

The burden of malaria mortality among African children in the year 2000

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Background Although malaria is a leading cause of child deaths, few well-documented estimates of its direct and indirect burden exist. Our objective was to estimate the number of deaths directly attributable to malaria among children <5 years old in sub-Saharan Africa for the year 2000.

Methods We divided the population into six sub-populations and, using results of studies identified in a literature review, estimated a malaria mortality rate for each sub-population. Malaria deaths were estimated by multiplying each sub-population by its corresponding rate. Sensitivity analyses were performed to assess the impact of varying key assumptions.

Results The literature review identified 31 studies from 14 countries in middle Africa and 17 studies and reports from four countries in southern Africa. In 2000, we estimated that ~100 million children lived in areas where malaria transmission occurs and that 803 620 (precision estimate: 705 821–901 418) children died from the direct effects of malaria. For all of sub-Saharan Africa, including populations not exposed to malaria, malaria accounted for 18.0% (precision estimate: 15.8–20.2%) of child deaths. These estimates were sensitive to extreme assumptions about the causes of deaths with no known cause.

Conclusions These estimates, based on the best available data and methods, clearly demonstrate malaria's enormous mortality burden. We emphasize that these estimates are an approximation with many limitations and that the estimates do not account for malaria's large indirect burden. We describe information needs that, if filled, might improve the validity of future estimates.

Keywords Malaria, mortality, Africa, epidemiology, child

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Introduction

Malaria is a leading cause of mortality among children in sub-Saharan Africa. Valid quantitative estimates of malaria mortality are useful for monitoring the impact of prevention and control activities, targeting interventions, and advocacy. Unfortunately, vital registration systems in most countries in sub-Saharan Africa have low coverage and do not produce dependable estimates.^{1–3}

To fill this gap, a variety of estimates have been made, but most are simplistic or lacked documentation of the methods and data.^{2,4–7} (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf) One approach,⁸ which the World Health Organization has used to produce annual estimates, identified populations at risk for malaria with a model that predicts where the climate is suitable for *Plasmodium falciparum* transmission.⁹ The median malaria

mortality rate, from studies identified in a literature review, was applied to these malaria-risk populations to produce an estimate of ~766 000 deaths among children <5 years old in sub-Saharan Africa for 1995. This model was recently revised to account for variations in malaria transmission intensity¹⁰ and urbanization,¹¹ resulting in estimates of 742 000 and 680 000 child malaria deaths, respectively, for the year 2000. Although these latter models were superior to previous ones, not all contemporary data were used, and use of the median to estimate the malaria mortality rate assumed all studies had equal precision and did not permit an investigation of factors that might have led to a prediction model that could better account for inter-country differences and time trends.

Our objective was to estimate the number of 'direct' malaria deaths for children <5 years old in sub-Saharan Africa for the year 2000 by refining the models by Snow *et al.*^{8,10,11} and using all available contemporary mortality data. By direct malaria death, we mean that malaria was the underlying cause (i.e. 'the disease or injury which initiated the train of morbid events leading directly to death'¹²). Our analysis does not attempt to quantify 'indirect' malaria deaths, in which malaria was a contributing cause (e.g. a child with malaria-associated anaemia dies after developing pneumonia, but neither the anaemia nor pneumonia would have been fatal in isolation); although we acknowledge that the burden of indirect malaria mortality is probably substantial.¹³ Nor does our analysis quantify 'consequential' malaria deaths, in which consequences of clinical management (e.g. exposure to HIV during a blood transfusion) or malaria sequelae (e.g. epilepsy after cerebral malaria) lead to death.¹⁰ The analysis was limited to Africa because this is where most malaria deaths (perhaps 80–90%) are thought to occur.^{2,14,15} Additionally, we sought to identify research areas or information that might improve future estimates.

Methods

Overview

First, we conducted a literature review to identify studies of childhood malaria mortality. Second, for each country, we estimated sub-populations of children with different risks of dying from malaria for the year 2000. Third, we estimated a malaria mortality rate for each sub-population using studies from the literature review. To estimate rates, we developed a prediction model with covariates that were available from studies used in the prediction model and from countries to which the predicted rates would be applied. As there were almost no mortality studies with results for the year 2000, we used studies from the past two decades, included a covariate for study year in the prediction model, and estimated rates by giving the study year covariate a value to indicate the year 2000. Fourth, for each malaria risk sub-population in each country, we estimated malaria deaths by multiplying the sub-population by its corresponding rate. Finally, we summed malaria deaths for all sub-populations from all countries.

Literature review

To identify studies of the causes of child deaths in Africa where malaria transmission occurs, we reviewed references used by

Snow *et al.*,⁸ conducted an independent search of the PubMed database, consulted experts, and asked researchers for unpublished studies. For the PubMed search, we searched for all 'malaria/mortality' Medical Subject Headings, and within these references, searched for articles on infants (birth to 23 months) and preschool children (2–5 years). The inclusion criteria were that studies: (i) were community-based, (ii) had results that permitted a malaria mortality rate to be estimated, (iii) had a duration of a multiple of 12 months (malaria is highly seasonal), (iv) included children exactly 0–59 months old (malaria mortality is unevenly distributed in this age range), (v) had a proportion of deaths with no known cause <30%, (vi) began in 1980 or later, and (vii) did not overlap with another study in the analysis in time and place. All studies used verbal autopsies (interviews with the deceased child's relatives are interpreted by clinicians or an algorithm) to determine causes of death,^{16,17} and we note that International Classification of Diseases¹² rules might not have been used to determine causes of death. For studies that were intervention trials, only results from control groups were included. Some studies met nearly all inclusion criteria but had a minor limitation (e.g. duration = 11 months). Therefore, we created two categories: Group A (studies meeting all inclusion criteria) and Group B (studies with minor limitations) (Table 1). For southern Africa, we included 16 estimates of the malaria mortality rate from disease surveillance reports, plus one community-based study of children 0–4 years (Table 2). To examine time trends, for multi-year studies, results were abstracted for individual years whenever possible; and, with one exception, results for all years were included. The exception was a 9-year study from Morogoro, Tanzania,^{18,19} which had some data completeness concerns;^{20,21} for this study, data for one recent year (2001) that were of good quality were included.

