Negative tissue staining for IL-4 and for development of Th2 cells. Immunity 4, 711-716.


A Preliminary Continental Risk Map for Malaria Mortality among African Children

R.W. Snow, M.H. Craig, U. Deichmann and D. le Sueur

Approaches to global public health are increasingly driven by an understanding of regional patterns of disease-specific mortality and morbidity. Current estimates of disease risks associated with Plasmodium falciparum in sub-Saharan Africa remain poorly defined. Through the integration of high-resolution population and climate probability models, and, at worst, misleading. Perhaps one of the best ways public health is conceived and implemented. Nevertheless, areas of the world that continue to experience the greatest burden of early childhood mortality and long-term disability have the least developed health reporting systems. Therefore, areas such as sub-Saharan Africa remain less well suited to the precise quantification of causes of mortality and morbidity. As a consequence, models and predictions of changing disease patterns and their demographic effects are, at best, guesses and, at worst, misleading. Perhaps one of the best

of malaria-attributable mortality using this approach ranged between 0.43 million and 0.68 million deaths per annum among an exposed population of ~66 million children in 1990. Despite the limitations of modelled transmission and population distributions, these empirical approaches to probabilities of infection risk and epidemiological data on mortality provide a novel approach to present and projected burdens of malaria mortality, as discussed here by Bob Snow, Marlies Craig, Uwe Deichmann and Dave le Sueur.

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reviews

Table 1. Malaria-specific mortality rates per 1000 children per annum

<table>
<thead>
<tr>
<th>Country and dates</th>
<th>Malaria-specific mortality</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senegal</td>
<td>5.2</td>
<td>16</td>
</tr>
<tr>
<td>1964–1988</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992–1995</td>
<td>12.4</td>
<td>17</td>
</tr>
<tr>
<td>1985–1989</td>
<td>0.4</td>
<td>18</td>
</tr>
<tr>
<td>1990–1995</td>
<td>3.3</td>
<td>17</td>
</tr>
<tr>
<td>1986–1991</td>
<td>4.2</td>
<td>17</td>
</tr>
<tr>
<td>1992–1995</td>
<td>10.3</td>
<td>17</td>
</tr>
<tr>
<td>The Gambia</td>
<td>9.5 (0.25–4 years)</td>
<td>19</td>
</tr>
<tr>
<td>1982–1984</td>
<td>10.0 (0.25–4 years)</td>
<td>19</td>
</tr>
<tr>
<td>1988–1989</td>
<td>20.3</td>
<td>20</td>
</tr>
<tr>
<td>1989–1990</td>
<td>9.3</td>
<td>20</td>
</tr>
<tr>
<td>1989–1992</td>
<td>5.7</td>
<td>21</td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td>18.7 (0–6 years)</td>
<td>22</td>
</tr>
<tr>
<td>1978–1979</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1990</td>
<td>8.0</td>
<td>23</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>10.3</td>
<td>25</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>5.0 (0–3 years)</td>
<td>24</td>
</tr>
<tr>
<td>1984</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>9.9</td>
<td>25</td>
</tr>
<tr>
<td>1992–1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>8.7</td>
<td>26</td>
</tr>
<tr>
<td>1977–1978</td>
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<td></td>
</tr>
<tr>
<td>Benin</td>
<td>8.0 (0–3 years)</td>
<td>27</td>
</tr>
<tr>
<td>1989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaïre</td>
<td>8.5</td>
<td>28</td>
</tr>
<tr>
<td>1986–1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989–1991</td>
<td>7.9</td>
<td>29</td>
</tr>
<tr>
<td>Burundi</td>
<td>14.4</td>
<td>30</td>
</tr>
<tr>
<td>1990–1991</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>1.7</td>
<td>31</td>
</tr>
<tr>
<td>1981–1982</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1988</td>
<td>0.4</td>
<td>32</td>
</tr>
<tr>
<td>1975–1978</td>
<td>0.1</td>
<td>33</td>
</tr>
<tr>
<td>1992–1993</td>
<td>4.7</td>
<td>34</td>
</tr>
<tr>
<td>Tanzania</td>
<td>14.4</td>
<td>35</td>
</tr>
<tr>
<td>1991–1992</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986–1985</td>
<td>9.0</td>
<td>36</td>
</tr>
<tr>
<td>1992–1994</td>
<td>17.6</td>
<td>37</td>
</tr>
</tbody>
</table>

