

MINUTES OF THE MERG TASK FORCE MEETING ON MALARIA MORBIDITY

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Participants

Rick Steketee (CDC)

Simon Hay (Oxford University)

Arantxa Roca-Feltrer, Ilona Carneiro (LSHTM)

Neff Walker (UNICEF)

Brian Williams (WHO/STB/M&E)

Colin Mathers, Kenji Shibuya (WHO/EIP)

Bernard Nahlen, Eline Korenromp, John Miller (WHO/RBM/M&E).

+ E-mailed inputs from:

Bob Snow (KEMRI/Oxford University)

Tom Smith and Christian Lengeler (Swiss Tropical Institute).

SUMMARIES OF PRESENTATIONS AND DISCUSSIONS

Introduction and rationale for malaria incidence estimation at country level (BN & KS)

In May 2003, the Roll Back Malaria (RBM) Monitoring and Evaluation Reference Group (MERG) recommended that a task force be established to define the appropriate indicator(s) and data collection for malaria morbidity, and to estimate this burden at country level. Country estimates will serve to evaluate impact of activities of RBM and the Global Fund to fight AIDS, TB and Malaria (GFATM), to evaluate the progress toward Millennium Development Goals (MDG) and as an input to the yearly Global Burden of Disease (GBD) estimation by WHO/Evidence and Information for Policy (EIP).

An indicator on malaria morbidity is appropriate, first, because morbidity forms part of the malaria burden (besides mortality), which RBM aims to reduce to 50%. MDG indicator 21 is 'malaria prevalence and death rates', and WHO RBM&EIP are required to submit an annual report on behalf of all malarious countries.

The concept 'malaria prevalence' is confusing, since it is often used to denote the prevalence of *parasite infection* rather than malarial illness. Especially among adult residents in areas of stable transmission, parasite infection is usually asymptomatic, so parasite prevalence would overestimate malaria disease burden. Also, parasite prevalence may not respond as fast to successful malaria control as does the incidence of malarial disease.

Until consensus on a more robust method to estimate incidence of clinical malaria has been achieved, WHO has taken the indicator 'malaria prevalence' to denote the malaria cases notified through national health information systems (HIS) in reporting on MDG progress 2002-2003. WHO is, of course, cognizant of the fact that reported cases do not present a valid picture of the full burden of malaria incidence. The completeness of malaria case notifications varies between countries and over time, depending on health care access, diagnostic practices and the quality of the HIS.

There is consensus that the incidence of acute malaria disease episodes is the indicator to be estimated by the MERG morbidity task force. Disease incidence can be extrapolated to DALY's for incorporation in GBD calculations. Previous estimation by WHO/EIP of malaria incidence were based on back-calculation from mortality estimates, assuming certain fixed case fatality rates (CFRs) for different world regions and age groups. This method is no longer felt appropriate because CFRs vary widely between different settings and over time.

The objective of this first meeting of the MERG Morbidity Task Force is to discuss a newly developed estimation method proposed by WHO/RBM¹ and to develop consensus on improvements or alternatives to this model. It is of note that there is no mechanism presently for changing MDG indicators; however, we can help define operational definitions. Thus, the term 'malaria prevalence' can be defined as the incidence of acute malaria episodes, for reporting on MDG indicator #21.

Malaria case notifications in HIS (JM)

The cross-country collection and dissemination of malaria case (and death) notifications is driven by the WHO regional offices, not WHO/HQ in Geneva. Type of disaggregation (by age, by type of diagnosis, imported versus autochthonous...) varies between countries and regions. Sub-Saharan African countries mostly report cases based on presumptive clinical diagnosis. Most countries outside Africa report only cases that are confirmed parasitologically, or they report numbers separately for cases with and without parasitological confirmation.

Case notifications reported to Geneva for the most recent year in which information has been received for countries thought to have areas of malaria transmission total around 55 million, but this may not be the true total number of registered cases, due to incomplete reporting from country to WHO regional office and from regional office to headquarters. Similarly, the types and disaggregations of notifications available at WHO headquarters do not always reflect the full level of detail available in countries, being constrained by the reporting forms used at regional level. Case reporting up to headquarters has improved over the past few years, but the data management capacity at regional and country level remains a challenge.

With data by district and month of the year, the completeness of HIS case reporting could be estimated, as is being done for tuberculosis by Stop TB. Discussions have been initiated with regional offices to begin to develop plans on how to systematically do this, as well as to develop a more standardized reporting format. It is of note that 'HIS reporting completeness' in this definition reflects only cases diagnosed and treated in the formal health system. Therefore, this estimate of reporting completeness will always be higher than the ratio of HIS reported cases to true incident cases in the population, because the latter includes cases that do not access the health system at all, as well as cases treated in (usually private) health facilities that do not participate in HIS reporting.

