Estimates of the burden of malaria morbidity in Africa in children under the age of 5 years

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Summary

OBJECTIVE To estimate the direct burden of malaria among children younger than 5 years in sub-Saharan Africa (SSA) for the year 2000, as part of a wider initiative on burden estimates.

METHODS A systematic literature review was undertaken in June 2003. Severe malaria outcomes (cerebral malaria, severe malarial anaemia and respiratory distress) and non-severe malaria data were abstracted separately, together with information on the characteristics of each study and its population. Population characteristics were also collated at a national level. A meta-regression model was used to predict the incidence of malaria fevers at a national level. For severe outcomes, results were presented as median rates as data were too sparse for modelling.

RESULTS For the year 2000, an estimated 545 000 (uncertainty interval: 105 000–1 750 000) children under the age of 5 in SSA experienced an episode of severe malaria for which they were admitted to hospital. A total of 24 000 (interquartile range: 12 000–37 000) suffered from persistent neurological deficits as a result of cerebral malaria. The number of malaria fevers associated with high parasite density in under-5s in SSA in 2000 was estimated as 115 750 000 (uncertainty interval: 91 243 000–257 957 000).

CONCLUSION Our study predicts a lower burden than previous estimates of under-5 malaria morbidity in SSA. As there is a lack of suitable data to enable comprehensive estimates of annual malaria incidence, we describe the information needed to improve the validity of future estimates.

Keywords child health, malaria, morbidity, epidemiology, sub-Saharan Africa

Introduction

Many people are surprised at the imprecision of malaria burden estimates currently in use; estimates of malaria fever incidence range between 300 and 500 million clinical cases per year for all ages globally (WHO 1999b, 2000). This uncertainty arises mainly because of the non-specific symptoms of malaria (fever with or without various other signs and symptoms), and the incomplete coverage of health information systems in much of sub-Saharan Africa (SSA) where the greatest burden lies.

An average of 19 million cases per annum were reported by Ministries of Health in Africa to WHO between 1982 and 1997 (WHO 1999a). These numbers are recognized to be underestimates of the true burden, and although WHO has undertaken a major effort to update its figures on malaria cases reported by each country, these are still subject to problems of incomplete reporting (WHO). The most recent attempt to provide clinical malaria estimates was carried out by Snow et al. (2005), who estimated 315 (range 300–660) million episodes of clinical Plasmodium falciparum malaria in all age groups worldwide for the year 2002. A new exercise to estimate the burden of malaria, among other conditions, is being embarked upon at present (http://www.globalburden.org), and it is important to review the methodology of previous attempts to ensure that each iteration of estimates can improve in precision.

The majority of malaria deaths occur in children under the age of 5 years of age (WHO 2005) A wide range of estimates of the incidence of malaria fevers in children under-5 in Africa have been presented in recent years, varying between 1.0 (Snow et al. 1999), 1.2 (Murray & Lopez 1996) and 1.4 (Snow et al. 2003) to 1.6–5.4 (Murphy & Breman 2001) episodes per child per year. This disparity of estimates is mainly due to differences in the study inclusion criteria, clinical malaria definitions, differences in transmission intensity and underlying assumptions about the proportion of fevers due to malaria. The first attempt to report clinical malaria figures was published by Murray and Lopez (1996) but this report lacked documentation of methods and data. Snow et al. (1999) based
their estimates on data from cohort studies, and originally categorized populations as being exposed to epidemic or stable malaria transmission; they later updated their estimates (Snow et al. 2003) using a modified risk criteria with four classes of malaria transmission intensity (for further details see Annexe 1 of Carneiro et al. 2005). Murphy and Breman (2001) based their estimates on cross-sectional fever surveys assuming that malaria was associated with 30–60% of all fevers, but did not take into account differences in transmission intensity.

In 2001, the Child Health Epidemiology Reference Group (CHERG) was established by WHO as an independent group of technical experts whose task was to review the available child health information and produce global and regional estimates of cause-specific mortality and morbidity among children <5 years old for the year 2000, using stringent and objective inclusion criteria and reproducible methodology (http://www.who.int/child_adolescent_health/data/cherg/en/). These estimates have since been used to assess the proportional burden of malaria relative to other childhood diseases, whose estimation suffers from similar constraints (Rudan et al. 2005).

This paper describes how estimates were obtained of the direct burden of malaria morbidity in under-5s in SSA in 2000, and all results presented here refer to this specific population unless otherwise stated. Direct burden includes non-severe malaria fevers from community-based studies, and severe malaria syndromes presenting to health facilities: cerebral malaria, severe malarial anaemia, respiratory distress and persistent neurological sequelae resulting from cerebral malaria, it does not include malaria-attributable anaemia or the effects of comorbidity.

