Introduction

A meeting of the Malaria Burden Estimation (MBE) Evidence Review Group (ERG) was convened by the Global Malaria Programme (GMP) of the World Health Organization (WHO) to:

- review current methods in malaria morbidity and mortality estimation with the participation of the experts involved in the development of currently used methods,
- try to achieve consensus on the methods that should be used by WHO and in the World Malaria Report (WMR), and
- identify research bottlenecks that prevent reconciliation of different methodologies/results and how these may be addressed.

Thom Eisele, Peter Gething, Li Liu, Christopher Murray and Tom Smith were invited to this ERG meeting to represent groups that have contributed substantially to malaria burden estimation in recent years. This report summarizes:

- presentations given by meeting participants,
- major discussion points arising,
- recommendations on how WHO should proceed with malaria morbidity and mortality estimation, and
- recommendations on future studies.
Estimating case incidence: Malaria Atlas Project. Peter Gething

The “cartographic risk-based approach,” which has been in existence for more than 10 years, enables malaria burden estimation in the absence of routine case reporting. The developers have assembled a large database of malaria prevalence surveys and have used these to construct a global map of prevalence rates. To convert prevalence information into incidence information, incidence data from longitudinal studies involving active case detection (ACD) are used in conjunction with a map of parasite prevalence to estimate location specific incidence rates. When multiplied by population, the method yields estimates of numbers of cases. An advantage of the cartographic method is that incidence rates can be estimated at a local scale rather than just as a national estimate.

An early map of malaria risk was produced by Lysenko in the 1960s, where limited PfPR data and expert opinion on climatic boundaries were used to estimate endemicity in 5 strata at the assumed endemicity peak in 1900. More recently, the Mapping Malaria Risk in Africa (MARA) project produced a map for sub-Saharan Africa that categorized areas according to climatic suitability for malaria transmission.

Identifying extent of malaria transmission. Annual parasite incidence (API) data were disaggregated to the lowest possible administrative unit; for some countries, this was very small (Brazil had admin5 data, which corresponds to approximately 150 people), but for others this was extremely large (India had admin2 data for which the median population size exceed 1 million).

Estimating malaria transmission intensity. The primary input data for MAP estimates are parasite rate surveys. The 7,953 parasite prevalence survey locations used in the 2007 MAP estimates measured PfPR by microscopy and RDT (not molecular diagnostics, which generally yield higher levels of parasitemia). The data were derived from published literature, MIS surveys with cluster-level GPS coordinates, and grey literature from researchers working in the field. Embedded in the modeling framework is an age-correction model that takes advantage of the >100 studies with prevalence reported by very fine age groups in order to standardize prevalence estimates to a 2-10 year age range. In addition to age, the model also takes into account how many years ago the survey occurred and whether it took place in an urban or rural location. Seasonality is not considered in the model (although seasonality is recorded in the data, and DHS occur in dry seasons while MIS occur in rainy seasons). The prevalence data reveal large numbers of 0 PfPR values, indicating that prevalence surveys are not only conducted in areas where malaria transmission is highest. The methods are depicted in a schematic in Figure 1.
Figure 1: schematic of geospatial model of stable risk. Source: Peter Gething

**Estimating malaria case incidence rates from parasite prevalence rates.** The data used to model case incidence from PfPR are from a systematic literature search, with the inclusion criteria that the data be no older than from 1985, come from community-based longitudinal studies of prospective ACD of fever (where ACD occurred at intervals of at least every 14 days), covered all age groups (which, surprisingly, did not eliminate many studies), and covered a complete 12-month period. These inclusion criteria would eliminate cross-sectional studies, surveys with restricted age groups, and rolling MIS surveys, but would include the control arms of case-control studies. Although longitudinal studies ensure the reliability of the incidence estimates, the studied populations often receive high-quality treatment and become less and less representative over time during follow-up (producing a downward bias). The case incidence data were matched to co-reported or mapped mean PfPR, yielding 141 ACD-PfPR\textsubscript{2-10} pairs that were used in the incidence-prevalence model.

