Meeting Report

Opening remarks
Dr. Robert Newman, director of the WHO Global Malaria Program (GMP), welcomed the members of the Malaria Burden Estimates Evidence Review Group (MBE-ERG) and outlined some of the issues relevant to its work. He noted that the scale-up of malaria control interventions has focused attention on measuring progress in reducing the global malaria burden, including WHO’s malaria burden estimates reported in the World Malaria Report (WMR), as well as those reported by other groups. The specific tasks for the MBE-ERG, outlined in its Terms of Reference (see attached), include mapping a way forward in producing malaria burden estimates, with a focus on use of the estimates by WHO headquarters and member states, as well as describing how to obtain better data for input into those estimates.

Dr. Peter Smith, the MBE-ERG chair, described the group’s general timeline. Currently, three meetings are scheduled over approximately 18 months, with supportive work by group members in between. The first meeting is designed to outline relevant issues, the second to elicit further expert opinion, especially from groups directly involved in malaria burden estimation, and the third to develop recommendations to Malaria Policy Advisory Committee (MPAC) on the way forward, which will be included in the final meeting report.

Overview of malaria burden estimation, use of burden estimates and scope of the MBE-ERG

Brief overview of malaria burden estimate methods
The group was provided with a brief overview of the different malaria burden estimates currently employed related to numbers of clinical cases and numbers of deaths.

For estimating the number of malaria cases, approaches can be grouped into two broad categories. One approach is case report based, in which reported cases are adjusted for health facility attendance, level of diagnostic effort, and underreporting in the health sector. The second can be described as risk based, in which geographical areas are categorized by level of malaria risk; risk is converted to malaria incidence based on relationships derived from longitudinal studies and adjusted for the estimated deployment of preventive measures (e.g.
bed-nets); the malaria incidence is multiplied by the relevant population to obtain the number of malaria cases.

Approaches to estimates of malaria deaths fall into three categories, two of which are similar to those for case estimates. There is a risk-based approach, in which the level of malaria risk is linked to malaria mortality rates and population through mapping. Another can be described as case report based, in which adjusted case counts are multiplied by a fixed case fatality rate (CFR) to derive number of malaria deaths. Lastly, a vital registration (VR) based approach has also been used, which may provide direct estimates from recorded deaths.

Group discussion noted: that uncertainty varies in these approaches; ultimately we need better reporting; implementation of diagnostics can be transformative in understanding malaria burden in a given area; it can be useful to understand motivations for reporting as these may drive changes in reported numbers.

**Uses of estimates at international level**
Uses of malaria case and death estimates at the international level were reviewed. These include: 1) Global advocacy for malaria control; 2) Global reporting to targets, such as for Millennium Development goals (MDG); 3) Global burden of disease analysis and the prioritization of malaria in relation to other conditions; 4) Prioritization of countries for resource allocation (e.g. Global Fund) – it was noted to be problematic for prioritization when different burden estimates were derived for a country with different methods. Discussion noted that, for these uses, estimates for malaria cases and deaths need to include the ability to measure change over time.

**Uses of estimates at national level**
Discussion on use of malaria burden estimates for Brazil, India, Tanzania, and Ghana highlighted how their use differs by country. For example, some countries made little use of the WHO estimates and used their own data, whereas others used WHO data for Global Fund applications. It was noted that WHO is required to follow a country consultative process for clearing estimates by country. Because this process currently takes several months, by the time country level estimates for one year are cleared, new global and regional estimates for the next year are ready for the WMR. Consequently, country level estimates for the previous year are out of date and global and country level estimates have not been released together.

**The scope and purpose of burden estimation: what does ERG want to achieve?**
The discussion on the scope and purpose of burden estimation noted that some of the first malaria mortality burden estimates proved useful for advocacy, even though the methods were crude. Methods for burden estimates need to further improve to meet needs of tracking progress in control. ERG should also consider how to improve the data inputs as well as the estimation methods, and that scale up of malaria diagnostic testing will be a key component of improved burden estimation. The group may also consider how plasmodium infection surveillance, in sentinel populations and in the community, could feed into malaria burden
estimates, as well as the role of tracking asymptomatic infections and measuring level of infection in individual patients.

**Review of malaria burden estimates**
The group was provided with supportive documents describing recently completed malaria burden estimates for cases and deaths (see page 8 for references). The different methods were summarized and discussed.

**Methods for malaria morbidity estimation: the Malaria Atlas Project (MAP) approach**
In brief, the MAP group uses a risk-based approach for all countries with stable malaria risk, a fixed incidence (1 case/10,000) for unstable areas, and accepts national reported case counts for seven countries considered to have complete and reliable national reporting. For countries with stable risk, MAP has constructed a map of *P. falciparum* parasite prevalence (PfP) based on community surveys conducted over 1985-2008. Parasite prevalence is converted to malaria incidence using a modeled relationship derived from malaria incidence survey data. Malaria incidence rates are then applied to a map of human population density in malaria endemic areas to derive malaria case counts. This results, for 2010, in an estimated 451 (349-553) million malaria cases globally, 271 (24-301) million in Africa, 177 (89-271) million in Asia, and 3 (1.2-6.8) million in the Americas. India accounts for most of the uncertainty in the global estimate due to the relative dearth of parasite prevalence data available.