Methods

Literature review

A systematic literature review was undertaken in June 2003 using PubMed and CAB Abstracts (BIDS) electronic databases to search for studies published since 1980. The search terms used were: ‘malaria (with major focus on epidemiology, complications, mortality, prevention and control and transmission) OR Plasmodium vivax’ AND ‘morbidity (incidence or prevalence)’ OR ‘fever’ OR ‘severe malaria’ OR ‘cerebral malaria’ OR ‘neurological’ OR ‘an(a)emia’. In addition, searches of the WHO library (WHOLIS) and of the grey literature database (SIGLE) were undertaken. Abstracts were then screened and the following inclusion criteria were applied: (i) study undertaken in 1980 or later; (ii) studies from SSA only; (iii) relevant data on children aged 0–59 months; (iv) study duration of a multiple of 12 months (to avoid confounding by seasonality); (v) longitudinal- and community-based studies for mild-malaria estimates, and community or health facility-based studies for severe outcomes and (vi) results that permitted a malaria morbidity rate to be estimated. For intervention trials, only results from pre-intervention or control children were included in the analysis. For severe malaria syndromes the author’s definitions were used.

Data on each malaria morbidity outcome together with information on the characteristics of each study and its population were doubled-abstracted and an agreement form used to verify the abstraction, and data were then doubled-entered and validated in EpiData (http://www.who.int/child_adolescent_health/documents/cherg_abstraction/en/index.html).

Estimating populations at risk for malaria

To estimate the population at risk of malaria, Africa was divided into northern Africa (assumed to have no malaria episodes because the climate is generally unsuitable for transmitting P. falciparum malaria), central Africa and southern Africa as done by Snow et al. (1999, 2003). For southern Africa, very low malaria morbidity rates were assumed because of a less suitable climate and intense control efforts of the mosquito vector (Mabaso et al. 2004). Northern Africa was defined as Algeria, Egypt, Libya, Morocco and Tunisia. Southern Africa was defined as Botswana, Lesotho, Namibia, South Africa, Swaziland and Zimbabwe. Central Africa was defined as any African country in neither northern nor southern Africa. Four countries with relatively small populations and low or no malaria risk (Cape Verde, Comoros, Mauritius and Seychelles) were excluded as there was no estimate for the population at risk.

Data from the Mapping Malaria Risk in Africa (MARA) Collaboration (1998) project were used to estimate populations at risk of malaria in the year 2000 for central and southern Africa. These estimates are based on models that predict the climate suitability for malaria transmission across Africa (Snow et al. 1999). Study populations were categorized as being exposed to one of three levels of malaria transmission intensity: zero (populations with MARA index = 0), low intensity (MARA index >0 and <0.75) or high intensity (MARA index ≥0.75) using a relationship proposed by Snow et al. (2003) where a MARA index <0.75 corresponded to a parasite prevalence <25%, and a MARA index ≥0.75 to a parasite prevalence ≥25%. Although this relationship has limitations (Omumbo et al. 2004), it is currently the only available method for estimating populations at risk for different
transmission intensities across Africa. The same approach was used for developing malaria mortality estimates (Rowe et al. 2006).

Epidemic malaria risk was not considered here as it was assumed that the true incidence of malaria fevers due to epidemics will be relatively small in children under 5 years of age in any given year.

The incidence of malaria in urban areas is lower than that in rural settings, although there are problems in defining the magnitude of the difference, and the respective populations at risk (Hay et al. 2000, 2005; Robert et al. 2003; Keiser et al. 2004). Hay et al. (2005) make an assumption that urban residence reduces malaria transmission intensity from marginal [climate suitability index (CSI) = 0–0.25] to zero risk (CSI = 0), or from stable endemic (CSI ≥ 0.75) to acute seasonal transmission (CSI = 0.25–0.75), but not from seasonal transmission to marginal risk. However, there are limited data on the incidence of malaria fevers by those categories of malaria transmission intensity, whereas data on the relative proportion of malaria in urban and rural populations were available for one study from high and low transmission intensity. Central African populations were therefore stratified according to urban or rural residence based on the United Nations’ estimates from census data of the proportion of residents living in urban areas for the year 2000; no uncertainty estimates were given (United Nations 2002). A different effect of urbanization in high and low transmission intensity settings was applied, recognizing that urban residence and malaria transmission intensity are likely to independently affect the risk of and burden of malaria.

Data analysis

The data were transferred into Stata version 8 (StataCorp, College Station, TX, USA) for analyses. Each malaria morbidity outcome was analysed separately, using the number of cases as the numerator and the person-time at risk as the denominator. For severe outcomes, due to the lack of information on catchment populations (denominators) from health facility studies, insufficient data were available to undertake any complex statistical analysis, and therefore results have been presented as median rates.