The relationship between age-specific incidence and age-adjusted PfPR is a noisy one. The non-parametric Bayesian regression used did not require prior parameterization of the relationship; rather, a family of curves (linearly increasing or decelerating) was specified (with some forms disallowed). In the next iteration of the MAP project, the incidence-prevalence relationship will be stratified by age (it is expected that the relationship between incidence and PfPR would be different in under-5s and in adults, given adult immunity, and would vary with overall endemicity), and will include covariates in the model, such as ITN coverage (this will be challenging as covariates are infrequently available).

**Estimating case numbers.** Case numbers are estimated by multiplying estimates of case incidence by the population estimated for each pixel. The availability of more detailed population maps is facilitating improvements in cartographic methods: Andy Tatem’s AfriPop (to be followed by AsiaPop and AmeriPop, and stratification by age and sex) is providing improved population distribution data to replace GRUMP and LandScan.
Estimating uncertainty. Uncertainty is propagated at every step in the modeling process. Although the mapped results appear very smooth, the model generates a complete posterior distribution of $P/PR$ for each pixel, and the variance of the distributions can be large. The posterior distribution of the incidence-prevalence model is applied to each $P/PR$ pixel’s distribution to get a distribution of incidence rates. Each incidence pixel’s distribution is applied to the pixel’s distribution of population in order to get a distribution for each pixel of cases per year. The computing power required to run the joint simulation to calculate this uncertainty costs $15,000. The temptation on behalf of policy makers is often to ignore uncertainty and simply consider the mean values; it is a challenge for researchers to present uncertainty in a way that can be used in decision-making. The smoothness of the resulting map may be misleading in elimination schemes because it can give false hope of elimination when the underlying distribution is much more uncertain than the mean values indicate.

The resulting estimates are most reliable in Africa, and least reliable in India, China, and Myanmar (India in particular has vastly insufficient data and prevalence surveys are mainly conducted in high risk population groups or during epidemics). Thus, the strength of the method varies from one setting to another, and it is particularly weak where data are only available at high administrative levels, which may lead to overestimation of populations at risk. The strengths of the method are that it is not reliant on routine reporting systems, is consistent across all countries, and can quantify uncertainty, including that in the assumptions and input data. Although the ideal metric is cases, parasite rates are a direct measure of transmission and can provide an empirical baseline that incorporates the effects of interventions (assuming that $P/PR$ surveys are up-to-date). The spatial (i.e. systematic choice of survey locations) and temporal (i.e. variable age of data and seasonality) fidelity of the data, and the potential for a wide range of confounders remain key challenges.

The 2010 MAP estimates use 22,212 survey points (over 2.5 times as many observations as the 2007 version), employ a refined methodology using 20 environmental covariates and regional modeling, and extend the studied relationship to $P/EIR$. The 2010 version is meant to replace, not be compared to, the 2007 version, and it is far more detailed/refined. As prevalence decreases, it will become increasingly important to discriminate between 10% and 20% prevalence, which the new model is better situated to do. Similar work has been done for $P. vivax$, which is most useful in Latin America. It incorporates the prevalence of Duffy negativity, but estimating relapses remains a challenge.

Future work includes BMGF-funded research to generate infection prevalence and case incidence time series from 2000 to present for 34 high-endemicity countries in Africa. With increasing use of mobile phones, geo-referenced facility data could be collected. Currently, validating the incidence-prevalence model is difficult (doing predictive validity tests on holdouts is impossible given the small sample size of 141 studies), but conducting studies at the community level to collect data on $P/PR$ and case incidence could help validate the results. Although there may be some appeal to generating country-specific maps using country-specific incidence-prevalence data, the downside is that
results across the globe will no longer be comparable because estimates for different countries will come from different years.

In high-endemicity, weak-HMIS areas, the cartographic approach may be the strongest option. In low-endemicity, strong-HMIS areas, the surveillance-based approach may be preferable. In intermediate settings, a hybrid of the two methods may be optimal. The next challenge will be to develop an application, potentially web-based, for this approach so that countries can generate their own estimates and adjust input data. Further discussion is required to assess whether this work is better done at the University of Oxford, or whether there is demand for developing a simplified application for use at country-level.

Case estimates from WHO. Richard Cibulskis

WHO uses two methods to estimate malaria cases: 1) the “surveillance/HMIS approach” (using data on reported cases) and 2) the “risk approach.”

