Malaria Policy Advisory Committee Meeting
11–13 April 2018, Geneva, Switzerland
Background document for Session 6

Meeting report of the WHO Evidence Review Group on malaria burden estimation methods

12–14 March 2018, WHO Headquarters, Geneva, Switzerland

1. Introduction

During the October 2017 meeting, the Malaria Policy Advisory Committee approved the convening of an Evidence Review Group (ERG) on methods for malaria burden estimation (MBE). The proposed Terms of Reference for this MBE-ERG were as follows:

1. Review existing methods for mortality estimation with a focus on addressing issues related to temporal trends in case fatality rate (CFR), age attribution of malaria mortality, and the role of geospatial approaches to modelling mortality estimation;
2. Revisit the pending recommendations from the ERG 2012–2013 in light of any new data, and develop proposals for best approaches to ensure those recommendations are fulfilled;
3. Re-focus on the indirect consequences of malaria infection and disease and their likely contribution to mortality (for example anaemia).

The main challenges regarding MBE identified for discussion were as follows:

1. As malaria parasitological diagnosis and routine reporting have improved considerably over the last few years in sub-Saharan Africa, several countries have reported, from the public health sector alone, more confirmed malaria cases than the whole population estimates generated by the parasite prevalence-to-incidence model. The implication is that in many of the very high burden countries, we are likely underestimating the burden of malaria morbidity;
2. The use of parasite prevalence as a covariate in the quantification of the malaria cause of death fraction also means that the effect it has on morbidity trends may be replicated in the mortality results;
3. Where routine information data are used, not all cases are tested and confirmation rates are sometimes below 100%. Available data are also often reported only from the public health sector, even though the private sector plays an important role. A substantial proportion of patients may not seek care and therefore will be missed by both public and private sector surveillance. Adjustments for confirmation, private sector reporting and non-treatment-seeking should therefore be made on the routine data.
4. The CFRs estimated for *Plasmodium falciparum (Pf)* and *Plasmodium vivax (Pv)* are computed using data from old studies. This approach fails to account for the substantial changes in malaria case management and the obvious variability between countries.

WHO/CDS/GMP/MPAC/2018.10

On 12–14 March 2018, the WHO Global Malaria Programme (GMP) and the Information, Evidence and Research (IER) departments convened the first meeting of the MBE-ERG in Geneva, Switzerland. The MBE-ERG was chaired by Professor Fred Binka (day 1) and Dr Rick Steketee (days 2 and 3). The objectives of the meeting were to provide advice to WHO GMP on the following questions:

1. What are the criteria for the use of routine data from sub-Saharan Africa? What levels of diagnoses and reporting rates over how many years would qualify a country in sub-Saharan Africa to transition from the parasite rate-to-incidence model to one based on adjustment of routine data. How does one apply these data to inform trends back to 2000?
2. What is the relationship between treatment-seeking for any fever, as used in routine reports of malaria data, and treatment-seeking for malaria fever?
3. What data are available to best quantify CFRs for *Pf* and *Pv* across different transmission and case management settings?
4. If routine data estimates are used for sub-Saharan African countries whose estimates were previously based on the parasite prevalence-to-incidence model, how do we integrate these into the analysis of the cause of death fraction for malaria?
5. How do we define and apply populations at risk to compute incidence from case estimates?
6. What are the best approaches for quantifying the severe and indirect burden of malaria?

This report summarizes:

- Presentations given by meeting participants;
- Challenges with current estimation approaches;
- Major discussion points arising; and
- Recommendations on how WHO should proceed with improving malaria morbidity and mortality estimation.

2. Summary of presentations and associated discussions

2.1 Estimation of malaria morbidity and mortality: overview and critical elements for consideration

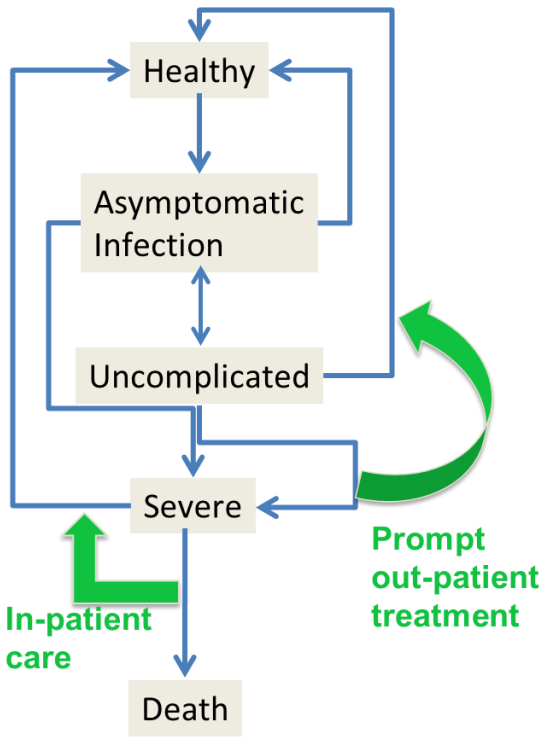
Presenter: Thomas Smith

The presentation began with an overview of the current approaches used to estimate malaria burden in terms of morbidity and mortality. Briefly, estimation methods in very low incidence countries with good-quality surveillance systems use official national data without adjustment. In low transmission countries with good-quality surveillance data with minor gaps, surveillance data is reported after adjustment for factors that bias estimates, including completeness of reporting, private sector use, and incidence among those who do not seek treatment. In high transmission settings, estimates are based on prevalence survey data according to known relationships between prevalence and incidence, also adjusted for key factors such as intervention coverage and access to treatment.

