del África subsahariana han demostrado ser una fuente de datos poco fiable respecto a la morbilidad y mortalidad por enfermedades específicas. Se requieren estimaciones fiables sobre la carga de enfermedades concretas para fijar las prioridades sanitarias mundiales y nacionales a fin de racionalizar el uso de unos recursos limitados y de ejercer presiones para obtener apoyo financiero. Hemos adoptado un enfoque empírico para definir los límites de la transmisión de Plasmodium falciparum a través del continente, e interpolado la distribución de la población a partir de las proyecciones demográficas de 1995. Combinando el análisis de la literatura sobre el paludismo en África y modelos de la inmunidad funcional adquirida, hemos estimado las tasas estructuradas por edades de las secuelas de mortalidad, morbilidad y discapacidad resultantes de la exposición a la infección palúdica en diferentes condiciones epidemiológicas.

Estimamos que 990 000 personas pueden haber muerto como consecuencia directa de la infección por P. falciparum en África durante 1995; el 75% de esas defunciones corresponderían a niños menores de cinco años. La incidencia por edades de ataques clínicos estrictamente definidos entre poblaciones expuestas a diferentes riesgos de transmisión del paludismo indica que durante 1995 se habrían producido en África aproximadamente 208 millones de episodios morbosos (más 13 millones en situaciones de epidemia). La carga oculta en condiciones endémicas estables, como las secuelas neurológicas por paludismo cerebral y el daño cerebral permanente y 19 000 de nuevas infecciones por el VIH entre los niños que han sobrevivido al paludismo grave.

El uso de sistemas de información geográfica, de los determinantes biológicos de la transmisión de P. falciparum, de nuestros mayores conocimientos sobre los modelos epidemiológicos de la enfermedad y la inmunidad y de más de 150 fuentes de datos empíricos proporciona una perspectiva informada para realizar estimaciones de la carga de paludismo. Sin embargo,
dicha perspectiva pone de relieve que nuestras fuentes de datos epidemiológicos y nuestros conocimientos presentan algunos puntos débiles, que es menester corregir con miras al futuro desarrollo de modelos dinámicos del impacto sanitario. Pese a esas limitaciones, creemos que podemos afirmar con seguridad que el paludismo se cobra de forma directa cada año en África aproximadamente un millón de vidas.

References

Research


Malaria mortality, morbidity and disability in Africa