1) Surveillance/HMIS approach. This approach is used for countries outside the WHO African Region and low transmission countries in Africa.\(^1\) Estimates of the number of cases are made by adjusting the number of reported malaria cases for completeness of reporting, the likelihood that cases are parasite-positive, and the extent of health service use. Suspected cases reported through the NMCP reporting system are split into presumed (unconfirmed) and tested; tested cases are further split into confirmed negative and confirmed positive cases. The test positivity rate from the confirmed cases is used to estimate the number of confirmed cases within the cases that do not receive a diagnostic test (presumed cases).

Since the NMCP data only provide information on cases coming through the public sector, household surveys (DHS, MIS, MICS) are used to estimate the percentage of patients with fever that receive care through the private (as opposed to public) sector. If data from more than one household survey were available for a country, estimates of health service use for intervening years were imputed by linear regression. If only one household survey was available, then health service use was assumed to remain constant over time; analysis (using multiple surveys from the same country) of percentage of fever cases seeking treatment in public sector facilities reveals that this percentage varies little over time. A limited number of studies indicate that the fraction of fever cases that are malarious and receive treatment in the private sector is the same as the fraction of fevers that are malarious in the public sector. For fever cases that do not seek treatment, the method calculates an estimate assuming that the fever cases not seeking treatment have the same likelihood of being malarious as the cases that do seek treatment, and an estimate assuming that the fever cases not seeking treatment are not serious enough to be malarious. Such a procedure results in an estimate with wide uncertainty intervals around the point estimate. The method uses spreadsheet software called @Risk to estimate

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\(^1\) Botswana, Cape Verde, Eritrea, Madagascar, Namibia, Swaziland, South Africa, and Zimbabwe
uncertainty using measured or assumed uncertainty ranges around each input to the model.

The strengths of this method include that countries can apply it themselves, and see first-hand that the reported number of cases are likely actually only a fraction of the true country-wide cases. A disadvantage of the method is that some of the inputs to the model are measured imprecisely. Reporting completeness is estimated by malaria programmes with wide ranges. The size of the health facilities from which reports are missing can have an influence on the reported number of cases and this is not taken into account. HMIS reports are sometimes more incomplete in poorer/rural areas with more malaria risk. In adjusting for treatment seeking outside of the public sector using household surveys, recall bias may occur with only more serious fevers requiring health facility treatment being recalled (potentially underestimating the number of cases not seeking treatment). In some situations fever cases that do not seek care may have a greater likelihood of being malarious than those that seek care (if because they live in remote and highly malarious areas without access to treatment). It is possible to further examine the propensity of fever cases to be malarious using MIS data (by comparing parasite prevalence rates among children who had a fever and sought care as opposed to those who had a fever and did not seek care).

2) The risk approach. This approach is used for high-transmission countries within the WHO African Region. For some African countries the quality of surveillance data does not permit a convincing estimate to be made based on the number of reported cases. For these countries, an estimate of the number of malaria cases was derived from an estimate of the number of people living at high, low or no risk of malaria. Malaria incidence rates for these populations are inferred from longitudinal studies of malaria incidence recorded in published literature. Incidence rates are adjusted downward for populations living in urban settings and based on the expected impact of ITN programmes. ITN coverage (estimated from a model developed by IHME) is then used in a post-hoc fashion to reduce incidence based on protection by ITNs. The protective effectiveness is assumed to be equal to the efficacy, and is taken from a Cochrane Review on the efficacy of ITNs. Thus, for each 1% increase in percent of households owning at least 1 ITN, incidence is assumed to be reduced by 0.5%. No other malaria control interventions are taken into account in the current model (although incidence rates may already take into account high levels of treatment since they were derived from longitudinal studies in which treatment was provided to all malaria cases). The number of cases is estimated by multiplying the population at different levels of risk by the incidence rates for each risk category. The procedure was initially developed by the RBM Monitoring and Evaluation Reference Group in 2004.

The method currently uses estimates of risk from MARA maps and could be improved by using parasite prevalence maps generated by MAP to better define levels of risk. The advantage of this method is that it is simple enough for countries to calculate themselves, and the approach facilitates calculation of the number of malaria cases expected to occur with different levels of ITN coverage. A disadvantage is that no contemporary assessment of malaria risk or case incidence is used as an input to the model. Rather, it
projects what might occur if ITNs had the same effectiveness as measured in randomized controlled trials (a multi-country analysis of observational data conducted by IHME suggested that the effectiveness of ITNs was highly consistent with results from clinical trials).