Discussion of the MAP approach focused on how PfP surveys used may be biased in time and place and on the validity of the modeled prevalence-incidence relationship. The most recent PfP surveys available for certain countries may have been conducted many years ago and may not reflect the current malaria situation, or the surveys were conducted in areas not representative of the country as a whole. All-age clinical incidence is modeled from malaria incidence surveys matched by time and place to age-standardized PfP surveys and results in a large uncertainty range in the prevalence to incidence conversion. Availability of more recent nationally representative surveys may address these issues.

**Methods for malaria morbidity estimation: the WHO approach**
WHO employs a case based approach (Method 1) for countries considered to have reliable case reporting systems, and a risk based approach (Method 2) for high transmission countries considered to have less reliable case reporting systems. In Method 1, case reports are adjusted for facility attendance for fever from DHS surveys, the proportion of suspect malaria cases tested (derived from country reported slide positivity rate), and completeness of reporting (from country reports to WHO). WHO Method 2 starts with the MARA map, a risk map based on climactic suitability for malaria transmission. (WHO did not previously have access to the MAP PfP based map, though an agreement has now been reached for WHO to access the MAP data.) Transmission levels in MARA map (high and low) are converted to incidence using a modeled relationship derived from malaria incidence studies, stratified by three age groups ( <5, 5-14, and 14+ years). Incidence for each risk-age category is multiplied by population to
calculate the number of cases. Incidence is reduced by 0.5% for each 1% increase in percentage of households owning an ITN.

WHO estimated 216 (149-274) million cases in 2010, 176 (113-293) million in Africa, 28 (23-35) million in Southeast Asia, all less than MAP. For Africa, the largest difference is for Nigeria; in Asia, India accounts for the largest difference. WHO questions MAP estimates for India, as they imply higher malaria incidence than anywhere in Africa, and would require a much higher SPR than reported or higher fever incidence than seems reasonable.

Discussion on Method 1 focused on how treatment-seeking and health facility reporting rates could be overestimated; for Method 2, use of the MARA map, validity of the transmission to incidence relationship and the effect of ITN coverage in the model were questioned.

Methods for malaria mortality estimation: the Institute for Health Metrics and Evaluation (IHME) approach
The approach to malaria mortality estimates employed by IHME in their recently published paper in the Lancet can be described as risk based. They use identified VR and verbal autopsy (VA) studies, corrected for misclassification due to so called “garbage codes”, to derive cause fractions of deaths. These are then modeled for missing place and time for 8 region/sex/age categories. They include three measures of risk, the Lysenko map of endemicity zones, the MAP PfP based map and WHO populations at risk, and covariates for other factors, including rain, health care access, drug resistance, ITN, IRS, income and education. The resulting models are ranked by an out of sample predicted validity method and all included in an ensemble model with varying weights based on their rank. By this method, IHME estimates 1.2 million (929,000-1,685,000) malaria deaths worldwide, compared to WHO’s estimate of 655,000 (537,000-907,000). Given the large uncertainty bounds, the only true difference in the two estimates is for deaths in ages 5 years and over Africa (307,000-658,000 for IHME compared to 42,000-75,000 for WHO).

The discussion on the IHME estimates noted the difficulty in following the description of methods put forth in the paper. In addition the ratio of adult to child malaria deaths indicated in the IHME study was not consistent with clinical experience, or other studies, and calls into question the validity of the results. It was noted that most sites in IHME’s validation study were either free of malaria or had low levels of transmission, and therefore not a good basis for validation. In the one site with significant amounts of malaria transmission previous studies had suggested that the quality of laboratory diagnosis was poor, which could lead to over-diagnosis of malaria in the validation study and to overestimates of the total number of malaria deaths.

Methods for malaria mortality estimation: the WHO approach
Outside of Africa, WHO uses the adjusted malaria case count multiplied by a fixed CFR (0.3%). The CFR is based on a single study from Burma 1998. For Africa, WHO starts with a risk map to delineate transmission level into two categories, “high” or “low”. A mortality rate for children
<5 years is derived from longitudinal studies for each level of transmission, and by urban or rural area. Deaths in those >5 years are derived from modeled relations of malaria transmission intensity (entomological inoculation rate) and age specific malaria death rates. The numbers of deaths are then estimated by multiplying the population at different levels of risk by the derived malaria death rate for each age, urban-rural category. Death rates are reduced 0.5% for each 1% increase in percentage of households owning at least one ITN. The Child Health Epidemiology Reference Group (CHERG) index for child deaths is entered into the model as a covariate so that the estimated malaria deaths fit into the estimates of deaths for all causes.