For southern Africa, we assumed that there was no malaria morbidity for populations exposed to low-intensity transmission. For populations exposed to higher intensity transmission, we were able to use routinely collected data from the countries (Snow et al. 2003). These data were modelled using regression analysis to adequately weight them according to the person-years at risk of observation. The data were reported for all ages combined, and although there is evidence of variation in age-specific incidence in some settings from one study in South Africa (Kleinschmidt & Sharp 2001), for southern African countries we assumed a constant incidence across all ages in order to derive an estimated number of cases in children under 5 years. Results presented here were rounded to the nearest thousand.

Adjustments for study duration and age groups

In order to include more studies into the non-severe malaria analysis, the following study duration and age adjustments were made: (i) studies that covered a full malaria transmission season but had a study duration of <12 months were included after assuming no episodes occurred outside the study period (person-time was adjusted to reflect the time at risk if the studies had been carried out for 12 months), and (ii) studies that reported malaria incidence only for restricted age-ranges were adjusted to the full 0–4 age-range based on an analysis of the age-pattern of six studies (T. Smith, personal communication; Velema et al. 1991; Delacollette & Barutwanayo 1993; Bloland et al. 1999; Saute et al. 2003; Schellenberg et al. 2003) in under-5s that reported fever incidence in 1-year age groups. This analysis showed that the age-pattern varied according to transmission intensity, as previously described by Trape and Rogier (1996). Therefore studies were adjusted according to the defined transmission intensity for the study area by adding the number of cases and person-time at risk for the additional age-groups to studies with incomplete age-ranges to obtain the full 0–4 malaria rate (Carneiro et al. 2005).

Adjustments for parasite density

As many children in endemic settings are asymptomatic for malaria, resulting in many slide positive fevers not truly due to malaria (Schellenberg 1994; Smith et al. 1994; McGuinness et al. 1998; Rogier et al. 2001, 2005), a more stringent definition of clinical malaria was assessed by using a cut-off parasite density, above which a malaria fever was more likely to be due to the malaria infection. Studies that reported malaria cases of any parasite density were adjusted to estimate the incidence of malaria cases with a raised parasite density by multiplying the total number of cases by 0.65 [incidence rate ratio (IRR) obtained from a Poisson regression model of 10 studies] (Velema et al. 1991; Alonso et al. 1993; D’Alessandro et al. 1995; Lemnge et al. 1997; McGuinness et al. 1998; Acosta et al. 1999; Schellenberg et al. 2001; Baird et al. 2002; Massaga et al. 2003; T. Smith, personal communication) that reported data both on slide
positive malaria fevers and on fevers associated with a parasite density cut-off (see Carneiro et al. 2005 for further details). Results shown therefore correspond to malaria fevers with a raised parasite density, as we consider this to better represent the fever cases truly attributable to malaria.

A Poisson regression model was used to model the incidence rate of malaria fevers for central Africa, using random effects to adjust both the point estimate and the SE to account for potential correlation between studies from the same study site. Study design characteristics that were thought a priori to be likely to affect the outcome (e.g. case definition, method of case ascertainment) and study population characteristics were tested for significance. All associations significant at the P < 0.1 level in the univariate analyses were considered for entry in multivariate models. The final model was used to predict incidence rates for each country, using a separate dataset with country-level population characteristics and denominator populations from the year 2000.

For estimating uncertainty a jackknife approach was undertaken (Efron & Tibshirani 1993). Subsequently, Monte Carlo simulation (10 000 simulations) was used to randomly perturb country-level estimates based on these SEs, and the 2.5th and 97.5th centiles were taken from these simulations to provide an indication of the level of uncertainty in our estimates (Lawn et al. 2006). Uncertainty intervals were obtained on the log-scale and back-transformed to give uncertainty intervals for the predicted number of cases and for the incidence rates. To examine the robustness of our results, we performed six sensitivity analyses (see Carneiro et al. 2005 for further details).

Results

In 2000, around 100 million (95 million in central Africa and five in southern African countries) lived in areas where malaria transmission occurred. Of these, about half (48 million) lived in rural areas in central Africa with high transmission intensity (Table 3).

Severe malaria

A considerable number of studies were found to report data on cerebral malaria (n = 102), severe malarial anaemia (n = 64), respiratory distress (n = 19) or neurological sequelae (n = 47). However, information of catchment populations was missing for many studies, so incidence rates were obtained from only a small proportion of the total (Table 1).