Issues with the current methodologies were highlighted. The use of different approaches and case definitions for different settings complicates comparisons between countries using different methods. With consistent case definitions and a good understanding of the relationships between data sources, it should be possible to shift between models; but this is not yet the case. It was suggested that the observed differences in trends could be due to the assumptions used in the modelling process or because the data sources used ultimately reflect different components of the malaria transmission system. With the increasing availability and quality of routine surveillance data resulting from the scale-up of DHIS2, such data should be accounted for in the estimates. Incorporating both sources of data into a hybrid modelled estimate was also highlighted as a potential way to improve current estimation methods.

Currently, the methods do not adequately allow for changes in treatment and case management. For example, the deployment of community health workers testing and treating cases in the community improves access to treatment, which is likely to increase the number of infections detected as part of routine surveillance. Current methods for estimating burden capture some of the effects of improved access but do not capture effects of treating infections earlier in the natural history on preventing, progression to severe disease or on mortality, and do not capture the effects of varying access to in-patient care on case fatality rates (Fig. 1).

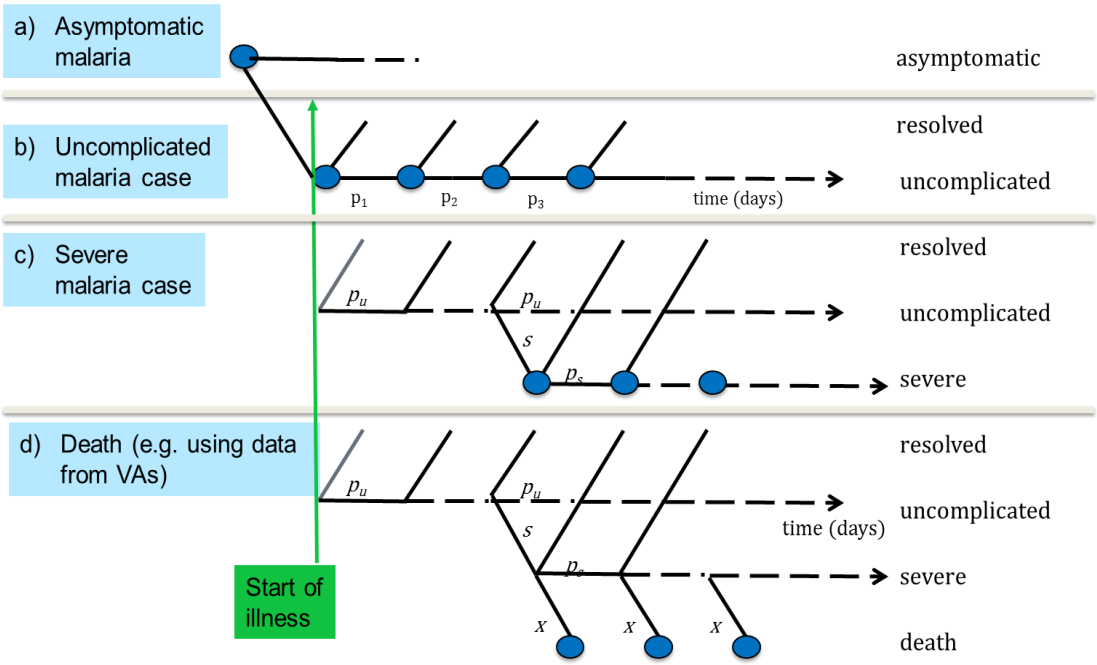
Fig. 1. The effect of treatment on malaria outcomes



One way to bring together data on effective coverage would be to build branching process models, parameterised using data on illness durations and care seeking, obtained from histories collected at different levels of the health care system (Figure 2). The data sources (blue circles in Fig. 2) should comprise cross-sectional community surveys, outpatient

interviews, admission interviews from in-patient facilities, and verbal autopsies. Analyses of such data could provide estimates of currently unknown variables such as the number of severe disease cases that do not reach health facilities. Finally, the over-reliance on verbal autopsies (VAs) was highlighted as a key challenge in mortality estimation. VA is typically the only data source available. However, VA is known to have poor specificity for malaria, as malaria can be both a contributory and an underlying cause of death.

Fig. 2. Branching process models for analysis of histories to estimate illness durations and recovery rates



Branching processes that might be reconstructed from history data (in this representation the health status is assumed to be updated every day. Dashed lines are intended continuation in the same state for an unspecified number of days.)

The ERG acknowledged that the CFR estimates being used to estimate mortality are based on a limited set of old studies and should be updated. Improvements in case management could mean that deaths are being overestimated in some transmission settings. Additional data on how changes in quality of care impact CFR across transmission settings are needed in order to refine the assumptions currently being used to estimate mortality.