Data from studies were abstracted onto standardized paper forms, double-entered into an electronic database, and validated. Key data elements (e.g. number of malaria deaths) were double-checked by two investigators. Data from disease surveillance reports from southern Africa were abstracted onto standardized paper forms and entered into an electronic database by one investigator.

Estimating populations at risk for malaria

We divided Africa into seven sub-populations (Figure 1). As done by Snow *et al.*,^{8,10} we first divided Africa into three regions: northern Africa (Algeria, Egypt, Libya, Morocco, and Tunisia; assumed to have no malaria deaths because the climate is generally unsuitable for *P. falciparum* transmission), southern Africa (Botswana, Lesotho, Namibia, South Africa, Swaziland, and Zimbabwe; very low malaria mortality rates assumed because of a less suitable climate and intense efforts to control the mosquito vector²²), and middle Africa (African countries in neither northern nor southern Africa; variable, including high, malaria mortality rates).

For middle and southern Africa, we used results from the Mapping Malaria Risk in Africa (MARA) project to estimate populations at risk for malaria in 2000.^{8,9,23} Briefly, a grid of 5 × 5 km² was superimposed on a map of sub-Saharan Africa. For each square, MARA estimated the 1990 population²⁴ and

Table 1 Studies from countries in middle Africa that were included in the analysis

Country and site	Time period	Deaths attributed to malaria	Deaths with no known cause	Total deaths (all causes combined)	Person-time (person-years)	Malaria mortality rate ^a (per 1000 per year)	Parasite prevalence (%)
Group A studies from rural settings with high-intensity malaria transmission (n = 46 estimates from 15 studies)							
Burundi (Nyanza-Lac District) ⁷⁵	1990–91	55	4	160	3815	14.8	75.0 ⁷⁵
Democratic Republic of Congo (Kivu) ⁷⁶	1986–87	44	0	358	5187	8.5	34.4 ⁷⁷
Gambia (Farafenni, South Bank) ⁷²	1988–90	75	0	296	5393	13.9	60.9 ⁷⁸
Gambia (Farafenni, North Bank) ⁷⁹	1982–83	24	0	171	2505	9.6	32.4 ⁷⁹
Gambia (Upper River Division) ⁸⁰	1989–93	891	953	3776	113 334	10.5	71.2 ⁸¹
Ghana (Central Region) ⁸²	1987	6	0	15	832	7.2	30.5 ⁸³
Guinea Bissau (Bandim) ⁸⁴	1987–90	22	22	153	2753	9.3	32.6 ⁸⁵
Kenya (Saradidi) ⁸⁶	1981–83	15	0	348	8107	1.9	83.5 ⁸⁷
Kenya (Asembo Bay) ⁸⁸	1997–98	96	43	359	4537	24.0	83.0 ⁸⁹
Senegal (Bandafassi) ⁵⁵	1984–95	99	0	1167	16 973	5.8	95.0 ⁵⁵
Senegal (Niakhar) ⁵⁵	1984–95	495	0	3242	58 985	8.4	50.0 ⁵⁵
Senegal (Mlomp) ⁵⁵	1992–95	19	0	86	3145	6.0	46.0 ⁹⁰ 51.0 ^{91 b}
Tanzania (Bagamoyo District) ⁹²	1983–84	67	0	325	8098	8.3	83.6 ⁹³
Tanzania (Tanga) ⁹⁴	1992–93	30	7	90	2051	15.9	69.5 ⁹⁵
Tanzania (Morogoro) ^{18,19}	2001	241	2	430	15 711	15.4	51.6 ⁹⁶
Group B studies from rural settings with high-intensity malaria transmission (n = 11 estimates from 10 studies)							
Burkina Faso (Kongodjan area) ⁹⁷	1982–86	2	11	43	1186	2.3	53.5 ⁹⁷
Gambia (5 areas along Gambia River) ⁹⁸	1992–93	84	218	424	13 469	12.8	38.7 ⁹⁸
Ghana (Kassena-Nankana District) ⁹⁹	1989–91	116	161	685	10 140	15.0	87.1 ¹⁰⁰
Ghana (Kassena-Nankana District) ¹⁰¹	1993–95	189	84	618	15 895	13.8	64.0 ¹⁰²
Guinea (Mandiana) ⁴⁰	1998–99	104	30	353	16 202	7.0	NA ^c
Kenya (Kilifi North) ^{103,104}	1991–93	155	0	455	20 679	7.5	49.0 ¹⁰⁵
Nigeria (Akoko North) ⁴¹	1987	23	0	120	1929	11.9	NA ^c
Sierra Leone (Bo) ¹⁰⁶	1990	9	2	35	776	12.3	61.0 ¹⁰⁷
Sierra Leone (Western Area and Porto Loko) ⁴²	1988–93	80	0	251	8468	9.4	NA ^c
Tanzania (Yombo Division, Bagamoyo District) ¹⁰⁸	1992–94	54	74	192	5850	15.0	82.0 ¹⁰⁹
Group A studies from rural settings with low-intensity malaria transmission (n = 19 estimates from 5 studies)							
Kenya (Brookebond Tea Estate) ⁵⁴	1997–98	58	0	325	30 623	1.9	11.7 ¹¹⁰
Senegal (Mlomp) ⁵⁵	1985–91	4	0	108	5527	0.7	3.0, ¹¹¹ 24.5 ^b
Sudan (refugee camps in eastern Sudan) ⁵⁶	1997	27	0	47	4269	6.3	0.8 ⁵⁶
Tanzania (Hai District) ^{18,19}	1993–2001	430	73	2449	191 980	2.3	4.0 ¹¹²
Uganda (Mbarara District) ⁵⁷	1988–89	14	0	104	4320	3.2	18.3 ¹¹³
Group B study from a rural setting with low-intensity malaria transmission (n = 1 estimate from 1 study)							
Kenya (Muranga District) ¹¹⁴	1985–88	13	16	232	37 000	0.4	24.0 ¹¹⁵
Group A study from an urban setting (n = 9 estimates from 1 study)							
Tanzania (Dar es Salaam) ^{18,19}	1993–2001	498	68	1809	88 528	5.8	27.8 ¹¹⁶

^a Malaria mortality rate = (Malaria deaths/[person-time × [1 - (deaths with no known cause/total deaths)]]) × 1000, where malaria deaths are shown in column 3 of the table, person-time is in column 6, deaths with no known cause are in column 4, and total deaths are in column 5. Note that the results in this column are the only results that do not come directly from the individual malaria studies (i.e. results in all other columns in the table come directly from the individual study reports).