Certain countries have implemented specific reporting systems, such as Integrated Disease Surveillance (IDS). When implemented for malaria (like in Uganda?), IDS has inherent monitoring of reporting completeness, which might be useful for understanding how well reporting systems work in Africa

There is agreement that the case notifications for most African countries are at the moment fairly useless for estimating disease burden. For example, Burkina Faso reports more cases than Nigeria, and the ratio between reported cases and reported deaths varies greatly, even between countries with similar treatment policies. Because of non-representativeness and incompleteness, age/sex patterns and time trends in reported cases are also of questionable use. Outside Africa, however, trends and patterns in reported cases do appear to reflect reality quite well, e.g. a predominance of malaria in adult males in Cambodia. In all regions, even when not a measure of total disease burden, reported cases do give an indication of the need for e.g. artemisinin-based combination therapy dosages in the public sector.

Outline of proposed estimation method, and inputs needed (EK)

Routine HIS data were not considered good enough to form the basis for the incidence estimations. As the basis instead is proposed a global map of malaria transmission risk, in various endemicities, to which fixed disease incidence rates for given endemicity categories are applied. The same basic

¹ Shared with participants in draft in September 2004 and in the meeting folder: *Malaria incidence estimates at country level for the year 2004 - proposed estimates and draft report* - Eline Korenromp for the RBM MERG on malaria morbidity, draft October 8, 2004.

incidence rates are applied for all countries, but country incidences are thereafter downward adjusted to account for the local impact of malaria prevention, according to the country-specific coverage of insecticide-treated nets (ITNS) and insecticide-residual spraying (IRS).

Outside Africa, this risk-based estimate is then triangulated against HIS case reports, whereby the risk-based estimate is discarded if it would be consistent with a reporting completeness in HIS of below 1% or over 100%. For countries for which no risk-based estimate could be made, because they were too small to appear on the risk map or because of very little malaria (Southern Africa), incidence is defined as reported cases and assumes a 100% HIS reporting completeness.

The endemicity categorization outside Africa was very crude, and data on ITN and especially IRS coverage are lacking for many countries, so that estimated incidence is very high compared to case notifications. As a result the incidence estimates are considered very uncertain for most countries, especially outside Africa. However, the estimate still seems to be more consistent with expert opinion in malaria epidemiology than are case notifications. Amongst others, the estimates show a clear pattern of increasing proportion of cases among under-fives with increasing endemicity and of increasing proportion of cases due to *falciparum* with increasing endemicity.

Country populations at malaria risk outside Africa (SH)

For African countries, malaria endemicity has been derived from the MARA climate-based map. Lacking such a map outside Africa, and considering that malaria endemicity outside Africa is not determined by climate alone, Oxford University produced an independent endemicity distribution for non-African countries, under an APW with RBM in early 2004.

The proposed endemicity distribution is based on a map of global population distribution, at the first subnational administrative level, from the UN-mandated Second Administrative Level Boundaries (SALB; WHO/EIP, http://www3.who.int/whosis/gis/salb/salb_home.htm), supplemented with data from WHO Public Health Mapper. 'International Travel and Health 2004' (ITH 2004¹) provided a map with boundaries of malaria transmission, which provides an upper limit to risk of malaria for international travellers. The boundary risk map was fine-tuned with textual descriptions in ITH 2004 at country level of districts and urban areas with and without malaria and altitude boundaries, although these were not complete or systematic. Categorization of endemicity level within these risk boundaries was taken from an existing map for 1900 (Lysenko, 1968), which defined endemicity as follows:

- prevalence of parasitemia in the 2-10 year age group:
 - *hypo-endemic* denoting <10% parasite prevalence,
 - *meso-endemic* 11-50%,
 - *hyper-endemic* 51-75%,
- and *holo-endemic* denoting a parasite prevalence among children aged 1 year of $\geq 75\%$.

Parasite prevalence rate surveys, available from a small and discontinuous part of the world, were used to define local endemicities, which were then extrapolated to the rest of the world, using expert opinion and global maps of temperature and rainfall.

The resulting map showed reasonable correlation with HIS case notifications at the first subnational administrative level (e.g., equally good as MARA for Kenya).

Discussion:

RS/EK: It is unclear to what extent this map accounts for the impact of vector control in reducing areas of malaria transmission, and endemicity levels, compared to the 1900 situation. SH: This could be solved either simplistically by scaling the whole map down by each endemicity category, or in detail by redoing the endemicity classification using more recent parasite prevalence survey data.

IC: Altitude thresholds may be obscured by cases of imported malaria. RS: To a small extent, however, because few people live at high altitude. SH: This cannot easily be corrected for, in the absence of migration data at detailed geographical level.