Table 1 summarizes the results for each severe malaria syndrome showing the median rates for paediatric admissions as well as for under-5s in central Africa in the year 2000, and the resulting number of episodes based on an estimated under-5 population at risk of 95 615 819. The extent to which symptoms overlapped were estimated using the only two previously published studies (both from Kilifi, Kenya) that reported the extent of overlap of all three classically defined severe malaria syndromes (Marsh & Snow 1997; Maitland et al. 2003). These studies report that 23–24% of cerebral malaria occurs together with severe malaria anaemia, and that 84–88% of respiratory distress occurs together with either severe malaria anaemia alone (7–37%) or with cerebral malaria alone (27–59%) or with both (20–21%). Applying the average of these percentages of overlap, we estimated an incidence of 3.6 per 1000 p.a. severe malaria anaemia episodes (alone or with other syndromes), an additional 1.77 per 1000 p.a. cerebral malaria episodes (without severe malaria anaemia but including those with respiratory distress) and an additional 0.32 per 1000 p.a. respiratory distress episodes (without either severe malaria anaemia or cerebral malaria), giving an overall incidence of severe malaria cases reaching hospital of 5.7 per 1000 p.a. (Figure 1). An ‘uncertainty interval’ for this estimate was calculated by multiplying the interquartile range (IQR) of the each rate by the overlap percentages as above.

Overall, we estimate that there were 545 000 (uncertainty interval: 105 000–1 750 000) episodes of severe malaria in hospitalized children under the age of 5 years in the year 2000 in SSA.

Non-severe malaria

Sixty-four studies reported data on malaria fever incidence in children in central Africa, but only 44 used a clinical malaria definition of ‘history of fever or current raised measured temperature, plus a positive slide for malaria’. Of these, only nine covered a study period of 12 months or multiple thereof in under-5s (but not necessarily covering the full age-range). After adjusting for study duration and age, 13 studies were included for analysis (Greenwood et al. 1987, 1989; Mbogo et al. 1993; Alonso et al. 1994; Kitua et al. 1996; Lemnge et al. 1997; McGuinness et al. 1998; Ijumba et al. 2002; Massaga et al. 2003) (11 from rural and 2 from urban areas), representing 3493 episodes of slide confirmed malarial fevers during 5636 person-years of follow-up.

For central African rural settings, the final random-effects regression model included region, mid-year of study and method of case detection as significantly related to the incidence of malaria fevers (see Table 2). This model was applied to the national populations at risk of malaria in high transmission rural settings to predict the number of
### Summary results of severe malaria syndromes for under-5s in central Africa in 2000

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Number of studies</th>
<th>References</th>
<th>Median rate per 1000 p.a. (IQR)</th>
<th>Estimated number of episodes* (uncertainty intervals)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malaria anaemia</td>
<td>64</td>
<td>J. Berkley (personal communication); Brewster and Greenwood (1993); Schellenberg <em>et al.</em> (2004); Seboxa and Snow (1997); Snow <em>et al.</em> (1993, 1994); two in Snow <em>et al.</em> (1997); T.E. Taylor (personal communication); Zucker <em>et al.</em> (1997)</td>
<td>3.7 (1.6–5.4)</td>
<td>354 000 (153 000–516 000)</td>
</tr>
<tr>
<td>Paediatric admissions</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under-5s</td>
<td>5</td>
<td>J. Berkley (personal communication); Schellenberg <em>et al.</em> (2004); Snow <em>et al.</em> (1993, 1994), T.E. Taylor (personal communication)</td>
<td>3.6 (0.4–14.8)</td>
<td>344 000 (38 000–1 415 000)</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>102</td>
<td>Two in Snow <em>et al.</em> (1997); Bondi (1992); Brewster and Greenwood (1993); Waller <em>et al.</em> (1995); T.E. Taylor and J. Berkley (personal communication); Crawley <em>et al.</em> (2000); Seboxa and Snow (1997); Snow <em>et al.</em> (1993, 1994)</td>
<td>2.5 (0.4–4.2)</td>
<td>239 000 (38 000–402 000)</td>
</tr>
<tr>
<td>Paediatric admissions</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under-5s</td>
<td>4</td>
<td>J. Berkley and T.E. Taylor (personal communication); Snow <em>et al.</em> (1993, 1994)</td>
<td>2.3 (0.9–3.8)</td>
<td>220 000 (86 000–363 000)</td>
</tr>
<tr>
<td>Neurological sequelae following cerebral malaria</td>
<td>47</td>
<td>van Hensbroek <em>et al.</em> (1996, 1997); Koko <em>et al.</em> (1997); Crawley <em>et al.</em> (2000); Commey (1980); Neequaye <em>et al.</em> (1991); Gellert <em>et al.</em> (1998); Kwiatkowski <em>et al.</em> (1990); Walker <em>et al.</em> (1992); Muntendam <em>et al.</em> (1996); Brewster <em>et al.</em> (1990); Bondi (1992); Cot <em>et al.</em> (1994); Goka <em>et al.</em> (2001); Schapira <em>et al.</em> (1993); Newton <em>et al.</em> (1994); Grau <em>et al.</em> (1989); Molyneux <em>et al.</em> (1989); Varandas <em>et al.</em> (2001)</td>
<td>0.11 (0.05–0.17)</td>
<td>24 000 (12 000–37 000)</td>
</tr>
<tr>
<td>Paediatric admissions</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under-5s</td>
<td>–</td>
<td></td>
<td>–</td>
<td>24 000 (12 000–37 000)†</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric admissions</td>
<td>4</td>
<td>Berkley <em>et al.</em> (1999); J. Berkley and T.E. Taylor (personal communication); Seboxa and Snow (1997)</td>
<td>2.6 (0.9–3.9)</td>
<td>249 000 (86 000–373 000)</td>
</tr>
<tr>
<td>Under-5s</td>
<td>2</td>
<td>J. Berkley and T.E. Taylor (personal communication)</td>
<td>2.3 (0.4–4.2)</td>
<td>220 000 (38 000–402 000)</td>
</tr>
<tr>
<td>Total severe malaria</td>
<td>–</td>
<td></td>
<td>5.7 (1.1–18.3)</td>
<td>545 000 (105 000–1 750 000)</td>
</tr>
<tr>
<td>accounting for overlaps (uncertainty interval)</td>
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</table>