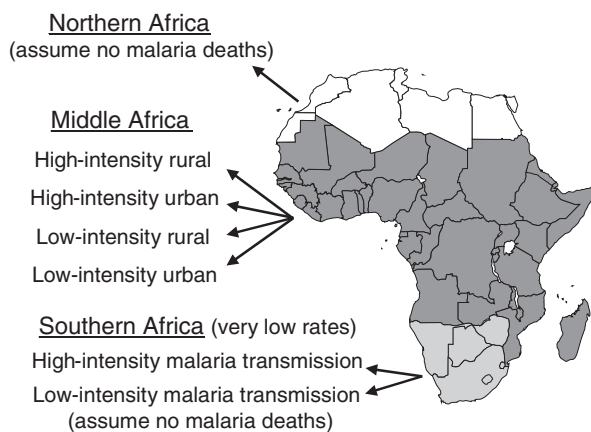
^b Over the long course of this study, four values for parasite prevalence were used: 3.0% (for 1985–89), 24.5% (for 1990–91), 46.0% (for 1992–93), and 51.0% (for 1994–95). For 1990–91, no value was available; so the values for 1985–89 (3.0%) and 1992–93 (46.0%) were averaged [24.5% = (3.0% + 46.0%)/2].

^c NA = Not available. Study population was assumed to have a parasite prevalence in the '≥25%' category based on a prediction model [see Methods and Ref. (43) for details].

Table 2 Studies and surveillance reports included in the analysis that were from areas in southern Africa categorized as having high-intensity malaria transmission

Country and site ^a	Time period	Age group	Malaria deaths	Person-time (person-years)	Malaria mortality rates (deaths per 1000 per year)
Hlabisa, South Africa	1987–90	All ages	9	150 218	0.0599
Ubombo, South Africa	1987–90	All ages	17	164 274	0.1035
Ingwavuma, South Africa	1987–90	All ages	25	211 161	0.1184
7 malarious districts, Botswana	1988–94	All ages	405	2 496 172	0.1622
Southern District, Namibia	1992–96	All ages	79	1 896 789	0.0416
Central District, Namibia	1992–96	All ages	115	1 214 125	0.0947
North Eastern District, Namibia	1992–96	All ages	526	1 133 340	0.4641
North Western District, Namibia	1992–96	All ages	690	3 462 498	0.1993
Manicaland Province, Zimbabwe	1997	All ages	409	1 819 338	0.2248
Mashona Central Province, Zimbabwe	1997	All ages	153	1 021 976	0.1497
Mashona East Province, Zimbabwe	1997	All ages	274	1 208 733	0.2267
Mashona West Province, Zimbabwe	1997	All ages	108	1 314 909	0.0821
Matabele North Province, Zimbabwe	1997	All ages	251	759 032	0.3307
Matabele South Province, Zimbabwe	1997	All ages	32	694 907	0.0460
Midlands Province, Zimbabwe	1997	All ages	70	1 552 593	0.0451
Masvingo Province, Zimbabwe	1997	All ages	196	1 453 557	0.1348
Agincourt, South Africa	1992–95	0–4 years	2	20 800	0.0962
Total			3361	20 574 422	0.163 (95% CI 0.113–0.214)

^a The reference for the study in Agincourt, South Africa is Kahn *et al.*⁵⁸ All other results were from reports that were summarized on a Malaria Burden of Disease in Africa data collection pro forma (RW Snow, personal communication, March 31, 2004).

**Figure 1** Seven sub-populations in Africa with different risks of dying from malaria

a 'climate suitability index' based on a fuzzy logic model of temperature and rainfall determinants of the parasite's sporogonic cycle and mosquito's survival.²⁵ The index describes the probability that the climate is suitable for *P. falciparum* transmission, and it varies continuously from 0 (probably unsuitable) to 1 (probably suitable). MARA results were applied to United Nations country population estimates for the year 2000.²⁶ Of the five middle Africa countries excluded from the MARA model, two were assumed to have no malaria deaths (Mauritius^{15,27} and Seychelles²⁸) and three had populations

at risk estimated from other sources (Cape Verde,^{15,28,29} Comoros,^{15,28} and São Tomé and Príncipe^{15,28,30}).

We categorized populations as being exposed to one of three levels of malaria transmission intensity: zero (populations with a MARA index = 0), low intensity (index >0 and <0.75), or high intensity (index ≥0.75). This categorization (developed by Snow *et al.*¹⁰) was based on the observation that a MARA index <0.75 generally corresponded to a parasite prevalence <25% and an index ≥0.75 generally corresponded to a parasite prevalence ≥25%.³¹ Parasite prevalence (percentage of a community-based sample of children who were parasitaemic with *P. falciparum*) was considered an approximate indicator for malaria transmission intensity and the malaria mortality rate.^{32,33} (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf) Results from our dataset suggested malaria mortality rates were lower in populations with low (<25%) parasite prevalence and generally higher in populations with high parasite prevalence (Figure 2).

This method does not explicitly include a category for epidemics. We assumed that much of what is called 'epidemic' malaria occurs in populations with low levels of endemic malaria transmission that occasionally have spikes of malaria deaths that appear to be epidemics. 'True' epidemic deaths (i.e. malaria deaths where no ongoing transmission occurs) were considered rare for a typical year (i.e. zero, for our estimates; although a sensitivity analysis explored the potential impact of epidemics—see model 'E' of Table 4).