2.2 Current WHO malaria morbidity burden estimation methods

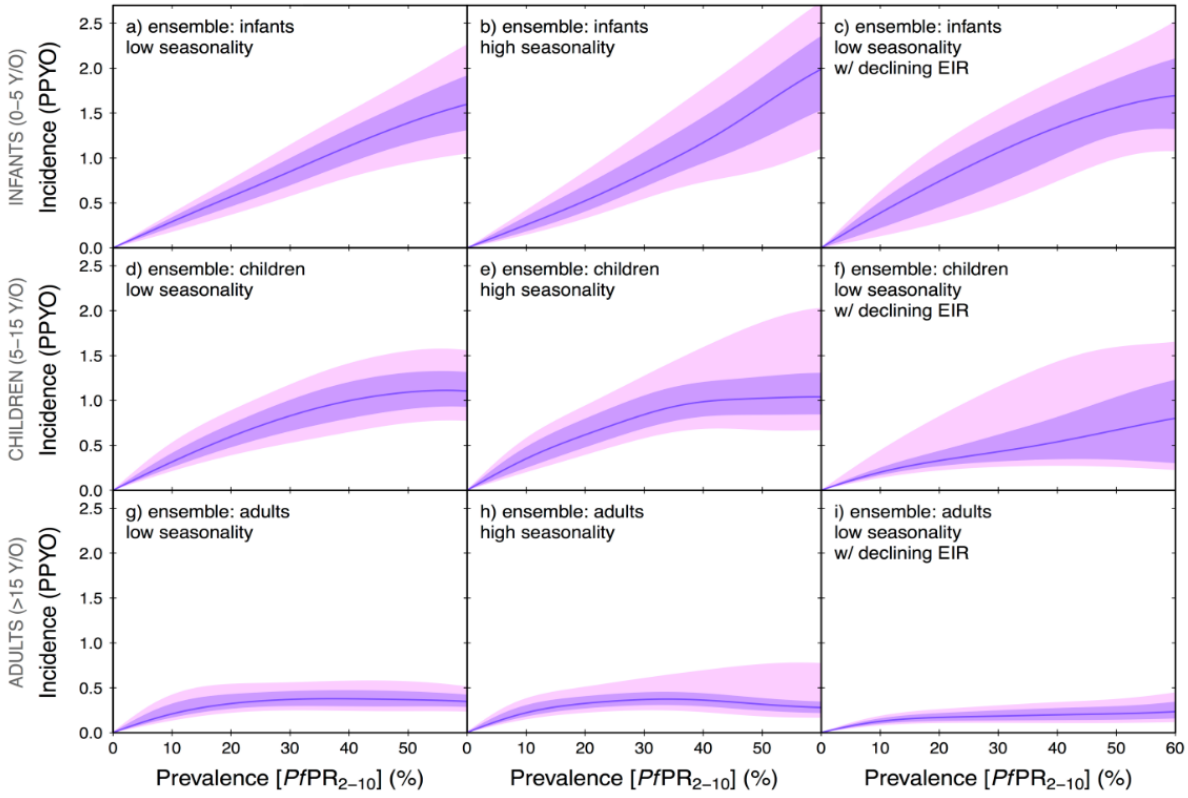
2.2.1 Moderate and high transmission sub-Saharan Africa

Presenter: Pete Gething

In the World malaria report (WMR) 2017 [1], the number of cases in moderate to high transmission countries in sub-Saharan Africa was estimated according to the Malaria Atlas Project (MAP) estimates of the *Pf* parasite rate (*Pf*PR)-to-incidence relationship within a model-based geostatistical framework [2,3]. This approach was used for 86% of the cases reported. Recent refinements to the geostatistical modelling framework were presented. Improved geospatial insecticide-treated net (ITN) coverage and effective treatment rate

models, as well as indoor residual spraying (IRS) coverage are used in the estimation of *Pf*PR. Treatment rate is estimated according to the specific drug used per country, the efficacy of that drug and other key determinants over time, as reported from household surveys. Inputs are then converted to *Pf* case incidence according to the *Pf*PR-to-incidence modelled relationship using the ensemble fit of three mechanistic malaria transmission models (Fig. 3). The *Pf* case incidence, defined as patients having clinical symptoms and parasite densities above a given threshold, and the number of non-fatal outcomes are then estimated per pixel. The malaria estimates for sub-Saharan Africa are currently based on 37 217 survey clusters from 48 countries conducted between 1975 and 2017.

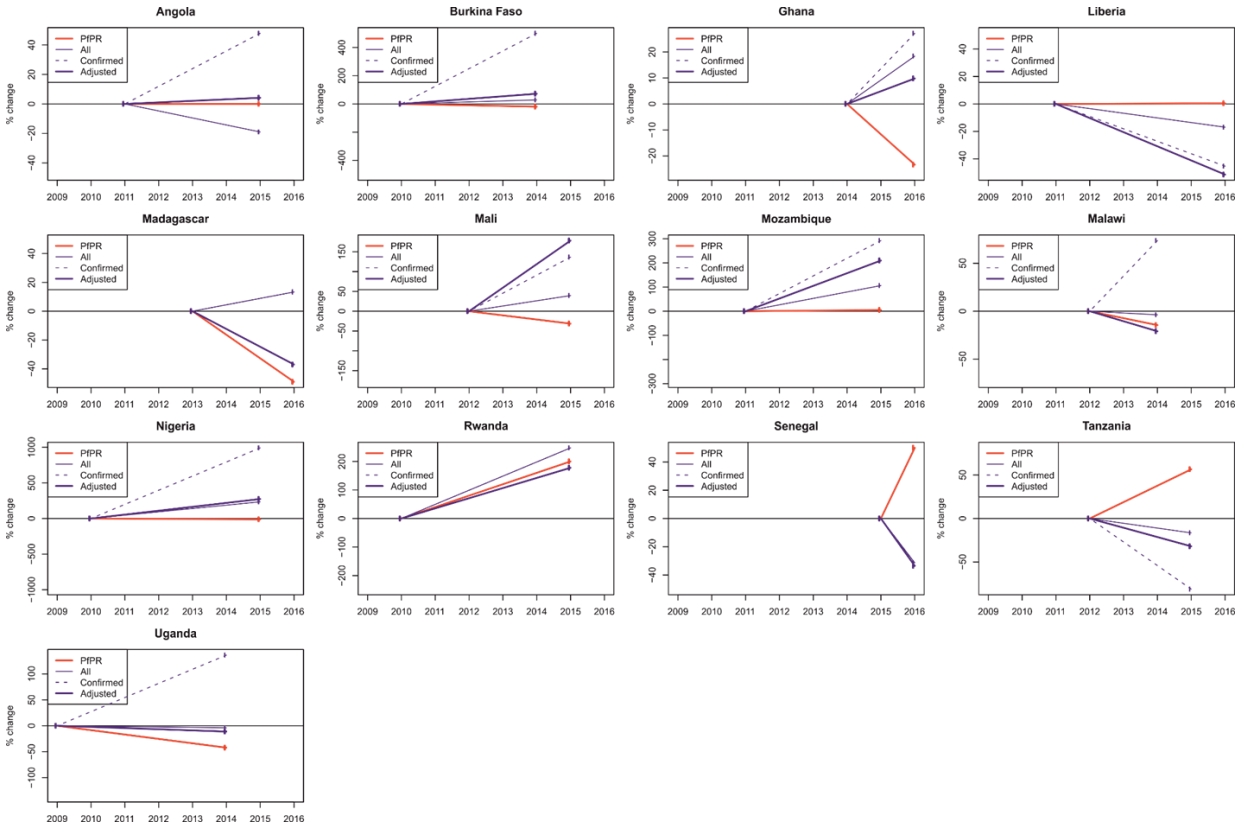
Fig. 3. Ensemble models of *Pf*PR-to-clinical case incidence used by MAP [3]