**Definition of a case**

In estimating malaria morbidity the definition of “malaria case” must be clear. However, defining a case of malaria is complicated; Figure 2 shows the parasite density over time for an individual (untreated) patient. Is this one case only, one case with multiple relapses, one case with multiple episodes, or multiple cases? For longitudinal studies in which malaria in patients is detected and treated promptly, multiple fevers arising from the same infection are unlikely. If malaria is untreated then multiple episodes of malaria can arise from a single infection. For most purposes it is the number of episodes that is of interest, as each will cause disability. However, it is necessary to be clear about the length of the interval between episodes (fever symptoms) that would define one episode or two. In practice this may be taken as one or two weeks.

![Graph showing parasite density over time](image)

○: Parasite density; ■ day with fever (core temperature ≥103 °F).

Figure 2: Pattern of parasitaemia and febrile illness in a malaria-therapy patient (Patient S-519).

*Source: Tom Smith*
Estimating malaria deaths

CHERG malaria mortality estimates among children under age 5. Li Liu

In 2012, CHERG published an update of its analysis on causes of death among children, producing a time-series for 2000-2010 for all-cause mortality and for 8 specific causes of death, including malaria. A strength of the multiple-cause approach is that the method is not focused only on malaria, making the method less prone to researcher bias and favoritism toward a particular disease. Malaria mortality for low-burden African countries and countries outside of Africa was estimated using a fixed case-fatality rate (CFR) and WHO’s estimates of malaria cases (as previously described). Deaths in high-burden African countries were estimated using studies which had employed the verbal autopsy, multi-cause model (VAMCM) among children aged 1-59 months.

The cause-specific mortality fraction (CSMF) data came from 113 community-based verbal autopsy (VA) studies that met the following inclusion criteria: two or more causes of death reported among children aged 1-59 months; from 1980 or later; 12 (or multiples of 12) month duration; at least 25 deaths each represented once; and <25% of deaths due to unknown causes. These criteria result in fewer than 20 data points in Africa and apparently exclude, for example, some high-quality VA studies in Ghana. It may be of value to examine which data points were excluded from the analysis. ERG members familiar with VA studies will provide a list of studies they think could be included in order to examine the effects of expanding the dataset. CHERG researchers may need to approach investigators in the field to ask for VA data in the form required to assess the inclusion criteria.

Among the 113 study data points, 68 did not have a malaria CSMF. In countries with *P. falciparum* transmission, deaths in the “other” category were re-allocated to missing causes using the probability patterns from studies with those causes reported; deaths with “unknown” causes were excluded. This procedure was done stepwise, whereby the missing CSMFs were imputed first for studies with only one cause missing, then two causes missing, etc., until all missing values were filled. Unfortunately, this imputation method does not take into account underlying risk of malaria. This may be problematic because in locations where malaria is well-controlled (and therefore no malaria deaths are reported) deaths may be inappropriately allocated to malaria from their “other” category.

A covariate selection process was undertaken in a stepwise fashion to identify significant covariates. It may be of concern that stepwise covariate selection was performed given the flaws inherent in that method, and that the covariate selection was not done using the same model specifications as used in the actual prediction model. The covariates that were chosen based on the selection process were the CHERG malaria risk index, which was assumed to be constant over time (the next iteration of CHERG malaria mortality work will use MAP’s upcoming PPR time series), and percent of births attended by a skilled birth attendant (SBA). Because only 29 of the 113 studies had site-specific SBA, values were borrowed from national and subnational sources such as DHS/MICS surveys,
and all site-specific malaria risk index values were assumed to be the same as the national values.