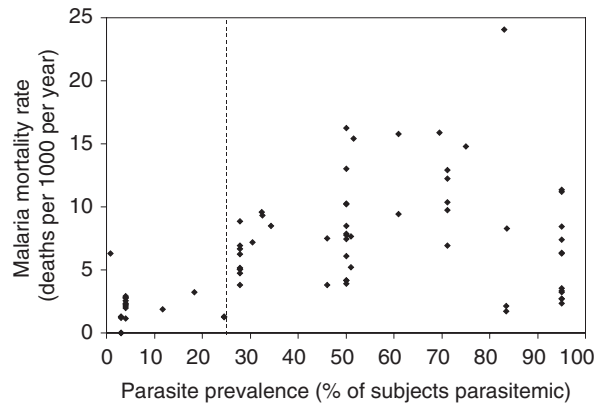


Figure 2 Distribution of malaria mortality rates as a function of parasite prevalence among studies of childhood mortality from middle Africa, 1980–2001 (74 estimates from 20 Group A studies; all studies except one were conducted in rural areas). The dashed vertical line indicates the chosen threshold between ‘low-intensity’ (i.e. parasite prevalence <25%) and ‘high-intensity’ (i.e. parasite prevalence \geq 25%) malaria transmission

Middle Africa populations were further subdivided into those living in urban and rural areas. Urban populations have relatively low malaria mortality rates,^{18,19,34,35} less malaria transmission,^{11,36,37} and better access to life-saving malaria treatment.^{11,38}

To estimate urban and rural populations for each malaria transmission category in each country, we used United Nations estimates of the proportion of all residents living in urban areas for 2000.³⁹ Because this source only provides national estimates, we assumed the proportion of a country’s population living in urban areas was the same for populations exposed to zero, low-intensity, and high-intensity transmission. For the 40 middle African countries in the analysis, the median urban residence proportion was 33.4% (range: 6.2–84.0%). Urban residence proportions were based on census data and assumed to have no uncertainty (T. Buettner, personal communication, UN Population Division, October 29, 2003).

Estimating malaria mortality rates for each at-risk sub-population

For middle Africa, results from mortality studies in middle African countries were analysed. To categorize studies as being from a low-intensity or high-intensity transmission area, we identified parasite prevalence values for all but six studies (Table 1). Parasite prevalence \geq 25% indicated high-intensity transmission, and prevalence <25% indicated low-intensity transmission. Regarding the six mortality studies without a parasite prevalence value, three were from West Africa;^{40–42} with a model of parasite prevalence for West Africa,^{23,43} we estimated that all three studies were in high-intensity transmission areas. The remaining studies (two from Ethiopia^{44,45} and one from Somalia⁴⁶) were excluded because the study sites were in areas with highly variable transmission levels and no conclusive determination could be made.

We calculated malaria mortality rates (expressed as deaths per 1000 children per year) with the formula: rate = malaria deaths/[person-time \times [1 – (deaths with unknown causes/total

deaths)]]. This expression ensures that the proportion of deaths attributable to malaria (PDAM) equals the malaria mortality rate divided by the all-cause mortality rate, and it assumes the PDAM for deaths with unknown causes equals the PDAM for deaths with known causes.⁴⁷ The calculation of mortality rates and all other analyses were performed with SAS version 8.0 (SAS Institute, Cary, NC).

We did not adjust results for the potential bias introduced by verbal autopsy’s imperfect sensitivity and specificity for identifying malaria deaths and that false-negatives probably do not equal false-positives.^{17,48} Although it is theoretically possible to correct this bias with sensitivity and specificity estimates from validation studies,⁴⁹ we did not believe that estimates of adequate quality and representativeness were available.⁵⁰

For middle Africa populations in rural areas with high-intensity transmission, we ran a series of univariate Poisson regression models to identify covariates (obtainable for studies in our dataset and countries in middle Africa) that explained the large variation observed in malaria mortality rates and that could be used to predict rates for individual countries. Modelling was performed with the SAS GENMOD procedure, which uses generalized estimating equations (GEE) to account for over-dispersion of the rates and the potential correlation of mortality rates for individual years from the same study.^{51,52} For precision estimates, we used results from the empirical covariance matrix.

We examined the following covariates: study year (mid-point of data collection; analysed separately as a series of dichotomous and trichotomous variables); proportion of births attended by a health professional, as an indicator of health care access and infrastructure [source = surveys near study sites, e.g. province-level Demographic and Health Survey (DHS)³⁸ results]; study location (East vs West Africa, longitude, and distance from coast); and malaria season duration [<8 months vs \geq 8 months, and as a continuous variable (source = MARA maps)].

Five other covariates were excluded: female literacy rate, access to clean water, study year as a continuous variable, coverage of three diphtheria-pertussis-tetanus vaccine doses (DPT3), and all-cause child mortality. Data on female literacy and access to water were not available for many studies. Study year (continuous variable) was excluded because it reflects both time and place (studies conducted in different years were often from different places) and, when study year is assumed to indicate time, outliers have a greater influence on model results. DPT3 coverage was excluded because, in our dataset, it increased from 1980 to 2001; therefore, we were concerned that study year and DPT3 coverage were collinear. All-cause child mortality, used in other disease burden models as an indicator of socioeconomic conditions,⁵³ was excluded because it ‘contains’ the malaria mortality rate and is, therefore, not very informative. In other words, a model with all-cause mortality models the malaria mortality rate with a ‘noisy’ version of itself. Additionally, in our dataset, all-cause child mortality was not significantly associated with malaria mortality.

Significant (P -value < 0.05) covariates in the univariate analysis were entered into multivariate models; selected interactions were tested.

For middle Africa populations in rural areas with low-intensity transmission, the five Group A studies from this population^{18,19,54–57} were analysed. The malaria mortality rate was estimated by a Poisson regression model (using the GEE approach described above) that only contained an intercept, which essentially pooled the five studies. This method was used to ensure the 95% confidence interval (95% CI) accounted for over-dispersion and correlation of the rates.