Malaria incidence rate in African under-fives (IC)

Since 2002, originally under the Child Health Epidemiology Reference Group (CHERG) project², the London School group has worked on estimating the incidence of malaria and of various complications of malaria, in African under-fives. The CHERG estimation of the overall incidence of malaria is nearing finalization, and will serve as input into the current global incidence estimation.

Due to rigorous inclusion criteria, such as strict age limits and the limitation to studies with a duration of a 12 months multiple (to avoid biases due to seasonal malaria), the incidence rate for middle Africa was based on 11 studies only, one from an area of low transmission intensity and 10 from areas of high transmission intensity; no study was from an urban area. None of the tested population characteristics were found to significantly correlate with the incidence of malaria, so that the overall estimated rate was 0.63 per person per year (pppa) for rural areas of low transmission, and 1.3 pppa for rural areas of high transmission.

For 7 countries in Southern Africa, existing estimates based on an average rate of 0.0061 pppa for all high-risk areas, and 0 incidence for the remainder of the countries, was applied.

Discussion:

The group saw no solution for the concern issued by Tom Smith, that active case detection studies by intervening reduce the incidence of malaria over time. Such a downward bias might explain why RS found the proportion of (EK's) estimated African cases in under-fives rather low. On the other hand, research studies probably oversampled areas of high malaria transmission, which may have compensated this bias.

All: The representativeness of the results are questionable in view of the inclusion of only 11 studies, of which half in Tanzania and the rest in West Africa. The small number of studies also increases the risk that the estimated increase in malaria incidence over time is confounded with site selection. The number of included studies could be increased by relaxing the age and 12 months duration criteria. (e.g., 6-years old may be quite similar to 4-year olds.) However, the value of the additional studies then included would have to be weighted against the additional uncertainty related to seasonality and age adjustments.

The value of community-based longitudinal incidence studies such as reviewed by CHERG for the purpose of RBM monitoring (as opposed to burden estimation) was discussed. Malaria incidence in such active case detection studies would respond to intervention, but the detection of such change would be time- and resource-intensive. Standardization of case definitions, sampling methods and seasonal timing of measurement would be important. An alternative data collection method for which rapid and widescale implementation would be more feasible might be cross-sectional surveys, of parasite prevalence rate (PR) and/or childhood anemia. To check the usefulness of surveying PR and/or anemia, it would be useful if LSHTM could explore whether there is a relationship between incidence and cross-sectional outcomes in the dataset of longitudinal studies.

SH: The lack of data in Central Africa, particularly DRC, is less for entomological inoculation rates (EIRs) and parasite prevalence rates (PR) than for the incidence of clinical episodes. So, if in the small CHERG dataset a relationship of incidence with EIR or PR could be demonstrated, these EIR and PR data might help to improve, or at least cross-check, the incidence estimate for Central Africa.

EK/RS: Angola and Zambia seem to be more similar to middle Africa than to the remaining southern Africa with respect to malaria endemicity and quality of HIS. Therefore, replace the incidence rate estimates for these countries by the middle African method.

Malaria incidence rate outside Africa (ARF)

Similar to CHERG for African under-5s, regression analysis were done on malaria incidence rates and their determinants from community-based longitudinal studies outside Africa. The analysis focused on the overall incidence of malaria (defined as fever symptoms + parasitemia) combining *falciparum* and *vivax* episodes. This was due to the facts that: 1) not all studies reported rates by parasite species, and 2) the proportion of cases due to *falciparum* malaria was not a significant determinant of overall incidence rate in univariate analysis.

For populations at hyper-endemic and meso-endemic risk, basic incidence rates were estimated from 40 studies. Available data seemed not to be representative since they oversampled high-malaria areas, but they revealed a general pattern of variation by endemicity, age and urban/rural residence. Basic incidence rates by endemicity, age and urban/rural residence were therefore estimated from the two modelled rates that appeared to be most representative: 1.09 ppa for children in hyper-endemic rural settings and 0.45 for children in meso-endemic rural settings. The average predicted ratio urban-to-rural of 0.3 was applied for all age groups in both endemicity categories.

For areas at hypo-endemic risk, lacking relevant studies an existing estimate for epidemic areas in Africa was proposed. For areas of holoendemic risk, the age-specific rates for African under-5s were assumed, because the only four relevant studies available, from Papua New Guinea, showed similar rates there for children under-five compared to African under-fives.

Discussion:

NW: The proposed basic incidence rates are much higher for hyper-endemic areas than for meso-endemic areas, while endemicity was only marginally significant in the multivariate regression. However, inclusion of endemicity as a parameter is acceptable because it is an *a priori* plausible determinant of malaria incidence.