*Estimated under-5 population at risk for central Africa = 95 615 819.
†As there were no studies reporting on under-5s, estimates were based on 19 studies on children aged under 13 years old.
‡Uncertainty intervals for severe outcomes are based on IQR, for non-severe outcomes see text for more details.
malaria fever cases which occurred in these settings for the year 2000 (see Table 3). Weekly active case detection was considered as the reference category as this is likely to better reflect the true incidence of malaria in the community compared with passive case detection which will tend to underestimate the number of fever cases in SSA (i.e. due to poor access to health facilities, use of other sources of health care such as traditional healers, etc.).

Although there were no high transmission intensity urban studies within our database, we were able to analyse a recently available dataset from the control group of a trial of malaria intermittent presumptive treatment in infants in Navrongo, Ghana (Chandramohan et al. 2005) to estimate the IRR of malaria fevers in children under 24 months in relatively urban compared with rural areas: 0.51 (95% CI: 0.40–0.64; \( P < 0.001 \)). This ratio is consistent with previous information on parasite prevalence among school children aged 5–9 years in Brazzaville with a ratio of 0.50 between urban (38.5%) and rural (76.4%) settings (Trape 1987). For low transmission intensity areas, two studies from Kilifi district (Mbogo et al. 1993) gave a rural-to-urban IRR of 0.40 (95% CI: 0.25–0.65), which is consistent with the estimate for high-intensity studies above. The predicted adjusted incidence rates were therefore reduced by a factor of 0.51 and 0.4 for high and low transmission rural settings, respectively, and then applied to the populations at risk of malaria in high and low transmission, urban settings in central Africa for the year 2000 (see Table 3).

Lower and upper uncertainty bounds for the total number of cases were calculated by summing the lower uncertainty intervals of cases and the upper uncertainty intervals of cases, respectively. The estimated incidence rates and associated uncertainty intervals were derived from the predicted number of cases divided by the population at risk. This gave a total of 115 592 000 (uncertainty interval: 91 195 000–265 270 000) predicted high density malaria fever cases in central Africa for the year 2000 (Table 3). The incidence rate varied between approximately 1–4 episodes per person per year in high transmission rural settings, and 0.2–0.9 episodes per year in low transmission, urban settings.

For southern African populations exposed to high-intensity transmission, the regression analysis of data from routine national surveillance reports predicted a total of 158 000 (95% CI: 48 000–525 000) malaria fever episodes occurring in southern Africa for the year 2000.

From the sensitivity analysis (data not shown), lower estimates were obtained assuming cases were detected through passive case detection. Moreover, when the urban–rural ratios were modified, total malarial fever estimates remained similar, suggesting that large changes in this assumption do not have a major effect on our

![Figure 1 Venn diagram of severe malaria overlaps (SMA, severe malarial anaemia; RD, respiratory distress and CM, cerebral malaria). Proportional Venn diagram obtained from Stirling and Rodgers (2005).](image)

Table 2 Poisson regression of raised density malaria fever incidence in high transmission rural settings

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted IRR (95% CI)</th>
<th>( P )-value</th>
<th>Adjusted IRR (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Africa</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>East Africa</td>
<td>3.81 (1.25–11.68)</td>
<td>0.019</td>
<td>4.06 (2.06–8.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid-year of study</td>
<td></td>
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<tr>
<td>Each year after 1982</td>
<td>1.04 (1.01–1.07)</td>
<td>0.015</td>
<td>1.11 (1.04–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Method of case detection</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Weekly ACD</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Less frequent ACD/PCD</td>
<td>1.21 (1.01–1.44)</td>
<td>0.035</td>
<td>0.63 (0.47–0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Access to safe water</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Every 10% increase above 40%</td>
<td>1.36 (0.99–1.87)</td>
<td>0.058</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
estimates. Finally, higher numbers of cases were estimated when using the definition of ‘fever with any parasite density’ and when the age-ranges and study durations were relaxed by including more studies into the analyses. These findings suggest that increasing the age-range and relaxation of study duration criteria may result in a bias towards studies from seasonal transmission settings that tend to be carried out in the high transmission season, thus overestimating the annual incidence.