To estimate urban rates for populations exposed to high-intensity or low-intensity transmission, we first considered using studies of urban populations; however, too few studies were available. As an alternative, we multiplied the rural malaria mortality rate for a population in a particular country by an estimate of the urban–rural malaria mortality rate ratio (i.e. urban malaria mortality rate/rural malaria mortality rate) for that country. We estimated country-specific urban–rural malaria mortality rate ratios with the urban–rural s_{q_0} ratio ($UR_{s_{q_0}R}$) (i.e. the country's s_{q_0} for urban populations/the country's s_{q_0} for rural populations, where s_{q_0} is the probability a live-born child dies before the age of 5 years). This method assumes the urban–rural mortality rate ratio is similar for malaria deaths and all non-malaria deaths. Although a rough assumption, we reasoned that if a main justification for adjusting for urban residence was that access to life-saving medical care was better in urban areas, such a benefit might exist for all major causes of child deaths. $UR_{s_{q_0}R}$ values were estimated with data from DHSs and Multiple Indicator Cluster Surveys (E. Loaiza, personal communication, UNICEF, May 19, 2004). (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf)

For southern Africa, we assumed no malaria deaths for populations exposed to low-intensity transmission.⁸ For populations exposed to high-intensity transmission, we analysed data from 16 government disease surveillance reports from southern Africa, and one prospective, community-based study from South Africa of children 0–4 years that used verbal autopsies⁵⁸ (Table 2). As with studies from low-intensity transmission areas, the malaria mortality rate was estimated by an intercept-only Poisson regression model using the GEE approach. The use of surveillance reports was justified because the quality of surveillance data for malaria was generally good in southern Africa in the 1990s.⁸ The use of all-age malaria mortality rates was justified because these populations have little acquired immunity against malaria, and malaria mortality rates are thought to be similar for all age groups. In fact, the malaria mortality rate of the one prospective study⁵⁸ of children (0.096 deaths per 1000 per year) was similar to the unweighted mean of the 16 estimates from the surveillance reports (0.155 deaths per 1000 per year).

Estimating precision

To estimate the precision of the number of malaria deaths, we derived a 95% CI formula using the delta method,⁵⁹ which estimates the variance of a function. We used the term 'precision estimate' instead of '95% CI' to remind readers that the interpretation of our precision estimate as a 95% CI rests on the assumption that the data were from a probability sample. Clearly, the data were not from a probability sample;

but they are the best data we could find after an intensive search, and they are at least representative of some groups of children in malarious parts of Africa. Sources of uncertainty included were the precision of the malaria mortality rates in rural areas with high-intensity and low-intensity transmission (from the two Poisson models) and the urban adjustment factor, $UR_{s_{q_0}R}$ (from DHSs). (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf) Uncertainty in population size and urban residence was not included because they were based on census data and precision estimates were not available. Uncertainty resulting from the non-representativeness of study sites and use of verbal autopsies was not included because the major type of uncertainty they could introduce is bias, not random error; and the delta method is designed only to combine multiple sources of random error. As the magnitude and direction of these potential biases were difficult to specify, we thought that attempts to make adjustments for them might introduce additional biases. Therefore, as mentioned above for verbal autopsies, no adjustments were made.

Sensitivity analyses

To examine the robustness of our results, we performed seven sensitivity analyses (brief descriptions in Table 4). (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf)

Results

Literature review

We identified 31 studies (20 in Group A and 11 in Group B; 16 in West Africa and 15 in East Africa) from 14 countries in middle Africa (Table 1) and 17 reports from four countries in southern Africa (Table 2). Essentially no studies were identified for central Africa, and nearly all were from rural areas. Altogether, Group A and B studies from middle Africa included 4039 malaria deaths during 708 267 person-years of follow-up.

Populations at risk and malaria mortality rates

In 2000, among 111 million children in sub-Saharan Africa, 100 million lived in areas where malaria transmission occurred (Table 3). About half (48 million) of these 100 million children lived in areas with the highest risk of dying from malaria—rural areas in middle Africa with high-intensity transmission.

In the analysis to estimate a malaria mortality rate for rural populations in middle Africa with high-intensity transmission, the only significant univariate associations were several dichotomous variables for study year. Although results for these variables were similar, the one with the best model fit coded study year as 1980–89 vs 1990 and later (rate of the 1990s+ period was 1.529 times the rate in the 1980s; 95% CI 1.165–2.007) (Figure 3). Thus, the final prediction model included only study year (1980s vs 1990s+), and the rate for rural areas in middle Africa with high-intensity transmission was predicted to be constant from 1990–2001 for all countries: 11.36 deaths per 1000 children per year (95% CI 9.80–12.92) (Figure 3 and

Table 3 Final results of the 'best' model to estimate direct malaria mortality among children <5 years old in sub-Saharan Africa for the year 2000: populations at risk, malaria mortality rates, and malaria death counts (Model A)

Description of sub-populations	Estimated population	Estimated malaria mortality rate (deaths per 1000 per year) (95% CI)	Estimated no. of malaria deaths ^a (precision estimate ^b)
Middle Africa, rural areas, high-intensity malaria transmission	47 869 554	11.36 (9.80–12.92) ^c	543 883 (469 111–618 656)
Middle Africa, urban areas, high-intensity malaria transmission	25 495 836	Varies by country; rate = (above rural rate of 11.36) × (urban s_{q_0} /rural s_{q_0}); average rate = 8.26	210 603 (174 734–246 472)
Middle Africa, rural areas, low-intensity malaria transmission	16 586 307	2.31 (2.11–2.51)	38 281 (34 985–41 578)
Middle Africa, urban areas, low-intensity malaria transmission	5 833 184	Varies by country; rate = (above rural rate of 2.31) × (urban s_{q_0} /rural s_{q_0}); average rate = 1.80	10 521 (9458–11 584)
Southern Africa, high-intensity malaria transmission	2 025 102	0.163 (0.113–0.214)	331 (229–433)
Southern Africa, low-intensity malaria transmission	2 624 145	0	0
Total at risk for malaria	100 434 128	Varies by country; average rate = 8.00	803 620 (705 821–901 418)
Total (including populations not at risk for malaria)	111 253 237	Varies by country; average rate = 7.22	803 620 (705 821–901 418)