The trends over time according to the different estimation methods (*Pf*PR-to-incidence model and adjusted routine data) were compared. Although the methods showed consistent trends in some of the countries, most often the trends diverged (Fig. 4). Suggestions as to why the modelled trends were discordant included: on the *Pf*PR side, a lack of data for some countries in recent years, uncertainty in trends of determinants, and failing to adequately capture the relationship being estimated. Another potential reason discussed for the discrepancies between models was the different case definitions used by the different approaches, which made comparisons between the two problematic. The *Pf*PR-to-incidence model estimates the number of infected individuals with fever and parasitaemia exceeding a density threshold (>5000 p/ul). The adjusted routine surveillance data estimates those captured in a health care setting according to the case definitions in treatment guidelines (mainly fever with parasitaemia) tested using routine diagnostics. The latter may include malaria-positive patients with an incidental fever caused by another pathogen (e.g., influenza), whereas the former assumes that any fevers in parasitaemic

individuals with a low parasite density are incidental and do not count as a case. This decision is based on a relationship built on relatively old active case detection (ACD) data. The proportion of incidental malaria could be particularly large in high transmission countries.

Fig. 4. Relationship between *Pf*PR and trends in case reports in selected countries



The ERG emphasized the importance of having a consistent case definition, as well as identifying the most critical sources of bias and how best to quantify them as the critical next steps in improving estimates.

2.2.2 Low transmission Africa, outside Africa

Presenter: John Aponte

Methods used in countries with low levels of malaria transmission and routinely reported data that are of sufficient quality to inform burden estimation were discussed. Briefly, for some countries with very good surveillance systems, the reported data are used without adjustments. These account for about <1% of the cases reported in the WMR 2017. For other countries with good surveillance systems but with considerable private sector use or where not all patients access treatment, routinely reported data are adjusted using a formula (equation 1) to address key biases, including incomplete reporting and cases not confirmed by a diagnostic test. The estimates from the public sector are added to the estimated cases that seek treatment in the private sector or do not seek treatment in a formal establishment. Standard methods are applied to provide estimates of uncertainty around the input parameters according to defined distributions. Country-level estimates are then aggregated into regional and global figures. This method accounts for 14% of all malaria cases reported in the WMR 2017.

Equation 1 – estimating malaria cases from routine reports

$$= \frac{\left(Cases_{public\ confirmed} + Cases_{public\ presumed} \times Test\ Positivity\ Rate_{\ public}\right)}{Reporting\ Completness}\left(1 + \frac{Treatment_{private}}{Treatment_{public}} + \frac{No\ Treatment}{Treatment_{public}}\right)$$

Despite the advantage of relying directly on actual case data, several challenges were identified with this approach. First, reporting rates can be highly variable over short intervals, and some of the statistical distributions used to produce estimates of uncertainty are inefficient or do not reflect the data well. Next, the adjustments assume that the test positivity rates in the public sector are similar to those of individuals attending the private sector or not seeking treatment. It is plausible that, in many settings, this assumption may not hold, particularly in populations experiencing high transmission and low access to care, or in low malaria transmission settings with low access to care and a considerable proportion of fevers for which care is not sought in the public sector. It is also unclear how overall treatment-seeking for fever relates to treatment-seeking for malaria.

The latter two points, in addition to the different case definitions used between methods as described above, were identified by the ERG as important gaps to improve understanding. Addressing these challenges could result in estimates that are a better reflection of the true state of malaria, and may partially explain some of the discrepancies between the burden estimations derived from the two methods.

2.3 Current WHO malaria mortality estimation methods

2.3.1 Quantification of cause of death methods

Presenter: Colin Mathers

Harmonization of country-specific estimates for total child deaths has taken place as part of the UN Inter-agency Group for Child Mortality Estimation (UN-IGME) [4,5]. The approach used assesses trends in neonatal, infant and under-5 mortality. Data sources being relied upon for estimation include vital registration (VR) data, if available; birth histories via Demographic and Health Surveys and Multiple Indicator Cluster Surveys, which provide direct estimates of infant mortality rate (IMR) and under-5 mortality rate (U5MR); and summary birth histories via any household survey, which provide indirect estimates collectively known as the envelope (Fig. 5). Briefly, for all-cause under-5 mortality, multi-cause models using VR and VA data are used to estimate deaths. Covariate selection is carried out through a stepwise selection of explanatory variables that are fit simultaneously to the model in order to estimate the proportionate cause of death. The multi-cause model is then applied to study-level data according to a standard multinomial logistic regression framework fit. The resulting fit is then applied to country-level covariates to derive country estimates. Post-hoc adjustments are then made to account for recently scaled-up interventions for areas with no reported malaria transmission.