**Discussion**

We estimate that 116 million African children under 5 years of age had a malaria episode in 2000, and 545 000 were admitted to hospital with severe malaria. Our severe malarial anaemia estimate of 3.6 per 1000 p.a. is similar to that of Snow et al. (2003) of 4.1 per 1000 p.a. for 0–9 year olds. It is lower than that of 15–60 per 1000 from Murphy and Breman (2001), as they inflated their estimates to account for a large proportion of children who do not reach health facilities, and made assumptions about the proportion of fever cases that are likely to represent malaria.

Our point estimate of 2.3 episodes of cerebral malaria per 1000 p.a. is higher than that of Snow et al. (2003) who estimated an incidence of 1.1 per 1000 (no IQR given) for children aged 0–9 years from seven hospitals with defined catchment populations within 5 km, but our IQR overlaps with their estimate. Our estimate falls within the range of 0.9–3.5 estimated by Murphy and Breman (2001) for 0–4 year olds. However, they included an adjustment for children who would not reach hospital, and any such adjustment of our result would suggest an even higher community incidence of cerebral malaria. Our estimate of neurological risk is consistent with that of 0.1–0.2 per episode of cerebral malaria from Murphy and Breman (2001). Snow et al. (2003) presented estimates for a much wider range of severity of sequelae and considered data after all episodes of severe malaria, not just cerebral malaria – our estimates are therefore not comparable with theirs. The only previous estimate for respiratory distress was 1.4–5.4 per 1000 p.a. from Murphy and Breman (2001), and although the estimates are consistent, ours is the first estimate based on data from two large studies on hospital admissions with respiratory distress; the previous estimate was based on data on the incidence of cerebral malaria and on the relative frequencies of cerebral malaria and respiratory distress (Murphy & Breman 2001).

Overall, we estimated 545 000 (uncertainty interval: 105 000–1 750 000) episodes of severe malaria in hospitalized children under the age of 5 years in the year 2000 in SSA, with 24 000 (IQR: 12 000–37 000) suffering from persistent neurological deficits as the result of a cerebral malaria episode (i.e. 11% risk). This is likely to be an overestimate of the numbers of children admitted to hospital with severe malaria for three reasons: (i) it is based on data from research sites with good quality functioning hospital facilities where hospital attendance tends to be higher compared with a typical hospital in SSA, (ii) these sites are more likely to be in areas with a reasonable burden of severe malaria, and (iii) although we were not able to make estimates for populations exposed to different malaria transmission intensities due to lack of data, areas of low intensity are unlikely to have such a high burden of severe malaria among children under-5s. On the other hand, given that many children with severe malaria in SSA do not reach a hospital, this is clearly an underestimate of

### Table 3

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Estimated under-5 population at risk</th>
<th>Number of studies</th>
<th>Incidence rate per 1000 p.a. (95% CI)</th>
<th>Estimated number of episodes (uncertainty intervals)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Central Africa, high TI</td>
<td></td>
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</tr>
<tr>
<td>Rural</td>
<td>47 859 220</td>
<td>11</td>
<td>1682 (1431–3849)</td>
<td>80 523 000 (68 505 000–184 224 000)</td>
</tr>
<tr>
<td>Urban</td>
<td>25 486 672</td>
<td>1</td>
<td>717 (588–1741)</td>
<td>18 282 000 (14 997 000–44 379 000)</td>
</tr>
<tr>
<td>Central Africa, low TI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>16 495 917</td>
<td>–</td>
<td>892 (414–1924)</td>
<td>14 715 000 (6 822 000–31 740 000)</td>
</tr>
<tr>
<td>Urban</td>
<td>5 774 010</td>
<td>1</td>
<td>359 (151–853)</td>
<td>2 071 000 (871 000–4 927 000)</td>
</tr>
<tr>
<td>Central Africa, total</td>
<td>95 615 819</td>
<td>–</td>
<td>1209 (954–2774)</td>
<td>115 592 000 (91 195 000–265 270 000)</td>
</tr>
<tr>
<td>Southern Africa, high TI</td>
<td>2 025 102</td>
<td>29</td>
<td>78.0 (23.5–259.4)</td>
<td>158 000 (48 000–525 000)</td>
</tr>
<tr>
<td>Southern Africa, low TI</td>
<td>2 624 145</td>
<td>–</td>
<td>–†</td>
<td>–†</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>100 265 066</td>
<td>–</td>
<td>–†</td>
<td>115 750 000 (91 243 000–257 957 000)</td>
</tr>
</tbody>
</table>

*Uncertainty intervals for non-severe outcomes (see text for more details).