Discussion noted that other data may be available to refine the fixed CFR applied to adjusted case reports for countries outside Africa and for the mortality rate by level of transmission for countries in Africa. India has embarked on a study to estimate malaria deaths using a modified WHO approach with alternate values for SPR and CFR.

**Other possibilities for burden estimation**

Other measures to assess malaria control were reviewed. These include entomologic (mosquito abundance and age), parasitologic (prevalence, in convenience sample populations), clinical (severe cases and admissions, malaria specific mortality in confirmed cases), and indirect ones (birth weight). The availability of these measures would be dependent on multiple groups, including academia, ministries of health operational research and routine information systems. Discussion noted that as their work proceeds, the MBE-ERG will need to think more about how these measures could be translated into high level burden estimates.

The group was also provided with a draft paper describing how not taking into account the effects of malaria treatment could lead to underestimates of malaria burden in both risk based and case report based approaches. For risk based approaches, treatment of cases in longitudinal studies, at a higher rate than usually observed in the community, likely lowers overall transmission, and, therefore, these studies may underestimate the true incidence-prevalence relationships. Similarly, treatment seeking for fever may be overestimated in surveys, since fevers for which treatment was sought are more likely to be recalled, and therefore the adjustment of case reports for care seeking may be inadequate. The paper proposes a new approach for estimating malaria burden based on the point prevalence of malaria-attributable disease.

**The way forward**

**Plans for this year’s WMR**

The question was raised what to do for this year’s World Malaria Report while longer term recommendations were being formulated by the ERG. Options discussed for this year include: producing new global and regional estimates for this year’s WMR (with same method as used in the past); not producing any new estimates for this year’s WMR; reporting country level estimates for 2010 (country clearance for these should be complete in time for the WMR 2012).
The group noted that all estimation methods for both cases and deaths were highly problematic and different methods had both weaknesses and strengths. Methods that use real current data are attractive, but are challenging currently in areas where the burden is greatest. A hybrid approach could be explored, combining the different methods in some way. The group noted the challenge in presenting uncertainty in the estimates and acknowledged the pressure to produce a single number – particularly for deaths.

Preparations for the next meeting
The group considered they had had a useful introduction to the current burden estimation methods but recognized that more details on current methodologies would be helpful. In accordance with the terms of reference for the MBE-ERG developed by GMP and MPAC, the process for inviting other groups who have worked on malaria burden estimates (MAP, IHME) to the next meeting was discussed. The invitation should be specific regarding presentation of methods—i.e. variables used, assumptions made, limitations—and also their willingness to collaborate on future burden estimate efforts. In particular, the group would wish to enquire of the modelers:

1. What are the main assumptions in your model?
2. What are your estimates most sensitive to in terms of assumptions or absence of data?
3. What data/information that could be collected relatively easily would be most useful in improving your model
4. How could your modeling methods be integrated with other modeling methods to produce (better) consistent estimates?
5. How good is your method at measuring trends in addition to absolute numbers?
6. How willing are you to share your basic data with other groups?

Examples from burden estimation approaches for other diseases may be relevant, for instance, what has been done by UNAIDS, and, therefore, UNAIDS modelers could also be invited to the next meeting. Input would also be useful from a country which has recently improved its data quality in surveillance and vital registration.

Time between meetings
The suggestion was made that the complex issue of improving malaria burden estimation may be best approached by breaking it down into smaller parts. For example, the group could focus on important smaller issues identified so far, such as age distribution of malaria deaths, case fatality rates, converting prevalence to incidence, and suggest specific studies to be done and groups that would be engaged.
Accordingly, three pieces of group work were identified that group members will be called upon to complete before the next MBE-ERG meeting, to be held during the first quarter of 2013.

1) Different group members would be asked to review each modeling method in order to lead the discussion at the next meeting to:
   - Identify the most important assumptions
   - Identify the most sensitive assumptions
   - Identify what data/information (easily collected) would improve model estimates.

2) Group members would seek to outline new approaches to estimating absolute numbers and/or trends – especially methods that would involve collecting data at national or sub-national levels.

3) Related to 2), group members would liaise with national malaria control programme staff and others to work out what data it might be possible to collect at national level (and assess its value to the national control programme).

The final meeting of the group was planned to be around June/July 2013.
REVIEW OF MALARIA BURDEN ESTIMATES - REFERENCE LIST

MALARIA CASES

MAP
http://www.malariajournal.com/content/10/1/378

http://www.malariajournal.com/content/8/1/186

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000290

WHO
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001142


World Malaria Report 2011, pg 72-75

MALARIA DEATHS

WHO/CHERG/MERG
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60549-1/abstract#


WHO. World Malaria Report 2011, pg 72-75
IHME
WebAnnex http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60034-8/fulltext