The different data sources used to estimate mortality each have inherent biases that affect their validity. Issues identified include sampling errors during surveys, omission of deaths from surveys or death registration, misreporting of child's age at death (direct methods only), selection biases, or violations of assumption in the indirect methods. Analysing the data requires regression techniques to smooth and project trends. Data quality also needs to be assessed in order to exclude data that do not meet the inclusion criteria or to weight data as appropriate. Results of the child mortality estimation are available online through www.childmortality.org. Cause categories and estimation inputs and methods are listed in Fig. 6.

Fig. 5. Causes of death estimation methods

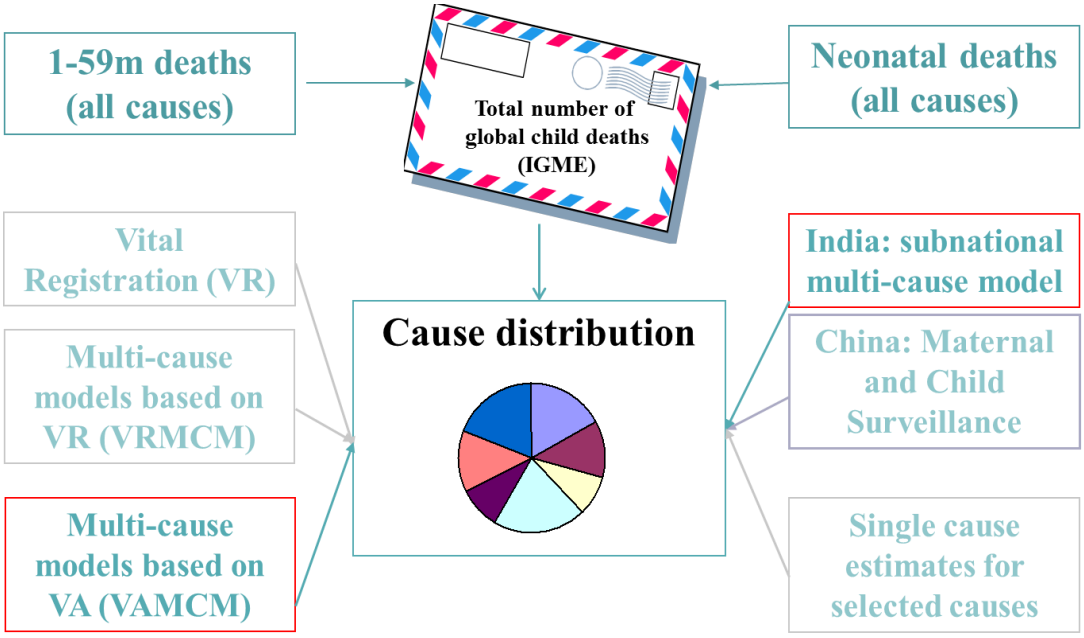


Fig. 6. Mortality codes for under-5 mortality estimation, including all causes as well as the data source and modelling approach used to derive estimates

	Causes	Source/method
1	**ALL CAUSES**	UN-IGME
2	HIV/AIDS	UNAIDS
3	Diarrhoeal diseases	VR, VRMCM, VAMCM, India model, China model
4	Pertussis	IVB (folded into "other Group 1" in 2017 update)
5	Tetanus (high mortality only)	Neonatal tetanus model
6	Measles	IVB "Ferrari" model
7	Meningitis/encephalitis	VR, VRMCM, VAMCM, India model, China model
8	Malaria	VAMCM plus WHO (from health system/survey data)
9	Acute lower respiratory infections	VR, VRMCM, VAMCM, India model, China model
10	Preterm (direct complications)	VR, VRMCM, VAMCM, India model, China model
11	Intrapartum-related complications	VR, VRMCM, VAMCM, India model, China model
12	Neonatal sepsis	VR, VRMCM, VAMCM, India model, China model
13	Other Group 1	VR, VRMCM, VAMCM, India model, China model
14	Congenital anomalies	VR, VRMCM, VAMCM, India model, China model
15	Other noncommunicable diseases	VR, VRMCM, VAMCM, India model, China model
16	Injuries	VR, VRMCM, VAMCM, India model, China model
17	War and disasters outside the envelope	WHO estimates

VR: vital registration; VAMCM: verbal-autopsy-based multinomial model; VRMCM: vital registration multi-cause model.

Overarching challenges with the all-cause under-5 mortality estimates were discussed. First, the estimates use the year 2000 as the baseline, as the initial goal was to assess improvements according to the Millennium Development Goals (2000–2015). However, methods and time series across this period should be consistent across groups of epidemiologically similar countries. The cause-specific mortality must add to envelopes (Fig. 6), with limited exceptions for major epidemics and mortality shocks such as conflict, which

are smoothed out to identify trends and added in as post-hoc adjustments. Better methods may be available to refine this approach. Finally, single-cause models generally can only be used where the cause is responsible for a relatively small proportion of deaths, which does not include malaria.

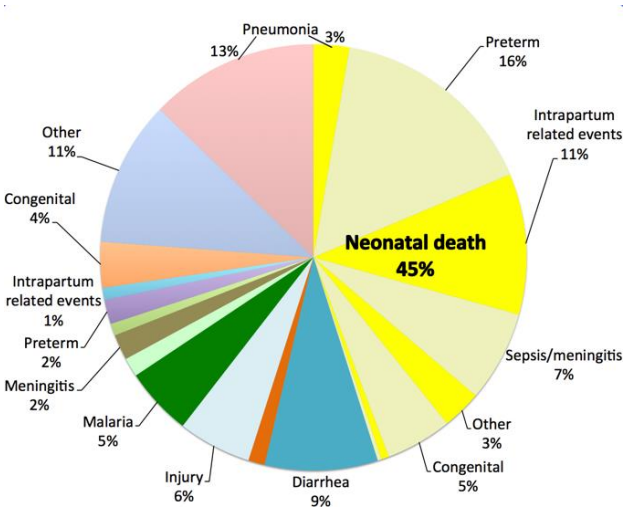
2.3.2 Under-5 mortality estimation

Presenter: Li Liu

VAs are relied upon for estimating malaria as a cause of death, with data currently available from 33 countries. Studies have suggested that VAs have a variable track record for measuring malaria mortality. However, a true 'gold standard' for assessing the accuracy of this tool is lacking. For modelling malaria deaths, the global VAMCM framework is used. Site-specific, national-level *Pf*PR values are extracted from the MAP global time series estimates ('the cube') and then used to inform the mortality predictions. Where countries have an estimated *Pf*PR of zero, malaria deaths are forced to zero in a post-hoc adjustment. The U5MR for malaria between 2000 and 2016 is estimated to have declined, down to an estimated 289 000 deaths in 2016.

