Plasmodium falciparum Mortality in Africa between 1990 and 2015

TO THE EDITOR: The recent reports in which cartographic approaches were used by Gething et al. (Dec. 22 issue)[1] to estimate malaria mortality in sub-Saharan Africa and by Bhatt et al.[2] to estimate the burden of malaria in that region are information-rich analyses of temporal and geographic patterns of this disease. One important methodologic advance is the use of local data on effective treatment for uncomplicated disease, thus accounting for direct benefits of treatment and permitting prediction of the effect on mortality of improving access to care. However, mortality is most directly affected by managing life-threatening episodes. The accompanying Perspective article by Maitland[3] notes that recent advances in inpatient treatment (e.g., injectable artesunate) also affect mortality. Existing estimates of disease burden ignore not just quality of but also access to inpatient care. Case fatality rates among patients with severe disease who do not access inpatient care are also unknown. We recently attempted to estimate national levels of access to inpatient care for severe malaria[4] and found both substantial data deficiencies and evidence of massive international variations. Total numbers of severe cases as well as improvements to both access to and quality of inpatient care should be considered in future estimates of disease burden and in the assessment of potential effects of different interventions.

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No potential conflict of interest relevant to this letter was reported.

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2. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature 2015;526:207-11.
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TO THE EDITOR: Gething et al. estimate a substantial decrease in the rate of death from malaria across sub-Saharan Africa. What they have not considered is that the human immunodeficiency virus (HIV) and AIDS may have considerable clinical effects on the treatment of malaria. HIV–AIDS may be associated with an increase in malaria-associated deaths. It complicates treatment of malaria, increases the risk of disease progression to severe malaria, and raises the chance of neutropenia in children by a factor of 7 or 8.[1] Gething et al. identify Nigeria as a country of high estimated malaria mortality; importantly, Nigeria is also the country with the highest number of deaths due to HIV–AIDS in the world.[2] Because it has been suggested that HIV–AIDS increases both the incidence of clinical malaria and its mortality,[3] it can be speculated that an improvement in the treatment of HIV–AIDS may contribute to a reduction in malaria-associated mortality. Additional investigation is required to further evaluate the potential associations between HIV–AIDS (and other possible cofactors) and malaria mortality.

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TO THE EDITOR: To determine *P. falciparum* mortality, Gething et al. used cause-of-death data that relies on verbal autopsy, which is the norm in sub-Saharan Africa. We have several questions that we would like to be clarified: How reliable can verbal autopsy be in a continent-level study with large differences in socioeconomic conditions across the study population? What was the detailed method of verbal autopsy? How was death from *P. falciparum* determined from verbal autopsy? Finally, what proportion of *P. falciparum* deaths was proved by microscopy or antigen-based tests?

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THE AUTHORS REPLY: One new aspect of our analysis was the development of geospatial estimates for the fraction of incident malaria infections that receive effective treatment. This was made possible only by the recent proliferation of open-access, high-quality, standardized, and geolocated data from national household surveys (e.g., those of the Demographic and Health Surveys Program[1]) with respect to various aspects of access to and quality of care for uncomplicated disease. Receiving prompt, effective antimalarial treatment dramatically reduces the likelihood of progression to severe disease and death, so inclusion of this variable allowed both improved estimates of mortality and an evaluation of how treatment or lack thereof mediates the pattern of malaria deaths across Africa. We strongly agree with Penny and Smith that access to and quality of inpatient care is a further factor influencing rates of death among patients with severe malaria. Unfortunately, current data are sparse and understanding of geographic variation is very limited. We welcome their efforts to better enumerate severe malaria incidence and treatment[2] and join them in highlighting the pressing need for more systematic collection of data.

Sub-Saharan Africa continues to host the highest prevalence of both HIV infection and malaria. Although the pathophysiological mechanisms of HIV–malaria coinfection are becoming better understood,[3] Vink and MacKinnon are absolutely correct that much epidemiologic work is still needed to reveal how the two diseases interact at the population level and how these interactions contribute to the overall burden of malaria death. One explanation may be that continent-wide estimates of the respective disease distributions have previously been available only at a highly aggregated national level, which probably obscures important subnational codistribution patterns. The fine-scale geospatial modeling of both malaria and HIV infection will lay the foundation for the spatially detailed analyses required to better understand these interactions.

Directly observed data on malaria deaths outside hospital settings remain sparse in sub-Saharan Africa, where most countries do not maintain reliable cause-of-death data. Tomar and Siddiqui raise the issue of using verbal-autopsy data as the only available metric on the local fraction of deaths caused by malaria in locations across the continent. Details of the studies that were used and subsequent data screening and standardization procedures have been provided elsewhere,[4] and the merits and limitations of verbal-autopsy data in estimating malaria mortality have been discussed in depth and summarized previously.[5]

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Since publication of their article, the authors report no further potential conflict of interest.

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