Malaria Burden Estimation Methods
Evidence Review Group

Meeting report

Abdisalan M Noor,
Team Leader, Surveillance, Monitoring and Evaluation
Burden ERG Meeting, 11-13 April 2018
Malaria burden

- Indirect malaria death
- Direct malaria deaths
- Severe malaria
- Uncomplicated malaria
- Infection

Increasing uncertainty
Comparisons of parasite rate-to-incidence vs adjusted routine data model estimates - 2016

80 million more cases from the adjusted routine data compared to the PfPR to incidence model
Uncomplicated malaria

Number of persons tested, household surveys vs routine data, SSA

921 million vs 1.7 million tests between 2006 and 2016

Global Malaria Programme
**Uncomplicated malaria**

Number of persons tested, household surveys vs routine data, SSA

921 million vs 1.7 million tests (x100) between 2006 and 2016
Approve terms of reference for Malaria Burden Estimation (MBE) Evidence Review Group (ERG):

• Review existing methods for morbidity and mortality estimation. Focus on addressing issues related to use of routine data, temporal trends in case fatality rate (CFR), age attribution of malaria mortality, and the role of geospatial approaches to modelling mortality estimation;

• 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;

• Re-focus on the indirect burden of malaria infection.
MPAC convening, 12-14 March 2018

Members
• Prof Fred Binka (Co-chair)
• Dr Richard Steketee (Co-chair)
• Prof Joana Armstrong-Schellenberg
• Prof Azra Ghani,
• Prof Simon Hay
• Prof Li Liu
• Prof Christophe Rogier
• Dr Alexander Rowe

Rapporteur
• Dr Gillian Stresman

Observers
• Dr Scott Filler
• Dr Bruno Moonen

Collaborating centres and presenters
• Prof Peter Gething
• Prof Thomas Smith
• Prof Clara Menendez (by phone)

WHO – GMP and IER
• Dr Pedro Alonso
• Dr John Grove
• Dr John Aponte
• Dr Richard Cibulskis
• Dr Kim Lindblade
• Dr Colin Mathers
• Dr Abdisalan Noor
• Dr Maru Aregawi Weldedawit
Estimating malaria case incidence

- Unadjusted routine data: <1%
- Adjusted routine data: 14%
- Parasite rate –to-incidence: 86%
Estimating malaria case incidence

Data mainly from the public health sector adjusted for:

- Confirmation rate
  - Country reported, not validated consistently
  - Can be highly variable between years

- Reporting rates
  - Country reported, sometime not clear if % HF or % district
  - Some countries do not know actual number of public health facilities and increase over time

- Proportion seeking treatment in the private sector
  - Based on self-reported fever – not validated, not clear on subsequent action, may be higher in non-malaria but highly populated areas

- Proportion not seeking treatment at all
  - Based on self-reported fever – not validated, not clear on subsequent action

Adjusted routine data 14%
Parasite rate – to incidence

- Considerable temporal gaps in parasite prevalence data that may affect recent estimates
- Estimates are based on an epidemiological model that quantifies the proportion of infections that are likely to be clinical cases, and may not be the same as symptomatic individuals who were tested and treated at health facilities
- Considerable differences in magnitude and trend compared with routine data
Direct malaria deaths - 2016

- Unadjusted routine data: <1%
- Adjusted routine incidence data x CFR: 11%
- U5 mortality data x malaria CoD fraction + fraction over 5, PfPR a variable in CoD model: 89%

Global Malaria Programme

World Health Organization
Affected by problems of computing cases from imperfect routine data

- Static case fatality rates (CFR) for both *P. falciparum* and *P. vivax*
# Direct malaria deaths - 2016

## Adjusted routine incidence data x CFR

<table>
<thead>
<tr>
<th>Study</th>
<th>Place</th>
<th>Year</th>
<th>CFR</th>
<th>CFR Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendis (summary)</td>
<td>Multiple (SE Asia, Africa)</td>
<td>1980s-1990s</td>
<td>0.1%-0.3%</td>
<td></td>
</tr>
<tr>
<td>Nyarango</td>
<td>Eritrea</td>
<td>2000-2004</td>
<td>0.14%-0.21%</td>
<td></td>
</tr>
<tr>
<td>Luxemburger</td>
<td>Thailand (Western)</td>
<td>1992</td>
<td>0.19%</td>
<td></td>
</tr>
<tr>
<td>Meek</td>
<td>Thailand (Southeastern)</td>
<td>1983-1985</td>
<td>0.31%-0.42%</td>
<td></td>
</tr>
<tr>
<td>Zucker</td>
<td>Kenya</td>
<td>1991</td>
<td>11%-33%</td>
<td></td>
</tr>
<tr>
<td>Dzeing-Ella</td>
<td>Gabon</td>
<td>2000-2002</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Reyburn</td>
<td>Tanzania</td>
<td>2002-2003</td>
<td>7% (6%-13%)</td>
<td></td>
</tr>
<tr>
<td>Marsh</td>
<td>Kenya</td>
<td>1989-1991</td>
<td>3.50%</td>
<td></td>
</tr>
<tr>
<td>Schellenberg</td>
<td>Tanzania</td>
<td>1995-1996</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Greenberg</td>
<td>Kinshasa</td>
<td>1985-1986</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>
Direct malaria deaths - 2016