†Assumed no malaria morbidity for populations exposed to low transmission intensity in Southern African countries.
the true rate in the community. The magnitude of these two biases is unknown, although they will tend to offset each other for severe disease estimates. Moreover, the true difference between community and health facility estimates is likely to vary between settings and between severe malaria syndromes.

The recent estimates of the burden of malaria-specific mortality in children under-5 in SSA developed as part of the CHERG initiative, and using the same inclusion criteria and similar methods to those presented here (Rowe et al. 2006), estimated 803 620 (precision estimate: 705 821–901 419) child deaths due to malaria in the year 2000. A recent review found that case fatality rates for hospital-based studies in Africa were highly site-specific, varying between 0% and 22% (E. Korenromp, unpublished observation). We attempted to triangulate our severe malaria results by applying the upper rate – likely to be more representative of non-research hospital settings – to the malaria mortality estimate. This suggests an incidence of severe malaria episodes in the community of $803\,620 \div 0.22 = 3\,652\,818$, which is 6.7 times (uncertainty interval: 2.1–34.7) greater than our health facility-based estimate of 545 000, suggesting that in some settings as few as one in seven children with severe malaria episodes may reach a hospital. This triangulation is clearly fraught with assumptions, and deserves further investigation to define possible uncertainty intervals, which was not within the scope of our work. However, it provides an order of magnitude estimate for the community incidence of severe malaria episodes.

Our ‘average’ rate of malaria episodes for central Africa after adjusting for transmission intensity and urban–rural residence was 1.2 per child per year (uncertainty interval: 1.0–2.8), which is similar to Snow’s estimate (2003) based on 28 studies with a median rate of 1.4 per child per year (IQR: 0.8–2.2) for children for the whole of central Africa. Murphy and Breman (2001) assumed that malaria was associated with 30–60% of all fevers, and estimated the annual incidence of malarial febrile episodes as 1.6–5.4 per child per year. Their approach did not take into account the fact that African countries are exposed to different transmission intensities and applied the same incidence rate to countries regardless of transmission intensity, which may have overestimated the burden of malaria fevers. While our estimate is similar to those of Snow et al. (2003), it has more comprehensively attempted to account for variations in age of study participants, study duration and urban–rural populations. Moreover, we attempted to account for differences in study design and population characteristics, in addition to using a more statistical approach to estimating uncertainty intervals.

To derive our estimates, we made a considerable number of assumptions, and a number of biases may also have distorted our estimates. Firstly, our literature review identified geographical clustering in the distribution of research studies for both severe and non-severe malaria, reflecting the bias in malaria research towards established research centres. If those centres were chosen because malaria morbidity was high, then we might overestimate the true burden of disease, despite our attempts to account for their potentially atypical settings. Secondly, although we used a random-effects model to reduce confounding in our non-severe malaria estimates, there may be residual confounding because of unmeasured characteristics of the study population or study design. Thirdly, extrapolation of data from studies to national and regional levels depends on a number of assumptions about the distribution of malaria risk. There is growing evidence that the MARA estimates of populations exposed to high and low climate suitability for malaria are crude as populations exposed to stable endemic transmission tend to be underestimated (Omombo et al. 2004) and do not take into account urban–rural differences. We have tried to improve on these denominator estimates by adjusting for populations living in urban and rural settings, but even these estimates of urban and rural populations are crude (Hay et al. 2005). Although these assumptions may have introduced biases, it is difficult to estimate their directions and magnitudes.

Despite these caveats and limitations, the present study is a valuable addition to previous estimates of the distribution of under-5 malaria morbidity in SSA, as it considers all data available, based on a systematic review including searches on the grey literature, under more stringent inclusion criteria and uses a statistical analysis that better reduces bias and controls for confounding compared with previous attempts. In order to cross-validate our results, two methods were used: First, comparison of the severe and non-severe malaria incidence estimates suggests that approximately 0.5% (545 000/115 592 000) of clinical malaria cases progressed to severe disease and were admitted to hospital for treatment. Applying this 0.5% factor to the maximum estimated number of the severe malaria episodes in the community of $803\,620 \div 0.22 = 3\,652\,818$ as mentioned above, would result in $3\,652\,818 \div 0.005$ approximately 73 million non-severe malaria episodes p.a.