CI = Confidence interval; s_{q_0} = probability a live-born child will die before his or her fifth birthday.
^a Number of deaths may not exactly equal the product of a malaria mortality rate and its corresponding population at risk because of rounding.
^b See the 'Estimating precision' sub-section of the Methods for an explanation.
^c Regression model: $\text{Log}_e(\text{malaria mortality rate}) = \beta_0 + (\beta_1 \times \text{YEAR2})$, where YEAR2 = 0 for 1980s and 1 for 1990 and later, $\beta_0 = -4.9019$ (standard error = 0.1229), $\beta_1 = 0.4244$ (standard error = 0.1388; $P = 0.0022$).

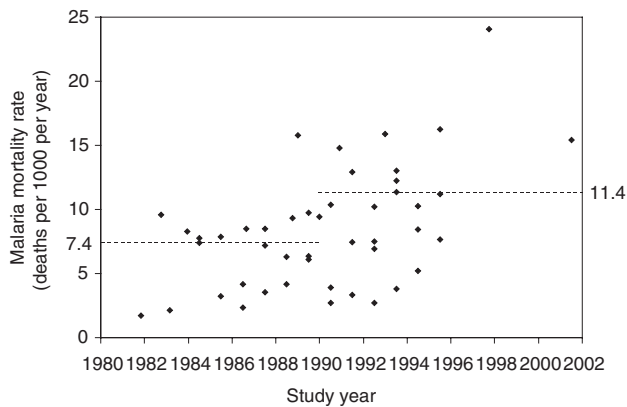


Figure 3 Distribution of malaria mortality rates as a function of study year (46 rates from 15 Group A studies; all studies of rural populations in middle Africa exposed to high-intensity malaria transmission) The dashed horizontal lines indicate the predicted malaria mortality rate from the final Poisson regression model for rural populations in middle Africa exposed to high-intensity malaria transmission: the predicted rate is constant over study years 1980–89 (7.43 per 1000 per year) and constant over study years 1990–2001 (11.36 per 1000 per year)

Table 3, first row). For urban populations in middle Africa with high-intensity transmission, the rate was different for each country but generally about three-quarters of the rural rate (Table 3, second row) (median $UR_{s_{q_0}R} = 0.72$, range: 0.54–0.94).

The estimated malaria mortality rate for rural populations in middle Africa with low-intensity transmission was 2.31 deaths

per 1000 per year (95% CI 2.11–2.51) (Table 3, third row). As above, the corresponding urban rate was about three-quarters of the rural rate (Table 3, fourth row). For southern Africa, we estimated a rate of 0.163 deaths per 1000 per year (95% CI 0.113–0.214) for areas with high-intensity transmission and assumed a rate of zero for areas with low-intensity transmission (Table 3, rows 5 and 6).

Africa-wide mortality estimates

By summing deaths for the six sub-populations in Table 3, we estimated that 803 620 (precision estimate: 705 821–901 418) child malaria deaths occurred in 2000. Nearly all (754 486/803 620, or 93.9%) malaria deaths occurred in areas with high-intensity transmission in middle Africa. Two-thirds (543 883/803 620, or 67.7%) of malaria deaths occurred in rural areas with high-intensity transmission in middle Africa, and one-quarter (210 603/803 620, or 26.2%) occurred in urban areas with high-intensity transmission in middle Africa. Only 6.1% (48 802/803 620) occurred in areas with low-intensity transmission in middle Africa, and 0.04% (331/803 620) occurred in southern Africa. For all of sub-Saharan Africa, including areas without malaria transmission, 18.0% (803 620/4 462 437; precision estimate: 15.8–20.2%) of all deaths among children <5 years old were directly attributable to malaria (Table 4, first row).

Sensitivity analyses

The first five sensitivity analyses for middle Africa (Models B–E, Table 4) produced results that were remarkably similar to the 'best' model (Model A, Table 4). As expected, extreme

Table 4 Summary of sensitivity analyses of the estimates of direct malaria mortality among children <5 years old in sub-Saharan Africa for the year 2000

Model description	Malaria deaths (precision estimate ^a)	Proportion of deaths attributable to malaria ^b (precision estimate ^a)
'Best' model		
Model A: Model for the malaria mortality rate in rural areas with high-intensity transmission included only study year ^c ; analysis only included data from Group A studies (see Methods)	803 620 (705 821–901 418)	18.0% (15.8–20.2%)
Other models		
Model B: Same as model A, except estimates are based on a dataset that includes a combination of Group A studies and Group B studies	774 572 (688 079–861 065)	17.4% (15.4–19.3%)
Model C: Same as Model A, except the urban malaria mortality rate for all malarious parts of Middle Africa is estimated by the rate from the one study in Dar es Salaam, Tanzania ^{18,19}	765 618 (688 971–842 266)	17.2% (15.4–18.9%)
Model D: Same as Model A, except 50% of the urban population of Middle Africa is re-classified as rural population to allow for possible overestimation of urban populations	844 628 (740 865–948 391)	18.9% (16.6–21.3%)
Model E: Same as Model A, except epidemic deaths are added to low-intensity transmission areas ^d	818 632 (720 831–916 434)	18.3% (16.2–20.5%)
Model F: Same as Model A, except the malaria mortality rate = malaria deaths/person-time (i.e. assume deaths with no known cause were <i>never</i> malaria deaths)	687 609 (546 369–828 849)	15.4% (12.2–18.6%)
Model G: Same as Model A, except the malaria mortality rate = (malaria deaths + deaths with no known cause)/person-time (i.e. assume deaths with no known cause were <i>always</i> malaria deaths)	1 028 000 (858 236–1 197 764)	23.0% (19.2–26.8%)
Model H: Estimates based on the proportion of deaths attributable to malaria (instead of the rate) ^d	1 094 444 (892 516–1 297 165)	24.5% (20.0–29.1%)

^a See the 'Estimating precision' sub-section of the Methods for an explanation.