The model used was a multinomial logistic regression (used to ensure that all the CSMF sum to 100%) of the malaria CSMF divided by the pneumonia CSMF. Given the higher reliability of the pneumonia CSMF, it was used to “anchor” the malaria CSMF:

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\ln \frac{CSMF_{\text{malaria}}}{CSMF_{\text{pneumonia}}} = f(\text{CHERG malaria index, } \% SBA)
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Given that ITN coverage was not retained in the model based on the covariate selection process, a post-hoc ITN adjustment was performed. Using the protective effect of ITNs (55% according to Eisele et al) and IHME’s ITN coverage time series, the resulting mortality estimates from the model were adjusted to account for the life-saving effect of ITN scale-up, and the “averted” malaria deaths were redistributed to the remaining 7 causes proportionally. This step may over-adjust for the effect of ITNs because the all-cause mortality envelope used by CHERG already takes into account mortality reduction due to reductions in malaria deaths. Bootstrapping was used to generate uncertainty intervals.

The results appear to be driven by the need for all diseases to fit into one mortality envelope (i.e. if measles and pneumonia decline rapidly, malaria deaths may appear to increase simply because other diseases must comprise the remainder of the envelope). Since the CHERG malaria index is constant over time, the SBA covariate and the ITN post-hoc adjustment are responsible for the trends seen. The inclusion of other covariates might result in very different results. More recent VA data may be required to yield a significant coefficient on ITN coverage (most VA data are from when ITN coverage was low).

Next steps for CHERG include incorporating the upcoming PfPR time series, modeling results for different age groups within the 1-59 months range, and exploring use of a Bayesian framework for comparison purposes.

**WHO malaria mortality estimates among adults. Richard Cibulskis**

WHO uses CHERG’s under-5 deaths in Africa to estimate deaths among those age 5 and over in Africa by using the relationship between age-specific malaria death rate and intensity of malaria transmission (Ross et al). The estimated malaria-specific mortality rates in children from CHERG were used to approximate the malaria transmission intensity and the corresponding malaria-specific mortality rates in older age groups. This relationship is inferred from mathematical modeling of malaria transmission and immunity with the primary data source being one study in Tanzania.

Outside of Africa, WHO applies a CFR of 0.3% (range 0.15% to 0.45%) to the total number of estimated cases of *P. falciparum*. A literature review of malaria CFR yielded
values that range between 0.1%-0.4% among all malaria cases and higher rates of 3%-33% among cases admitted to hospital. The ERG was not convinced that there was currently a strong case for changing WHO’s choice of 0.3% CFR among all malaria cases. Additional consultation should be taken regarding a CFR for *P. vivax*.

**IHME malaria mortality estimates. Christopher Murray**

IHME spearheaded the recently-published Global Burden of Disease Study (GBD) 2010, which generated estimates of morbidity and mortality of nearly 300 causes in a highly comparable way. The 5 principles of cause of death (CoD) modeling used by IHME include 1) identify all available data, 2) maximize comparability and quality of each dataset, 3) develop a diverse set of plausible models, 4) assess the predictive validity of each plausible individual model or ensemble of models, and 5) choose the model or ensemble model with the best performance with regard to in- and out-of-sample predictive validity tests. For CoD modeling, the 4 families of models considered are 1) mixed effects linear models of the logit cause fraction, 2) mixed effects linear models of the log mortality rate, 3) spatial temporal models of the logit cause fraction, and 4) spatial temporal models of the log rate. IHME supports putting faith in data and limiting choices based on expert opinion, and has developed its methods accordingly. Ensemble modeling, used in the Netflix Challenge and weather forecasting, uses weighted averages of individual models. The ability to use multiple models and to test them with predictive validity helps eliminate the need for a researcher to select a preferred model.

Some of the predictive validity tests include train (70% of the data) and test (2 x 15% of the data) samples, knocking out historical data or using knock-outs that mimic the pattern of missingness in the data. The root mean square error (RMSE), the predictive validity of the first difference, and the percent of data included in the uncertainty interval are used as metrics of model strength.

The covariate selection process tested all combinations of identified covariates, such as rainfall, ITN coverage, Lysenko patterns of malaria risk, MAP PfPR, female education, etc. Other covariates such as interactions between drug resistance and PfPR, and HIV seroprevalence (to account for misclassification of HIV deaths to malaria) were also examined, but not retained in the final modeling process. Cases of malaria were not included as a covariate. Although the covariate selection process may select models with collinear covariates, the aim of the Cause of Death Ensemble model (CODEm) is to generate predictive models with the best fit, not evaluate causal relationships.

