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PERSPECTIVE
COMPARING METHODS OF ESTIMATING THE GLOBAL MORBIDITY BURDEN FROM *PLASMODIUM FALCIPARUM* MALARIA

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Carter and Mendis[1] provide some welcome clarity to their methods to estimate *Plasmodium falciparum* morbidity in regions of the world outside of Africa.[2] The entry point to their estimation of morbid burdens is malaria-specific deaths reported by national governments. These reflect national mortality statistics generated through civil registration systems that allow for cause of death reporting and invariably only represent deaths that occur in health facilities able to diagnose malaria. In many resource-poor settings, these recorded events represent only a small fraction of the universe of mortality in a given community.[3,4] To redress this, Carter and Mendis have adjusted for under-reporting rates. How this was achieved in the absence of comparisons with prospective demographic surveillance system data remains unclear. To illustrate the problem inherent in any method using national vital event reporting systems, one need look no further than the national malaria mortality data reported in the WHO's 2005 World Malaria Report.[5] In 2003, mortality data are available for only 29 of 49 countries at risk of malaria transmission outside of Africa; a total of 5,865 malaria deaths were reported; 42% were reported from a single country—Myanmar. Sri Lanka reported only two malaria deaths. Estimates of reporting coverage were provided for only four countries.

Despite this uncertainty, Carter and Mendis apply a series of country-specific case-fatality estimates derived from a combination of expert consultation, personal opinion, and unreferenced literature. This step in their calculations is critically dependent upon reliable estimates of the true incidence of malaria morbidity and mortality. The probability of a clinical event resulting in death is the subject of fierce scientific debate surrounding the relationships between acquired functional immunity,[6,7] access to care,[8] and the role of cross-species protection[9,10] versus disease outcome. Outside Africa there are only a handful of carefully conducted studies of *P. falciparum* clinical incidence and mortality undertaken using active-case detection methods within well-characterized populations subjected to prospective demographic surveillance with cause-of-death attribution of all fatal events.[11,12] Empirical evidence upon which to reliably model global variations in case-fatality is largely absent, and therefore estimating subregional case-fatalities must be the subject of guesswork and speculation.

The area of largest uncertainty, for which Carter and Mendis fail to define in their methodology, is the denominator. The numbers of people living under differing levels of *P. falciparum* transmission risk is arguably the single largest determinant of precision for morbidity and mortality burdens definitions globally.[13] Our approach to defining population-attributable risks involved a conservative downregulation of historically mapped global malaria endemicity distributions.[14] We acknowledged that these must be improved during future iterations of the estimation of malaria burden worldwide. In 2005, we started to extend our earlier work on transmission mapping to other regions of the world using empirical parasite rate survey data within spatially explicit models of dominant vector species *P. falciparum* transmission globally—the Malaria Atlas Project (MAP). These should provide a more robust and dynamic approach to defining the denominators for future disease burden estimations. This is particularly important for the rapidly changing ecological context of the Western Pacific and Southeast Asian regions, which are home to some of the most densely populated malarious areas on the planet.[13,14]

Rather than make assumptions about the quality of national civil reporting systems, presumptions about the complex nature of case-fatality, and construct theoretical models to extrapolate morbidity incidence, we have elected to use empirical data on malaria morbidity recorded through active case-detection.[14] Herein lies the most obvious difference in the estimates of malaria burden outside of Africa. In 1999, the WHO[15] chose to use our method of morbidity estimation for Africa[16] but adopted the method used by Mendis and colleagues[2] for all other regions on the grounds that there were insufficient empirical data and maps of malaria risk to reproduce what we were able to provide for Africa. This is clearly no longer true, and our paper in *Nature* is the first attempt to model risks at a global scale using a single method and driven by empirical data.[14]

In the absence of universal, complete national health reporting systems, we must continue to use informed epidemiological approaches to estimating disease burdens worldwide. We concur with Carter and Mendis that any approach that attempts to model imperfect data will produce margins of error around the true estimate. These must be made explicit, quantified, and transparent. We are therefore grateful to the authors in their elaboration of the methods originally provided in 2001, but the authors fall short of quantifying their likely errors or providing the data used in their calculations of under-reporting of national malaria-specific mortality. Ignoring semantics, our estimates based on transparent and reproducible methods are three times higher[14] than those of Carter and Mendis.[2,15] Being able to compare methods, input data, and measurements of uncertainty is a fundamental prerequisite to the science that underpins global disease burden estimation.[17]

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