^b Total number of deaths (all causes combined) for children <5 years old from 48 countries in sub-Saharan Africa was estimated as 4 462 437.¹¹⁷

^c Dichotomous variable for the mid-point of when data for a malaria mortality estimate were collected: 1980–89 vs 1990 and later.

^d For details, see the Methods section of the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf

assumptions led to estimates that were either considerably lower (Model F) or greater (Model G) than the 'best' estimate.

The last sensitivity analysis for middle Africa (Model H, Table 4), based on the PDAM (conceptually, the malaria mortality rate/all-cause mortality rate), produced estimates that were considerably (36%) higher than the 'best' estimate. Model H probably overestimated malaria deaths because the PDAM was probably overestimated. The PDAM was probably overestimated because: (i) studies in the Model H analysis had all-cause mortality rates (the PDAM denominator) that were much (28.2%) lower than rates in the general population;²⁶ (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf) and (ii) as two-thirds (10/15) of the studies had a malaria focus, we suspected that the malaria mortality rates (the PDAM numerator) from these studies probably did not greatly underestimate the rate in the general population (e.g. malaria-focused studies might have been more likely to be conducted in areas with high malaria mortality, or to classify deaths as malaria deaths).

Discussion

Our result of 803 620 (precision estimate: 705 821–901 418) child malaria deaths in 2000 is generally consistent with three recent estimates of the direct burden of malaria mortality among children in sub-Saharan Africa for the year 2000, although the studies used different methods and data. Snow *et al.*¹⁰ estimated 742 318 malaria deaths (interquartile range: 541 491–1 069 153); Hay *et al.*,¹¹ who used the method by Snow *et al.* adjusted for urbanization, estimated 679 658 malaria deaths (interquartile range: 478 118–944 024); and Morris *et al.*⁶⁰ estimated a PDAM of 23.7% (95% CI 17.0–37.0%), which corresponds to ~1 058 000 malaria deaths (95% CI 759 000–1 651 000). Remarkably, when our malaria mortality rates were applied to the populations at risk estimated by Hay *et al.*,¹¹ the result (802 373 deaths; precision estimate: 701 059–903 687) was nearly identical to our estimates.

Our estimates have several important limitations. First, data from research sites are clearly not a probability sample of African children. If research sites were chosen because malaria was especially common, results (when generalized to the

entire African population) might overestimate the true burden. In contrast, burden might be underestimated if study populations had above-average socioeconomic status because they were located near a city or main roads or if the presence of the research project improved the population's health.

A second limitation is the use of verbal autopsies. Although non-specific and insensitive, verbal autopsies do not introduce bias if false-positives (e.g. bacterial sepsis death incorrectly classified as malaria) equal false-negatives (e.g. death from malaria-related anaemia incorrectly classified as pneumonia). Unfortunately, verbal autopsy validation studies do not reveal a clear trend in the way verbal autopsies misclassify deaths. Depending on the study and diagnostic algorithm (some studies examined several algorithms), false-negatives can outnumber false-positives or vice versa.^{61–65}

Additionally, the finding that malaria mortality rates may decrease at high parasite prevalence levels^{66–68} (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf) suggests that verbal autopsies may lose sensitivity in settings with high-intensity transmission (i.e. more false-negatives occur because more malaria deaths result from severe anaemia, which verbal autopsies may misclassify as pneumonia deaths). However, by defining transmission intensity with broad parasite prevalence categories, this potential problem probably was not an important source of bias for our estimates.

A third limitation is that our methods require numerous assumptions, some with unknown validity. Fourth, some data

had unknown validity and precision, e.g. population estimates, MARA results, parasite prevalence estimates, and covariate data used in the models. Although our assumptions and data almost certainly introduced biases, it is difficult to estimate their directions and magnitudes.

To address the preceding two limitations, at least partially, we conducted a variety of sensitivity analyses. We found the estimates were relatively insensitive to varying assumptions about the urban malaria mortality rate, urban population size, and deaths from epidemic malaria. In addition, the estimates changed little when we included studies with minor deviations from our ideal inclusion criteria. The estimates were, however, sensitive to extreme assumptions about deaths with unknown causes. The analysis based on the PDAM gave results that were much higher than our best estimates, but differences may be explained by the fact that all-cause mortality rates in study sites are not representative of the general population.

Finally, we caution readers that our precision estimates can only be interpreted as 95% CIs if the data are assumed to be a probability sample. Also, the precision estimates are probably too narrow, because they do not account for uncertainty in population size and urban residence.

For these reasons, our estimates should be considered an approximation of the true burden of direct malaria mortality. Information and data that might improve future estimates are listed in Box 1. Some issues are already being addressed. For example, the Global Rural Urban Mapping Programme, which distinguishes urban and rural areas with satellite-measured

Box 1 Information that might improve future estimates of malaria mortality

- Better understanding of the relationship between verbal autopsy results and true malaria deaths (e.g. a verbal autopsy validation study conducted in a community setting)
- Better understanding of how malaria mortality rates from research sites differ from rates in the general population
- Community-based, longitudinal data on the malaria mortality rate in central Africa
- Better definitions of and data on:
 - Malaria transmission intensity (and a better understanding of how transmission intensity affects malaria mortality)
 - Urban populations (and a better understanding of how urban residence, including different types of urban residence, affects malaria mortality)
 - Malaria's indirect impact on mortality
 - The impact of malaria epidemics on malaria mortality (e.g. community-based, longitudinal data on malaria mortality during epidemics)
- Better estimates of the size of populations at risk for malaria, especially sub-populations that potentially have different levels of mortality risk, such as:
 - Populations living in areas with higher vs lower levels of malaria transmission intensity
 - Urban and rural populations
 - Populations exposed to malaria interventions (e.g. insecticide-treated bednets)

night-time light levels, is being used to provide more precise estimates of urban and rural populations.¹¹

How should our results be used? First, it is probably safe to say that in 2000, a rough approximation of the burden of direct malaria mortality among children <5 years old in sub-Saharan Africa was between 700 000 and 900 000 deaths. Second, the validity of estimates for specific countries is even more questionable than for continental estimates. Third, our results cannot be reliably extrapolated to years outside those in the dataset (e.g. if the child population in 2005 is 5% higher than in 2000, increasing our estimates by 5% may not provide a valid estimate for 2005). Fourth, our results should not be used to monitor trends in malaria mortality over time by comparing our estimates with other estimates based on different methods and data. For example, it would be inappropriate to conclude that malaria mortality had increased because our estimate for the year 2000 (803 620 deaths) is higher than the estimate by Snow *et al.*⁸ for 1995 (765 775 deaths).