In addition to available VR data, VA and subnational VA data from both published and unpublished studies were included. The ITN effects are driven primarily by studies in Ghana and Zambia where the VA studies report ITN coverage. A limitation of both the IHME and CHERG analyses is a dearth of CoD data during the period of ITN scale-up.
The dependency of malaria mortality estimation on VA studies introduces a wide array of uncertainty and unreliability. Most VA studies rely on physician coding (PCVA), which has an accuracy of less than 45% at the all-cause level. Based on the sample of 12 thousand deaths from the 5 GC-13 study sites (Philippines, Mexico, Andhra Pradesh, Uttar Pradesh, Tanzania) in a VA validation study, physicians correctly assigned the cause of malaria to a true malaria death 30% of the time. It may be of concern that few of these areas have high malaria endemicity; further study is required to examine physician coding in areas of higher malaria risk. Specifically, performance of VA at different levels of malaria risk could be evaluated by conducting studies in several areas whose primary difference is malaria endemicity. Looking at the VA validation study, comparing the cause fraction of death from gold standard diagnosis and that from VA assigned cause of death shows a substantial systematic bias to over-assign malaria as the cause of death when the true cause fraction is below 10%. In this way, VA studies conducted among populations with a low true cause fraction of death for malaria are more likely to report overestimates of the malaria cause fraction of death and studies conducted among populations with higher true malaria cause fractions are more likely to be accurate. The pattern holds for both children and adults. The generalizability of these results, and the underlying true diseases that are commonly coded as malaria should be areas of further study. Giglioli’s study in Guyana was mentioned as an example of a natural experiment in malaria cause of death coding before and after implementation and control phases. The magnitude of the overestimation of malaria cause fraction where the true cause fraction is low was not adjusted for in the modeling (VA results were not adjusted at this level in the overall GBD study due to the effect on other disease’s cause fractions). The quality of the gold standard diagnosis in the validation study was not assessed though it was assumed to be high given the reputation of the chosen sites. It was noted that the validation study site in Tanzania was not the same as a site in the same country where a quality of diagnosis study showed substantial overdiagnosis of malaria.

Deaths assigned to garbage codes (ill-defined or impossible causes of death, such as from disseminated intravascular coagulation or unspecified parasitic disease, unspecified fever, convulsions) were redistributed based on observed proportions or information from studies. This may be problematic because in areas of high malaria endemicity, doctors recording a cause of death are likely to know which deaths are due to malaria and which are not; therefore, if a death is coded as “other parasitic”, it is likely truly not malaria. In published studies, up to 10% of under-5 deaths are misclassified; in all studies up to 30% can be. Currently, the uncertainty in the garbage code redistribution process is not propagated through the IHME modeling process due to computational limitations.

IHME’s high estimates for adult deaths are driven empirically by verbal autopsy data in older age groups and by redistribution of deaths from unspecified causes to malaria. For example, in South Asia age 60+, a large number of unspecified deaths are reassigned as malaria resulting in a 2.5 fold increase in malaria deaths. Redistribution of deaths from unspecified causes resulted in about 20% increase in malaria deaths globally. Other studies also show a significant number of deaths in the oldest age groups, but have generally been assigned out of malaria owing to perceived implausibility.
The results show a peak of deaths in 2004. The covariates that have the most influence on the predicted trend are ITN coverage, \textit{PfPR}, and antimalarial drug resistance. Another key finding is the level of uncertainty in predicting malaria mortality. While for cardiovascular disease the RMSE hovers around 0.5, the RMSE can be as high as 1.45 in some age-sex-region groups for malaria, which is not a surprise given the generally non-specific nature of malarial illnesses and the overlap with other febrile conditions.

After all diseases are modeled, the program CoDCorrect sums the draws from the posterior distribution of each cause and scales them to equal the draw of the all-cause mortality distribution for each country-year-age-sex group. The net effect of this process is that causes that have larger uncertainty are scaled up more than causes that are more certain; this approach is better than a multinomial approach because it is better suited for situations of spatial and temporal correlation. After “squeezing,” malaria deaths only change by 10% at the global level, but the country-level results can be quite different, primarily due to the large number but high uncertainty of malaria deaths in DRC and Nigeria.