U5 mortality data x malaria CoD fraction + fraction over 5, \( PfPR \) a variable in CoD model

1-59m deaths (all causes) → Vital Registration (VR) → Multi-cause models based on VR (VRMCM) → Cause distribution → Neonatal deaths (all causes) → India: subnational multi-cause model → China: Maternal and Child Surveillance → Single cause estimates for selected causes

Neonatal death 45%

Global Malaria Programme
• PfPR a covariate in quantification of CoD fraction for malaria, but there are some limitations in estimates and trend in PfPR
• PfPR discordant with confirmed cases from routine systems
• A fixed over 5 fraction is applied to U5 malaria estimates across a wider range of highly variable epidemiology
Direct malaria deaths - 2016

U5 mortality data x malaria CoD fraction + fraction over 5, PfPR a variable in CoD model

89%

From Ross *et al* 2006.

Relationship between death rates under 5 and % deaths under 5 years of age

\[ y = -0.2289x^2 + 0.8233x + 0.2239 \]

Relationship also used to infer % of deaths <5 outside of Africa
Severe malaria

Some countries submit inpatient malaria data
Indirect malaria deaths

Consequences of malaria in pregnancy

Aneamia
Population at risk

• Countries report population in high risk (in areas where incidence is ≥ 1 case per 1000 population), and low risk (<1 case per 1000 population)
• These are scaled to UN population estimates for a given year
• We assume PAR used to computed incidence = high risk + (0.5 * low risk)
Objectives of ERG convening

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?
Objectives of ERG convening

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 populations (at risk) denominator to compute incidence from case estimates?

6. What are the best approaches for quantifying the severe and indirect burden of malaria?
Agenda

- General issues in malaria burden estimation
- Estimation of malaria morbidity
- Estimation of all cause mortality and quantification of cause of death fractions
- Estimation of malaria mortality
- Discussion and recommendations
Immediate action (3-12 months)
1. Clear definition and purpose of metrics: currently, the following metrics of malaria morbidity are produced through various estimation processes:

i. **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);

ii. **Fever with infection** (standard case definition in treatment guidelines and reported by routine health information systems);

iii. **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).
Conclusions and recommendations – case incidence

2. Improvements to PfPR models:

i. Revisit current assumptions on the relationship between determinants and PfPR, 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 sub-nationally, on intervention coverage is required to improve assumptions.

ii. Where there is substantial divergence in trends between PfPR and routine reports, incorporate routine data to adjust trends, particularly in countries without recent parasite rate (PR) surveys.
Conclusions and recommendations – case incidence

3. Improvements to the *PfPR*-to-incidence model:

i. Identify and assemble recent active case detection surveillance data in sub-Saharan Africa in order to update the model.

ii. Identify and assemble other contemporaneous *PfPR* and clinical data from studies in order to add to the information that can be used to improve the *PfPR*-to-incidence model.

iii. Use the *PfPR*-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.
4. Use of routine data – assessment of biases in routine data:

i. 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.

ii. 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.

iii. 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.

iv. Based on the assessment data and confidence in the stability of the surveillance system, use routine data for MBE.

v. Develop methods that will allow the use of routine data back to 2000.
5. Improvements to assumptions and methods for mortality estimation:

i. Use updated and improved PfPR estimates to inform the magnitude and trends in the cause of death fraction for malaria in moderate to high transmission countries.

ii. Assemble new data to update assumptions regarding over-5 mortality fractions applied to the under-5 mortality estimates.

iii. Assemble new CFR data for low transmission areas in southern Africa and outside Africa for both Pf and Pv.

iv. Examine MAP-implied CFR against current estimates used in the WMR and compare magnitude and trends.
Conclusions and recommendations – indirect burden

6. Anaemia and malaria morbidity and mortality:

i. Assemble available data to assess the relationship, and implement exploratory analysis of distribution and the relationship with malaria for the next WMR.

ii. Develop a mechanism for developing a comprehensive repository of data and a mechanism for analysis for future WMRs.
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.
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.
11. Roadmap and resources
12. Communication
13. Next meeting
Please check out the WMR App

Available in the app stores for both Apple and Android products