A second triangulation could be made by using the estimated mortality rate of 1–10% after a malaria fever episode (Greenwood et al. 1991). Applying this range to the CHERG mortality estimate would imply 8–80 million malaria disease episodes p.a. which is in line with the first cross-validation method. Our estimate of 116 million
episodes exceeds both cross-validation methods and therefore it should be considered as a rough approximation of the true burden of direct malaria morbidity. However, the estimates reported here can be used to assess the proportional burden of malaria relative to other childhood diseases, whose estimation suffers from similar constraints (Rudan et al. 2005).

In any comprehensive picture of the malaria burden in Africa, the ‘indirect’ components of the burden of malaria need to be considered. These include anaemia, low birth weight, under nutrition and the role of malaria infection in enhancing susceptibility and severity of other infectious diseases through immune suppression. Although they were outside the scope of this project there has been an attempt to measure them elsewhere (Snow et al. 2003).

Future estimates of malaria morbidity will need to address some of the following issues: Firstly, further work

### Table 4 Checklist for reporting data on clinical malaria studies

<table>
<thead>
<tr>
<th>Item</th>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Study population</td>
<td><strong>Essential</strong> Geographical location within the country&lt;br&gt;<strong>Desirable</strong> Reason why study population selected&lt;br&gt;Representativeness of wider region</td>
</tr>
<tr>
<td>2</td>
<td>Geographical context</td>
<td><strong>Essential</strong> Number and nature of the seasons&lt;br&gt;<strong>Desirable</strong> Altitude</td>
</tr>
<tr>
<td>3</td>
<td>Socio-cultural and health care context</td>
<td><strong>Essential</strong> Classification of population as rural, peri-urban or urban&lt;br&gt;<strong>Desirable</strong> Prevalence of malnutrition&lt;br&gt;Prevalence of hookworms and AIDS&lt;br&gt;Prevalence of micronutrient deficiency (vitamin A or zinc)&lt;br&gt;Immunization coverage against measles, pertussis and Hib access to health care</td>
</tr>
<tr>
<td>4</td>
<td>Local malaria intervention coverage</td>
<td><strong>Essential</strong> Insecticide-treated mosquito nets among under-5s and pregnant women&lt;br&gt;Indoor residual spraying&lt;br&gt;Intermittent preventive treatment of pregnant women (IPTp)&lt;br&gt;Prompt and effective treatment of malaria cases</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Study duration (multiples of 1 year)</td>
<td><strong>Essential</strong> Month and year at start and end of surveillance&lt;br&gt;<strong>Desirable</strong> Time trends of estimates (to identify ‘Hawthorne effect’)</td>
</tr>
<tr>
<td>6</td>
<td>Surveillance procedures</td>
<td><strong>Essential</strong> Surveillance type: Active or passive case detection&lt;br&gt;Frequency of surveillance visits</td>
</tr>
<tr>
<td>7</td>
<td>Cohort structure and size</td>
<td><strong>Essential</strong> Age structure of the cohort&lt;br&gt;Cohort size</td>
</tr>
<tr>
<td>8</td>
<td>Case definition</td>
<td><strong>Essential</strong> Parasite density thresholds adopted&lt;br&gt;Temperature thresholds adopted&lt;br&gt;Details of how children with malaria fevers were identified&lt;br&gt;Laboratory procedures (e.g. thick or thin blood films), – method of parasite count (i.e. per 200 white blood cells)&lt;br&gt;Details of types of Plasmodium species identified</td>
</tr>
</tbody>
</table>
is needed to define hospital catchment populations and to understand the relationship between estimates of severe malaria from health facilities and the true incidence in the community, and how this might vary according to syndrome of severe malaria. Secondly, additional data on the incidence of non-severe malaria in children are urgently needed, especially from countries in central Africa and the Horn of Africa, and from countries other than those with established research settings. Such studies would need to cover the full malaria transmission season, in order to enable estimates of annual malaria incidence. Finally, current malaria estimates are likely to be much lower than our estimate of 1.2 non-severe malaria attacks per child for the year 2000, due to the scaling-up of malaria interventions such as insecticide-treated mosquito nets and changes to artemesia combination therapies for first-line treatment. However, due to the paucity of useful data available for estimating the burden of malaria, variation in methodologies and the bias towards non-representative research settings of malaria epidemiological studies, it is unlikely that future estimation attempts will be sufficiently comparable to enable a realistic assessment of the impact of increasing coverage of interventions. This emphasizes the need for greater priority to be given to longitudinal community-based studies to monitor the global burden of clinical malaria estimates and for guidelines for the proper conduct and reporting of these studies. We propose a set of minimum reporting criteria needed to develop comprehensive estimates of the burden of malaria disease (Table 4). With the increasing move towards open access to data, these guidelines will enhance the utility of such data for secondary analyses, and help to monitor progress towards Roll Back Malaria and the Millennium Development Goals (http://www.developmentgoals.org).

Acknowledgements

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Malaria morbidity in African children


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Malaria morbidity in African children


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