There are now plans for the GBD study to be updated yearly; it will continue to re-predict back to 1980. The anticipation is that over the years, the numbers will fluctuate less and less and converge on well-validated estimates. IHME has also been requested to produce estimates for a wider range of causes of death and to include forecasts for the next 15-25 years. The downsides to forecasting include the reliance on large assumptions and the concern that policymakers may rely too heavily on projections whose assumptions are not evident to them.

CODEm methods produce similar results for children as the WHO methods do, but vastly different estimates of adult deaths. Tom Smith’s hypothesis is that VA studies are more accurate for children than for adults. IHME could rerun its models without the redistribution of VA deaths to see how much the results change. Ideas for validation of adult death estimates include surveillance of adult febrile illness, which would involve performing an HIV test, chest X-ray, and RDT on each patient. Ideally, odds ratios of adult deaths given various levels of parasitaemia should be generated. Adult mortality case-control studies should also be conducted. Cases would be adult deaths in hospital (where the severely sick patients are all given an RDT prior to death), and controls would be age- and sex-matched individuals from the same communities (with same \textit{PfPR}). The Ghana DSS sites could be a resource for examining adult malaria deaths, and a proposal could be developed to appeal for Gates Foundation funding to run a case-control or cohort study to elucidate the issue of adult deaths appearing in CoD coding.
Ways forward for malaria morbidity estimation.

1. For 2013, WHO should continue to estimate case numbers as currently, but WHO should vary the value of ITN effectiveness used on the post-hoc ITN adjustment to examine the effect of doing this on estimates. Using MIS data, WHO should examine the test positivity rate from survey finger/heel sticks among children who had a fever and sought care as opposed to those who had a fever and did not seek care.

2. In 2014 and subsequent years, it is recommended that WHO case estimates are derived from surveillance data for countries outside of Africa and selected countries in Africa with adequate surveillance systems as is presently done. For countries in Africa that lack adequate surveillance data, it is recommended that WHO derive case estimates from maps of estimated current parasite prevalence and population density assembled by MAP. This requires MAP to develop methods to estimate parasite prevalence by year for 2000 to 2014. Models of the relationship between prevalence and incidence will then be used to derive case number estimates. In refining the prevalence-incidence model, survey data (not just longitudinal studies, which may be biased by treatment of incident cases) and seasonality data should be incorporated, as well as other covariates (including treatment). In the WMR 2013, WHO should clearly state its plan to change the methodology in 2014 for sub-Saharan Africa.

3. As surveillance systems are strengthened in Africa it should be possible for case estimates to be derived from surveillance systems in an increasing number of countries. WHO should develop clear criteria that determine when a country in sub-Saharan Africa is ready to transition from the risk-based approach to the surveillance-based approach. These should include comparing parallel estimates of case numbers derived from surveillance and risk-based approaches.

4. For countries which have abundant parasite prevalence and surveillance data (such as Indonesia and Zambia) it is recommended that MAP/WHO apply both the surveillance method and the risk-based method and compare the results to understand why differences arise and in what settings a surveillance approach or risk-based approach might be preferred. Further work in resolving uncertainties in estimates may also be possible in India through the National Institute of Malaria Research.

5. WHO should aim to report not only on malaria cases (defined as any episode of fever with parasites) but also aim to estimate the number of infections, malaria attributable fever cases and severe malaria cases.

6. WHO should further examine how the HIV team estimates HIV infection rates to see whether there are lessons to be learned from them.

7. While estimates produced by WHO HQ would make use of the full computing capacity offered by MAP, country consultations will continue to be crucial in order to understand data quality and anomalies, and to validate results. There will be value in
developing a stripped down version of the cartographic approach that can be implemented on a spreadsheet which countries could employ themselves.

8. MAP/WHO should identify countries in which there are a dearth of prevalence data, as well as those with limited studies examining the incidence-prevalence relationship, and work with partners to find ways of filling the gaps. Future surveys should consider collecting prevalence data from a wider range of age groups and ask questions about why people do not seek treatment for fever. ERG members have agreed to compile a list of data that could supplement the MAP database.