Fifth, our results should not be used to estimate how many deaths would be prevented if malaria transmission were reduced or eliminated. Such estimates would probably be a gross underestimate because they do not include the large burden of indirect malaria mortality. Studies in Kenya, Nigeria, and Tanzania from the 1950s and 1970s found that after malaria transmission was drastically reduced with insecticide spraying, which would have had little or no effect on other causes of child mortality, all-cause mortality rates for infants and children 1–4 years old decreased by as much as 40–50%.^{69–71} Similarly, when malaria chemoprophylaxis and insecticide-treated nets were used to prevent malaria in The Gambia, the all-cause child mortality rate decreased by 42%.⁷²

Finally, caution should be exercised in using our results to evaluate malaria prevention and control efforts, such as those of the Roll Back Malaria partnership. Such an evaluation would presumably involve repeating our estimation method using similar data after interventions were implemented with reasonably high coverage. However, if the interpretation of verbal autopsies remains unchanged, even if malaria were eradicated, verbal autopsy's high false-positive rate will show erroneously that malaria is present. In 2000, when coverage of most interventions was very low, false-positives were 'helpful' because they partially counterbalanced false-negatives; but as coverage increases and the malaria burden is reduced and false-negatives disappear, one is left with 'unpreventable' malaria-like deaths (false-positives due to bacterial infections, etc., that could not be prevented with malaria-specific interventions). Such results would underestimate the impact of malaria prevention and control efforts.

Our results suggest that malaria mortality rates have increased between the 1980s and 1990s, although we were unable to find a difference between West and East Africa [results not shown (For details, see the complete report, which is available on the Internet at: http://rbm.who.int/partnership/wg/wg_monitoring/docs/CHERG_final_report.pdf)]. It is important to remember, however, that 'study year' may also

represent study place. In other words, increasing mortality rates may simply reflect a trend in which areas with higher malaria mortality rates were more often selected as study sites in the 1990s relative to the 1980s. However, some studies lasting many years found increasing trends,⁵⁵ with increasing resistance to the commonly-used antimalarial, chloroquine, often cited as the cause.^{35,55,68,73}

In conclusion, we do not know how many direct malaria deaths occurred among children in sub-Saharan Africa in 2000. However, our study has several strengths: we conducted an intensive literature search, selected studies with rigorous inclusion criteria, introduced stringent quality controls on the data abstraction process, incorporated a novel approach to account for urbanization, utilized a statistically-based method for estimating uncertainty, and made extensive use of sensitivity analyses to evaluate assumptions. Although the results are clearly imperfect, we hope that they are less imperfect, and methods more transparent, than earlier efforts.

One important byproduct of this work is a better understanding of the inadequacy of current data as a basis for developing estimates and measuring the impact of malaria interventions. Relatively few data of adequate quality could be identified, and no data were found for vast geographical areas with some of the world's poorest populations.⁷⁴ Sound epidemiological estimates are an essential part of public health decision-making. More and better studies are needed to support prevention and control programmes addressing malaria, which is directly responsible for ~18% of all child deaths in sub-Saharan Africa.

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KEY MESSAGES

- The burden of malaria mortality among children in countries without adequate vital registration systems can be estimated by extrapolating mortality rates observed in small-scale community studies, stratified by level of malaria transmission intensity, to continent-wide populations at risk using maps of malaria risk and population distribution.
- In sub-Saharan Africa, where most malaria deaths occur, a rough approximation of the burden of direct malaria mortality for the year 2000 among children <5 years old is between 700 000 and 900 000 deaths.
- Current models of malaria mortality estimated direct malaria deaths and do not account for malaria's probably large indirect burden (where malaria is one of several diseases leading to death, but the death is attributed to another primary cause).
- The small number of community studies, their inherent problems in identifying malaria deaths, and other knowledge gaps limit the validity of epidemiological models and estimates; more community-based mortality studies with greater standardization, and updates and refinements of malaria risk maps are needed.

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Commentary: Malaria death rates remain highly pertinent

Tom Smith

Scientific papers and media coverage of malaria alike expose us so frequently to figures for the number of child deaths from *Plasmodium falciparum* in Africa that we become insensitive to the magnitude of the carnage. The numbers are so large that they overwhelm the imagination.

Until recently it was hard to work out where these estimates came from, since there was rarely any explanation of the primary sources or the way in which the data were analysed. However several papers in recent years^{1–3} have provided good documentation of their methods, which have steadily become more convincing as more data and appropriate methodology become available. The paper by Rowe *et al.*⁴ in this issue of the

International Journal of Epidemiology presents the best substantiated set of estimates to date in this series, using the latest population estimates for denominators and stratified analyses of an extensive database of verbal autopsy (VA)-based rates. Importantly, they include analyses that show that the estimated number of just over 800 000 deaths in children <5 years of age, for the year 2000, is not very sensitive to their main assumptions.

This paper is not the last word on the subject. The assembled estimates of malaria-specific mortality rates from different sites in Africa vary enormously. We do not know the reasons for this variation. Most of it does not relate to transmission intensity. If we knew the main factors that lead to the diversity in quoted malaria mortality rates in endemic areas it would help to focus control efforts on what works. It would also