Examples is that of malaria. The oft cited number of people exposed to the risk of *Plasmodium falciparum* infection in Africa is 250 million, with widely divergent annual estimates of its direct cause of mortality, ranging from 0.46 million deaths among children in Africa, to estimates among all age groups of 0.86 million; or global figures of between 1.5 and 2.7 million deaths[5]. It is widely accepted that the greatest burden of malaria mortality (>90%) is experienced by children living in sub-Saharan Africa and is a result of infection with *P. falciparum*. It is not clear how these estimates of between 0.5 and 2 million childhood deaths in Africa each year are derived, but they are probably ‘best guesses’ based upon limited data and demographic models. One of the cornerstones of the global burden of disease approach is to provide a geographical perspective to assess which targeted interventions are likely to have the greatest and most cost-effective impact upon disability-adjusted life years (DALYs). Cause-specific risk assessment will become the benchmark by which intervention packages are decided upon. Although few would argue against the importance of *P. falciparum* in child survival, the malaria research community has failed to define the precise distribution of this parasite across the continent or to provide a framework to explain the relationship between parasite exposure and the risks of disability or mortality.

Estimating malaria-specific mortality in childhood

Protective host genes, clinical immune responses, parasite phenotypic variation and human behavioural factors all contribute to the risks of death following infection with *P. falciparum*. There is considerable variation in many of these factors across Africa, including the distribution of sickle cell trait, the age patterns of clinical immunity and access to essential health services for effective clinical management, all of which combine to determine the current levels of malaria-specific mortality among African children. The precision quantification of malaria-specific mortality among the majority of fatal events in Africa that occur outside of clinical settings is fraught with difficulties. The most commonly used method of defining specific mortality uses interviews with bereaved relatives about symptoms and signs related to the terminal event; this technique has been shown to have a low predictive value for paediatric malaria mortality, particularly in areas where competing causes of death, such as acute respiratory tract infections, coexist. Facility-based studies of disease allow for a more precise definition of aetiology, although they are usually unable to correct for the precision utilization patterns of surrounding populations, which determine the proportions of fatal events seen at a given hospital. Finally, there is a widely held view that malaria infection per se leads to an increased risk of a fatal outcome from other major paediatric infectious diseases, and neither the verbal autopsy nor facility-based studies will measure the indirect effects of *P. falciparum* upon child survival. Our only estimates of these indirect effects derive from malaria-specific randomized intervention trials. Tables 1–3 represent the abstraction and correction of available data using the three basic approaches to estimating malaria’s contribution to mortality among African children.

The median malaria mortality estimate of the 28 studies (Table 1) that used complete vital registration systems of mortality events in childhood, combined with verbal autopsy diagnosis of the direct cause of death was 8.6 per 1000 children aged 0–4 years per annum (interquartile range (IQR): 4.9, 10.3). The facility-based estimates of accurately diagnosed malaria mortality combined with crude estimates of hospital utilization among five populations was 3.8 per 1000 children per annum (IQR: 3.4, 4.9) (Table 2). Finally, the median estimates of the direct and indirect malaria-attributable mortality from six malaria-specific intervention trials was 6.7 per 1000 children per annum (IQR: 6.2, 16.2) (Table 3). The results demonstrate the wide geographical and methodological variation in estimates of malaria.
the inherent difficulties in ascribing, on the basis of a
children. Perhaps the most important of these include
the measurement of malaria mortality among African
top approaches estimated malaria mortality to be 9.9 per
and dates population aged 0–4 years that occur in hospital 0–4 years per annum
mortality in childhood. At a site in northern Ghana, the
and hospital use during terminal childhood diseases had been defined.