9. Additional prevalence data could be collected through RDTs at antenatal visits (a population that has been used extensively for estimating HIV prevalence rates), EPI visits, or when testing for helminths in school deworming campaigns. These additional data from sentinel sites on malaria parasite prevalence could be used to strengthen cartographic methods of prevalence estimation.

Ways forward for malaria mortality estimation

1. Some concern was expressed about both the (over) simplicity of WHO’s estimation methods and also about IHME’s estimate of the large number of adult deaths in sub-Saharan Africa, based predominantly on a limited number of verbal autopsy studies. The problem of discrepant estimates for adult deaths in sub-Saharan Africa from IHME and WHO was not resolved and is unlikely to be resolved in the short-term. For 2013 it was recommended that WHO continues to estimate malaria deaths as currently but considers including *P. vivax* mortality. WHO should clearly present the uncertainty in its estimates and the reasons for the discrepancies between its and IHME’s estimates. Ways forward beyond 2013 are not yet clear. Some areas of further research were proposed, however:

2. **Assembling existing data to examine the evidence-base for the IHME estimates of malaria mortality in adults.** The IHME method relies heavily on verbal autopsy studies and research is required to determine why these studies are indicating higher proportional mortality rates from malaria than seems to accord with clinical experience and opinion. WHO and IHME should also engage with INDEPTH to investigate the reliability of the designation of malaria deaths in adults in verbal autopsy studies - Seth Owusu-Agyei should be involved in these discussions and can provide a link with INDEPTH research. In addition, the proportion of adult deaths attributed to malaria should be plotted against malaria endemicity to investigate whether or not this shows an expected pattern. Tom Smith’s model should be re-examined with the age 65+ data included to see how the results compare to IHME’s.

3. **Assembling high quality data on malaria deaths in those aged over 5 years.** Peter Byass, Fred Binka, Alan Schapira, Brian Greenwood (11 African RTS.S sites), John Aponte (Mozambique and Brazil sites) and Ashwani Kumar (India study of mortality in 3 different areas with different API) are potential sources of information and data
to further examine adult mortality. It may be useful to also examine the age
distribution of admissions to hospital for severe malaria.

4. *Empirical research to reduce dependence on VAs for malaria.* Alternative sources of
data on malaria specific mortality rates would be: (i) case-control studies comparing
malaria parasite prevalence rates in those dying (of any cause) and controls (hospital
and/or community controls), and (ii) prospective (cohort) studies of all-cause
mortality in relation to malaria exposure as measured either by prevalence or EIR.
Data relevant to (ii) exist in a number of DSS sites, in particular the MTIMBA
database. Malaria prevalence surveys have been carried out in many DSS, making it
possible to consider a multi-site prospective analysis of age-specific mortality in
relation to prevalence This could probably be done for at least the following sites:
Kilifi, Manhica, IHI (Kilombero-Ulanga, Rufiji?), CDC Kisumu, Kintampo,
Navrongo, Farafenni, and Basse, The Gambia.

5. *Examining the effect of model choices on estimates:* CHERG inclusion criteria may
have caused several high-quality VA studies to be excluded, and investigation is
recommended as to why some studies were dropped and the impact of doing so. ERG
members with knowledge of VA studies will compile a list of studies they believe
should be included that may have been not included. Important differences in results
may be illuminated if CHERG runs their models on the same malaria VA datasets
used by IHME. It would also be of interest to rerun IHME’s CODEm procedure
without redistribution of unassigned deaths from VA studies. Since VA studies are
the heart of malaria mortality estimation, and many of the differences between
WHO’s and IHME’s estimates may be due to redistribution of VA deaths to malaria,
the ERG is interested to see whether IHME’s adult death estimates change
substantially if the redistribution step is skipped.

**Conclusion**

While there seems to be a reasonable way forward with respect to the estimation of
malaria case numbers, including retrospective adjustments of numbers in previous years,
the most appropriate method for estimating malaria deaths is currently unclear. After
reviewing this report and engaging in a follow-up teleconference, the ERG will decide on
the necessity for, and the timing of, any additional meeting. As estimation methods and
relevant data for estimating the burden of malaria are likely evolve, the ERG and MPAC
should consider whether a standing committee on malaria burden estimation is required
to advise WHO on a continuing basis as new studies and methods are developed.
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