Due to the unique epidemiology and availability of data, an India-specific malaria mortality model was developed. The natural history model described in the WMR 2008 was used for estimating malaria deaths in India. Briefly, this model consists of estimating the number of malaria deaths, regardless of species, as the product of incident cases measured by routine reporting and reporting completeness, health service utilization rate according to household surveys, and the CFR estimated from any existing studies. Data used to drive the model include data from routine health system reporting, VAs and household surveys. Overall, the model estimated 6000 malaria deaths in 2016. Estimates were derived subnationally, with higher rates observed along the eastern border. In 2015, about 5% of under-5 mortality was estimated to be due to malaria globally (Fig. 7)

Fig. 7. Cause of death fractions globally in 2015



Overall, the limited information on deaths from *Pv* was identified as an area where better data are required. The current approaches to estimate mortality use a *Pf*-specific or 'any malaria death regardless of species' approach. The contribution of *Pv* to malaria mortality should be further explored in addition to the mortality burden from any species in adults. The difficulty in the retrospective analysis of malaria mortality was highlighted, due to both

the lack of data that have been consistently collected across landscapes and the change in case definition for malaria mortality. The introduction of the new definition may provide a natural starting point for a time series analysis. Using consistent definitions and having a good understanding of the relationships between the methods used for mortality estimation would facilitate comparisons across time and settings. Identifying key data to be collected, initially focusing on areas where data of sufficient quality exist, was suggested as a starting point for improving estimates and understanding observed trends (e.g., true declines vs improvements in health systems).

2.3.3 WMR mortality estimation and over-5 mortality fraction

Presenter: Richard Cibulskis

The methods currently employed to estimate malaria mortality in the WMR were described. In areas with good VR data, reported deaths are used directly with little adjustment. The second approach estimates death according to reported deaths adjusted by the percent of deaths being reported. The third approach applies the CFR to the number of estimated cases. The reliance on VAs to estimate malaria deaths in children under 5 and how deaths in those over 5 are estimated according to Ross et al.'s [6] model, which extrapolates over-5 deaths based on under-5 deaths, was emphasized. The challenges of identifying malaria deaths that are attributable to the malaria parasite rather than to ancillary causes (e.g., anaemia) or incidental parasitaemia were highlighted. Finally, it was noted that the age distribution of deaths observed in settings such as Papua New Guinea and India differ from the distribution currently being assumed in the modelling approach, which may impact the validity of the resulting mortality estimates.

There was a discussion of the limitations and data gaps with the methods as they are currently being employed. The difficulties in estimating CFR are currently reflected in the wide uncertainty bands presented. A fixed CFR for *Pf* and *Pv* is currently being applied to the estimated number of cases. However, the CFR rates used are based on data generated around 2000, which likely do not reflect current realities. Improving mortality estimates would benefit from aggregating any contemporaneous studies that have collected CFR data and identifying key variables that should be prospectively collected. Updating CFR estimates is particularly relevant so they can better reflect differences in the quality of care across settings and transmission intensities, as well as any changes to quality of care that are likely to reduce the CFR.

The members of the ERG agreed that the over-5 correction currently being applied could be improved. Additional data sources and more advanced modelling techniques should be explored in order to improve on the current approaches. Moreover, the lack of validation of VA across transmission landscapes was reiterated as a gap in malaria mortality estimation.

To improve mortality estimations, it was agreed that any existing data should be collated and used to refine the assumptions applied to mortality estimation. It was highlighted that, in the short term, sites could be identified based on the availability of good-quality data as a starting point. The optimal data that should be collected to improve the validity of estimates could then be identified so that data generation in all settings, and thus overall estimates, could be improved over the long term.

2.3.4 Global Burden of Disease mortality estimation

Presenter: Pete Gething

Geostatistical models are being used to estimate malaria mortality, particularly in areas with limited or poor-quality VR data. Mortality is estimated according to a combined model of VR, VA and routine surveillance data, corrected to ensure quality. Data sources are added to the Global Burden of Disease (GBD) cause of death database, with the fraction of deaths due to malaria estimated in conjunction with the all-cause mortality rate, resulting in the estimated malaria-specific mortality rate. The CFR is estimated according to the untreated case incidence, which is a product of the case incidence and how effective malaria treatment was at that time. Results are input into a mixed effects regression model to estimate the malaria mortality rate and scaled according to the population at risk to estimate the number of malaria deaths. Current estimates are based on 282 data points, with the breadth of data from Africa coming from VAs.

Mortality outside of Africa is estimated using a modified geospatial framework. The input data are the same as described above. However, the Cause of Death Ensemble model (CoDEm) for malaria is used to estimate the number of malaria deaths. Deaths from countries with only *Pv* transmission are estimated using a zero-inflated negative binomial model on the cause of death fraction and added to the number of malaria deaths. It was suggested that the estimated CFR be explored as part of the intermediate processing step for its potential to provide more reliable estimates than those currently available.