Table 2. Hospital deaths recorded during prospective paediatric ward surveillance from discrete communities where population estimates and hospital use during terminal childhood diseases had been defined

<table>
<thead>
<tr>
<th>Hospital site and dates</th>
<th>Deaths in hospital due to malaria per 1000 catchment childhood population aged 0–4 years</th>
<th>Proportion of all deaths in community that occur in hospital</th>
<th>Corrected total mortality estimate per 1000 children 0–4 years per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babou, The Gambia (1991–1994)</td>
<td>0.13</td>
<td>0.269</td>
<td>1.2</td>
</tr>
<tr>
<td>Kifit, Kenya (1990–1995)</td>
<td>1.22</td>
<td>0.320</td>
<td>3.8</td>
</tr>
<tr>
<td>Chonyi, Kenya (1992–1996)</td>
<td>0.80</td>
<td>0.234</td>
<td>3.4</td>
</tr>
<tr>
<td>Sayia, Kenya (1992 and 1994–1996)</td>
<td>1.38</td>
<td>0.279</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* Serial observations over 3–5 years at hospitals from five widely differing malaria-endemic settings in Africa within easy reach of the clinical facilities were used to define the epidemiological parasitic and risks of severe falciparum malaria. The facilities used in this study had well-developed epidemiological surveillance systems and upgraded diagnostic facilities to define the precise resilience and clinical presentation of each paediatric admission. The surveillance of admissions from the five communities represented a total of 102266 person-years of observation among children below five years of age and recorded 123 fatal events in hospital due to falciparum malaria. During the course of these studies community-based interviews were conducted with between 167 and 596 mothers at each setting to establish the numbers and locations of previous live births that had subsequently died. The combined rate of hospital based malaria-specific mortality was corrected by the estimate of hospital-to-community mortality to provide a minimum estimate of malaria specific mortality at each of the five communities.

Table 3. Mortality among children aged 1–59 months attributable to malaria-specific interventions derived from six studies conducted in Africa

<table>
<thead>
<tr>
<th>Treatment, site and dates</th>
<th>All-cause mortality among children 1–59 months per 1000 person years of observation</th>
<th>Protective efficacy estimated as a risk ratio of all-cause mortality among intervention to control populations (%)</th>
<th>Malaria-attributable mortality rate per 1000 children aged 1–59 months per annum</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITBN Ghana (1993–1995)</td>
<td>34.2</td>
<td>18</td>
<td>6.2</td>
<td>37</td>
</tr>
<tr>
<td>ITBN Burkina Faso (1994–1996)</td>
<td>49.03</td>
<td>14</td>
<td>6.9</td>
<td>38</td>
</tr>
<tr>
<td>ITBN Kenya (1993–1995)</td>
<td>15.3</td>
<td>30</td>
<td>4.6</td>
<td>39</td>
</tr>
<tr>
<td>Mass drug administration and house spraying Nigeria (1972–1973)</td>
<td>140.0</td>
<td>46</td>
<td>6.4</td>
<td>40</td>
</tr>
</tbody>
</table>

* The trials were conducted under experimental conditions achieving optimal coverage and compliance providing efficacy estimates against all-cause childhood mortality. Thus they accommodate both the direct and indirect effects of reducing malaria exposure upon the risk of death. However, despite the experimental nature of the trials they did not achieve either complete coverage or compliance, and consequently underestimate the real effect of reductions in parasite exposure on mortality. Protective efficacies described through these experimental trials were applied to baseline mortality estimates defined within the populations where the trials were conducted (or when not available among the contemporaneous control population’s mortality estimates) to define the annual mortality incidence attributed to the intervention among children aged 1–59 months of age. ITBN, insecticide-treated bedsheets.

symptom history alone, clinical malaria in young chil-
dren, particularly in areas of intense P. falciparum trans-
mission, where the predominant life-threatening con-
dition is severe anaemia. It has also been argued that
the risk of mortality is dependent upon the intensity of
parasite exposure on mortality. Protective efficacies de
dcribed through these experimental trials were applied to baseline mortality estimates de
dined within the populations where the trials were conducted (or when not available among the contemporaneous control population’s mortality estimates) to define the annual mortality incidence attributed to the intervention among children aged 1–59 months of age. ITBN, insecticide-treated bedsheets.
from 12 countries shown in Tables 1–3 are our only empirical source of malaria’s contribution to child survival and these estimates probably represent the varied epidemiological, demographic and social structures of sub-Saharan Africa. Combining estimates from the different methodological approaches provided a median estimate of 8.0 malaria deaths per 1000 children under five years of age each year (IQR: 4.6, 10.3). These mortality risks apply to communities exposed to frequent parasite exposure; however, there are densely populated areas of Africa that have negligible risks of parasite exposure. The following sections set out to define the geographical limits of parasite transmission in relation to population density.

Continental limits of parasite exposure

Although there have been several historical attempts to provide maps of malaria transmission distribution in Africa, these were based on expert opinion, rather than an empirical approach to the biological determinants of malaria vector dynamics, and none has related the exposure patterns to human population dispersion. It has long been recognized that the length of the sporogonic cycle of the *P. falciparum* parasite within the mosquito becomes shorter as the ambient temperature increases, which decreases the duration of the gonotrophic cycle, and thus enhances vector-human contact. A short gonotrophic cycle is also important when related to the decreasing cohort of adult mosquitoes, with time, which survive long enough to be infective. Low temperatures also limit mosquito larval development and thus impact upon adult abundance. Furthermore, rainfall patterns have consistently been shown to determine the extent and magnitude of local vector proliferation.

In our work, combined temperature and rainfall was used to define the vector and parasite viability for transmission within fixed seasonal windows of time. ‘Fuzzy logic’ models were used to define the suitability for stable malaria transmission across the continent at approximately a 5 × 5 km resolution (M.H. Craig, R.W. Snow and D. le Sueur, this issue). Fuzzy logic assumes a continuum of conditions ranging from suitable to unsuitable, and has been developed to deal with uncertainty. In our model, climate data were derived from weather station data from between 1920 and 1980 (Ref. 47) and interpolated into mean monthly temperature and rainfall stations using the geographical information system (GIS) package IDRISI. The model was structured to define distribution by setting the lower temperature cut-off point at 18°C and assuming a saturation of the temperature effect by 22°C; similarly, rainfall values between 0 and 80 mm were used to determine the range within which transmission is limited, combined, these features must coincide on a month-to-month basis for five consecutive months, and a frost-factor would eliminate transmission at any point in a contiguous period (M.H. Craig, R.W. Snow and D. le Sueur, this issue). In North Africa, the combination of high temperatures of sub-Saharan Africa, and thus enhances vector-human contact. A short gonotrophic cycle is also important when related to the decreasing cohort of adult mosquitoes, with time, which survive long enough to be infective. Low temperatures also limit mosquito larval development and thus impact upon adult abundance. Furthermore, rainfall patterns have consistently been shown to determine the extent and magnitude of local vector proliferation.

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360 million were exposed to a >50% probability of stable malaria transmission and 294 million people were exposed to a >90% probability of being exposed to stable malaria transmission. Table 4 shows a range of estimates of annual mortality events in children (0-4 years old) derived from two different probabilities of transmission potential using the fuzzy logic model.

Realistic estimates of childhood malaria mortality across Africa

Table 4 shows the possible ranges of estimates of annual numbers of childhood deaths as a result of malaria under a variety of assumptions. Given the caveats in estimating mortality risk, it seems appropriate to consider the interquartile range around the median rather than a single estimate. The data used to define malaria-specific mortality in Table 1 include several studies conducted within the same populations ~5–7 years apart16–18,35,36. These studies, in Senegal and Tanzania, suggest that mortality from malaria might have doubled during this short period, coincidental with the rapid emergence of chloroquine-resistant infections in both areas. These observations are supported by other data from around Africa51 indicating temporal changes in survival following the failure of front-line drugs used for clinical management. It is from this perspective that we consider that the more realistic estimation of present malaria mortality in childhood would probably lie between the median and upper quartile range. The transmission model defines climatic suitability for stable transmission occurring or not: consequently, populations within the lowest probability of transmission risk (0–49% probability) are least likely to experience the conditions of stable endemicity or mortality in an average year. However, these fringe areas are susceptible to rapid temporal expansion of infection risk giving rise to high mortality among immunologically naïve populations during epidemics22. Our model does not allow for special conditions of transmission in areas where either rainfall or temperature do limit the chances of transmission, for example dams and seasonal rivers. Consequently, our estimates of exposed childhood populations must be viewed as conservative. Under the combined assumptions of mortality risk in the face of drug resistance and 0.5 fuzzy membership for stable transmission we regard the range of mortality among African children of between 0.43 million and 0.68 million deaths in 1990 to be the most realistic estimate. These conservative estimates suggest that recent attempts to define childhood malaria mortality burdens in Africa in 1990 (Refs 4,5) might be comparable, although their inputs assumed an exposed childhood population of around 95 million and malaria specific mortality rate of 6.23 per 1000 children aged 0–4 years per annum5.