Next, the use of VA data in GBD estimates was explored in more depth in order to elucidate any potential source of the observed discrepancy between the different estimation approaches. For VA studies to be included in the GBD database, the study has to meet the following criteria: i) it is representative of the population, with a sufficient sample size, ii) it uses methods for cause assignment that do not employ the InterVA approach, and iii) it includes sufficient detail on the real underlying cause of death. The data are then prepared for inclusion in the cause of death estimation by adjusting for age distributions, correcting for non-informative codes, and controlling noise resulting from the fluctuation of data. The cause fraction is then applied to all-cause mortality according to age, sex, location and year before being input into the model to estimate the number of malaria deaths.

Some of the key challenges with mortality estimation were discussed. First, the extrapolation of deaths in the over-5 population should be revisited. Hospital data on the age patterns of malaria deaths were identified as a potential source of information that could be routinely collected. Better information on the age distribution of severe malaria would be useful to better understand the assumptions used in the Ross model. The potential difference between the age distribution of deaths recorded in hospital settings and deaths in the community was acknowledged and represents an important gap in malaria mortality estimation.

The discrepancies between the WHO and GBD estimates were highlighted as requiring further evaluation. Differences may be due to the modelling approach used; however, the different inclusion criteria for the input data may also be a contributing factor. The lack of data to inform estimation was acknowledged as a limiting factor. Aggregating existing data and conducting additional studies would be important for better understanding of the epidemiology of malaria mortality, but would also provide insight into the reasons for the differences between the two estimation methods. The limited understanding and quantification of the drivers behind care-seeking behaviour for malaria and the other

diseases included in the all-cause death estimation methods was highlighted as a major gap in understanding mortality trends.

2.3.5 Validation of InterVA tools for cause of death at hospitals

Presenter: Clara Menendez by phone

Results of research being conducted to assess the validity of current tools for cause of death classification at a hospital in Mozambique were presented. Briefly, the first phase of the study involved pathological exams to ascertain cause of death and comparing results to the classification recorded in the hospital registry. The objective of phase 1 was to determine the validity of the 'best' quality of data routinely available in most malarious areas, based on clinician records. The second phase is currently ongoing and its focus is on comparing the gold standard with VA. Results of phase 1 suggest that the sensitivity and specificity of hospital-recorded cause of deaths were very poor at the individual level compared to the sample autopsy results as gold standard. Despite the cause of death being misclassified at the individual level, the population-level estimates of malaria were closer between methods, when broad disease categories were used– essentially obtaining the right answer for the wrong reasons. It was agreed that there is potential to use this type of study protocol to assess different VA tools and create a standardized data collection instrument as a way forward in improving the validity of the VA approach for cause of death estimation.

2.4 Summary of challenges with current estimation approaches

Discussions facilitated by Abdisalan Noor

2.4.1 Metrics

Several metrics that are currently being measured as outcomes include parasite prevalence, fever with infection (clinical case as defined in treatment guidelines), and fever with infection that is attributable to the infection. Each reflects a different component of the transmission system. The ERG suggested that metrics be clearly defined when reported so that clear comparisons can be made between the various outputs, in both their magnitude and their trend.

2.4.2 Identifying and measuring biases and other key determinants

A better understanding of key sources for adjusting routine data is required in order to improve the accuracy of estimates. This includes understanding the biases in the data across the diversity of health systems and transmission landscapes, as well as identifying the different data sources available to measure such biases. The treatment-seeking pathway for malaria was identified as one of the main assumptions that would benefit from an improved evidence base. Understanding what proportion of malaria-infected individuals are seeking treatment by sector and not seeking treatment is important for refining how estimates are derived. Key questions include: What proportion of malaria patients seek care in different settings, and is there the same prevalence of infection in those seeking care for fever in different health sectors?

Second, a detailed assessment of health system capacity will provide critical context for interpreting the strengths and weaknesses of surveillance data. Key variables include confirmation and reporting rates, as well as age distribution of cases and deaths. Assessment could include the use of supervisory forms to evaluate the quality of care

received in facilities and to provide better temporal data on key determinants used to adjust case estimates. Such information will be critical to help adjust the data generated if needed, but also to explain any changes in the malaria trends observed. Third, the biases in the modelling of the *Pf*PR and the estimation of incidence from the *Pf*PR-to-incidence model described in section 2.2.1 need to be accounted for more effectively.

2.4.3 Populations at risk

The definition of population at risk of malaria used by the WMR includes those residing in high transmission areas plus half of those residing in low transmission areas, as delineated by country programmes. This approach is confusing, as other definitions of population at risk are used in different settings. It was deemed preferable to present estimates of national incidence, including the entire population as the denominator. For the purposes of allocating resources/interventions, a second estimate of population at risk will be included to represent heterogeneity within countries, using populations within countries with active transmission as the denominator. Clearly defining the metrics presented as part of communication strategies (national incidence vs local incidence) was highlighted as critical.

2.4.4 Modelling approaches

Improving the understanding of how different sources of information relate to each other and reflect the different components of malaria transmission, and how this impacts the resulting burden estimates was identified as a critical challenge. Making use of all available data, including routine health systems data and prevalence surveys, was deemed to be an important step forward. This approach is reliant on understanding how the different data sources reflect malaria transmission and the resulting burden estimates.

Furthermore, parasite rate-to-incidence analyses are currently impacted by years without data. The models are particularly less reliable in capturing recent trends, as there is a time lag for inputting contemporary data into the models. Revisiting some of the assumptions around key determinants (e.g., ITN and IRS coverage) being modelled and the parasite rate-to-incidence relationship is recommended to ensure that models are as good a representation of reality as possible.

3. Conclusions and recommendations

3.1 For immediate action (3 to 12 months)

3.1.1 Malaria morbidity estimation

1. Clear definition and purpose of metrics: Currently, the following metrics of malaria morbidity are produced through various estimation processes:
    - Parasite prevalence (proportion of population with *Plasmodium* parasites in their peripheral blood following a test using microscopy or standard rapid diagnostic test. Data mostly from household surveys interpolated in time and space using statistical methods);
    - Fever with infection (standard case definition in treatment guidelines and reported by routine health information systems);
    - Fever attributable to infection (a model estimate based on the relationship between parasite prevalence and clinical episodes of malaria, defined as parasite density >5000 p/ul by age).

The MBE-ERG recommended that in the comparative analysis of the magnitude and trends of burden of disease, these metrics should be clarified and the meaning of each defined in relation to the burden of malaria.

2. Improvements to *Pf*PR models:
    - Revisit current assumptions on the relationship between determinants and *Pf*PR, which are important for filling gaps in space and time and have a major influence on trends, especially in years without data. Assembling new data, preferably subnationally, on intervention coverage is required to improve assumptions.
    - Where there is substantial divergence in trends between *Pf*PR and routine reports, incorporate routine data to adjust trends, particularly in countries without recent parasite rate (PR) surveys.
    - Use the *Pf*PR-to-incidence model to estimate infections among fevers in addition to the current estimates of infections among fevers that are likely to be due to malaria.
3. Improvements to the *Pf*PR-to-incidence model:
    - Identify and assemble recent active case detection surveillance data in sub-Saharan Africa in order to update the model.
    - Identify and assemble other contemporaneous *Pf*PR and clinical data from studies in order to add to the information that can be used to improve the *Pf*PR-to-incidence model.
4. Use of routine data – assessment of biases in routine data:
    - Implement detailed surveillance assessments of select countries, with strong emphasis on the quality and completeness of routine data. Focus on countries with significant recent improvements in surveillance systems.
    - Assemble subnational data that are disaggregated by age over several years, preferably from 2010 when the large scale-up of diagnostics began in some countries, but where possible from 2000.
    - Where available, collect additional data on changing policies and quality of care over time in order to understand case management practices that may influence trends in routine data.
    - Based on the assessment data and confidence in the stability of the surveillance system, use routine data for MBE.
    - Develop methods that will allow the use of routine data back to 2000.

3.1.2 Malaria mortality estimation

5. Improvements to assumptions and methods for mortality estimation:
    - Use updated and improved *Pf*PR estimates to inform the magnitude and trends in the cause of death fraction for malaria in moderate to high transmission countries.
    - Assemble new data to update assumptions regarding over-5 mortality fractions applied to the under-5 mortality estimates.

- Assemble new CFR data for low transmission areas in southern Africa and outside Africa for both *Pf* and *Pv.*
- Examine MAP-implied CFR against current estimates used in the WMR and compare magnitude and trends

3.1.3 Estimation of indirect burden of malaria

6. Anaemia and malaria morbidity and mortality:
    - Assemble available data to assess the relationship, and implement exploratory analysis of distribution and the relationship with malaria for the next WMR.
    - Develop a mechanism for developing a comprehensive repository of data and a mechanism for analysis for future WMRs.

3.2 For medium- and long-term action (6 to 24 months)

7. *Comparative clinical and prevalence studies across different transmission settings, including pathways of treatment-seeking*: The ERG acknowledged that there were gaps in the understanding of community parasite prevalence and the clinical cases seen from health facilities used by these communities. This relationship is critical to the joint interpretation of parasite prevalence and case reports and is influenced by levels of transmission, malaria interventions, seasonality of fevers, socioeconomic status, access to care and the pathways for treatment-seeking for fevers. Primary studies that reflect different endemicities, health systems and socioeconomic contexts should be conducted across sub-Saharan Africa.
8. *Risk factor analysis in relation to malaria mortality*: Given the uncertainty of defining malaria mortality even under high-quality case management conditions, the ERG suggested that an analysis of changes in potential risk factors for malaria mortality would strengthen the interpretation of the trends in malaria burden and should be explored for future WMRs.
9. *Ways of incorporating emerging tissue sample autopsy data from moderate to high transmission countries*: There are a few studies that are ongoing, and the ERG recognized that such data may provide opportunities for improving VA-based mortality models. In addition, they may serve as a concrete source of data for adult malaria mortality quantification. Data from these studies should be explored as they emerge.
10. *Severe disease due to malaria*: It was recognized that the quantification of the burden of severe disease was a critical gap in the WMR. The ERG also recognized emerging new opportunities, such as community health worker referral data on severe disease in areas where rectal artesunate has been scaled up; and ongoing sentinel studies of inpatient facility data for severe disease and hospital CFR estimation. The ERG recommended that WHO explore the possibility of working with partners to assemble these data for future quantification of severe malaria burden.

4. Strategic issues

11. *Roadmap and resources*: The MBE-ERG noted that several of the recommendations from the meeting were similar to those suggested in the MBE-ERG 2012, but many of them had not been achieved. To avoid similar inaction, in addition to separating tasks into immediate, medium- and long-term actions, the MBE-ERG recommended that a clear roadmap be developed by WHO with activities, timelines, potential implementers and resources needed, based on the recommendations of the meeting. It was acknowledged that progress will be hindered without adequate resources available to support the key recommendations resulting from this meeting. Once the scope of work is described in detail and the roadmap developed, resources will be requested to address the above-mentioned recommendations.

12. *Communication strategy*: The MBE-ERG emphasized the critical need for a clear communication strategy associated with the WMR so that the numbers presented can be interpreted accordingly, particularly in the future when estimation methods change. The use of case studies may help to communicate some of the uncertainties and complexities of the methodologies. A commentary in a high-impact publication and through WHO communications channels was recommended as a potential communication mechanism.

13. *Next ERG meeting*: To assess progress on the recommendations for immediate action and to concretize plans for the medium- to long-term activities in preparation for the next WMR, it was suggested that a second ERG be convened by September 2018.

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