We have used an empirical approach to estimate the distribution of infection risk based upon an understanding of the ecological and physiological factors affecting *P. falciparum* transmission dynamics. These conservative limits of distribution across Africa indicate that ~360 million people are exposed to the risk of *P. falciparum* infection. This is 48% higher than previous estimates1. Integration of high-resolution transmission models, projected population structures and epidemiological surveys within GIS have created the opportunity to define disease burdens according to their geographical relevance across continents or within national boundaries. They also provide preliminary models that can be refined as new data emerge and allow for the projections of effects upon transmission or mortality according to demographic changes in Africa, such as rural-to-urban migration, climate change, and the economic and epidemiological implications of targeted geographical intervention or drug failure. It is within this framework that mapping disease risk and burdens goes beyond simple advocacy for priority to a more rational basis for disease control.

Acknowledgements

This study received financial support from The Wellcome Trust, UK, International Development Research Center, Canada, the South African Medical Research Council and the Kenya Medical Research Institute. RWS is a Senior Wellcome Trust Research Fellow (033340). This paper is a product of the international collaboration, Mapping Malaria Risk in Africa (MARA/ARMA). The authors are grateful to Don de Savigny for his comments on the manuscript. This paper is published with the permission of the director of KEMRI.
References

1. World Health Organization. Ad Hoc Committee of Health Research
   Relating to Future Intervention Options (1996) Inventory in Health
   Research and Development, WTO, Geneva (Document TDH/GS/96.1).
   morbidity and disability by cause 1990–2020: global burden of disease
   Compendium of杜点. Problems and Mortality Estimates for over
   200 Conditions. Harvard University Press.
   Compendium of Trichine. Problems and Mortality Estimates for over
   200 Conditions. Harvard University Press.
11. Snow, R.W. et al. (1995) Relation between severe malaria mor-
    bidity in children and level of Plasmodium falciparum trans-
    Health, Oxford University Press.
15. Molines, L. (1997) Malaria and other epidemiology: some epidemiologi-
18. Foxon, G. et al. (1996) Reposition of two strategies for control of malaria within a primary health care programme in
    on the Epidemiology and Control of Malaria in the Sudan Savanna
    Importance with Special References to some Vectors of Malaria. WHO
    Monograph Series 107, Geneva.
25. le Suerus, D. and Sharp, B.L. (1988) The breeding requirements of
    Anopheles gambiae Giles complex (Diptera: Culicidae) in the endemic malaria area in Natar, South Africa.
    Flamingo Press.
    Database. Version 1.0, Centre for Geographic Information and Analysis, Australian National University, Canberra, Australia.
    base, World Resources Institute, Washington, DC, USA.
    and Documentation, National Center for Geographic Information and Analysis, Santa Barbara, USA (http://grid2.cr.usgs.gov/
    globalpop/africa/).
    Information and Policy Analysis, New York, USA.
31. Greenwood, A.E. et al. (1998) Hospital-based surveillance of
    malaria-related paediatric morbidity and mortality in Khinsha,
32. le Suerus, D., Sharp, B.L. and Appleton, C.C. (1993) Historical per-
    spective of the malaria problem in Natar with emphasis on the period

Note added in proof
The epidemiological and GIS approaches presented in this paper for 1990 estimates of malaria burden have been refined in collaboration with Epidemiology and Burden of Disease and Roll Back Malaria Programmes of WHO, to provide more comprehensive estimates of malaria morbidity, mortality and disability for Africa’s population in 1995. For further details contact RWS.

Parasitol Today, vol. 13, no. 3, 1999

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