IC: Care should be taken to use the same methodology in estimating basic incidence rates studies outside Africa and for Africa, as much as possible. First, the large difference in malaria incidence between urban and rural areas outside Africa (ratio 0.3) implies that estimating an urban rate for Africa is important. Second, if reliance on passive case detection studies is acceptable for Southern Africa, why not for outside Africa? Third, the statistical model used for African under-fives is a negative binomial model, but for outside Africa linear regression. Although this does not critically influence point estimates, it influences the associated uncertainty ranges and the eligible studies (for negative binomial, person-time is needed, thus excluding studies reporting an incidence rate with reporting underlying person-time).

ITN and IRS coverage (JM)

Available data on ITN coverage come mainly from household surveys, DHS, MICS, Netmark and 'RBM baseline' surveys and they vary somewhat in indicators measured (children sleeping under nets, or households possessing nets...) and in sample (national, subnational and season of the year). In future, ITN coverage data will become available for more countries and be more mutually consistent, because DHS and MICS questionnaires have now been standardized and a model Malaria Indicator Survey (MIS) questionnaire and tabulation plan have been developed. The MICS can potentially be used either as a stand-alone survey or as a module in larger household surveys. Also, the recently published 'Guidelines for Core Population Coverage Indicators for Roll Back Malaria: To Be Obtained from Household Surveys' should help to improve the availability of standardized high-quality data. Besides surveys, programmatic data on nets distributed, nets (re-)treated and households sprayed might be used to infer coverage.

For IRS coverage, the forthcoming report from WHOPES on volumes of insecticides used for different types of vector control should be especially relevant. Definitions and data collection methods are less advanced for IRS coverage, resulting in relatively large uncertainty in the incidence estimates for countries with high IRS coverage.

If the estimation assumes a large difference in incidence rates between urban and rural areas, differences in ITN coverage between urban and rural areas become important. This should be assessed using the same urban/rural definitions as for urban and rural country populations and basic incidence rates (from GRUMP, see below).

Impact on incidence of ITNs and IRS - short term and long term (RS)

The available evidence suggests that the morbidity impacts of ITN and IRS are similar, as the proposed incidence estimation assumed. The incidence of acute clinical malaria responds more readily to these interventions than do the prevalences of parasitemia and of high parasitemia. This supports the use of clinical malaria incidence as the MDG malaria morbidity indicator - although for RBM childhood anemia and childhood parasite prevalence are likely to be useful additional indicators.

Long-term follow-up after ITN trials in Kenya and Burkina showed that for mortality the protective efficacy of ITNs remains stable after the first 2 years; the same might be assumed for morbidity. Further empirical evaluation of long-term impacts is problematic because withholding ITNs in areas where they are recommended would be unethical. Mathematical modelling such as done at the Swiss Tropical Institute may provide further insight. Based on trial data, the assumption that impact increases linearly with coverage seems to be justified.

Discussion:

BN: Since these trials were all in high-endemic Africa settings, their representativeness for areas with unstable transmission is unknown. SH: The same is true for urban areas, and for age groups above 5 years, the study group in most ITN trials.

BN: Is it justified to ignore the potential impact of treatment on incidence in the country incidence estimates? This might be reconsidered once coverage of artemisinin-based combination therapy, which might reduce the patient's infectivity, has been demonstrated to have gone up considerably. There is little data on the exact impact of malaria treatment on malaria burden, but modelling studies by Gerry Killeen, Dave Smith and Ellis McKenzie might provide insight.

Resulting draft country estimates and global distribution (EK)

Across 111 malarious countries, estimated incidence in 2004 totalled 352 million cases, of which 54% in AFRO and 28% in SEARO. This includes an estimated 264 million cases of *falciparum* malaria, of which 70% in AFRO and 18% in SEARO. In comparison, the 55 million cases reported through HIS are around 14% of this global estimate, but this 'reporting completeness' is an average of countries for which reporting completeness was simply set at 100% (e.g. in Southern Africa) or even left at over 100% (Tanzania), and gross underreporting in others.

For 22 non-African countries, including China, the risk-based estimate was over 100 times higher than the cases reported in HIS, in which case the risk-based estimate was replaced by 100 times the reported cases. Such discrepancies illustrate the uncertainty in the incidence estimates (see also below). Also for countries where the national coverage and (historic) impacts of IRS and ITNs are imprecisely known and for which malaria endemicity was known very crudely (especially countries at the border of ongoing transmission), the incidence estimate was very uncertain. In total, 64 of the 111 countries received the label 'very uncertain'. Uncertainties are generally larger outside Africa than for Africa, because outside Africa endemicity is more uncertain and there is a larger, but usually unquantified, coverage and impact of IRS.

Despite these uncertainties, the proposed estimates seem to conform better than case notifications to general patterns in malaria epidemiology, notably that the proportion of cases in young children and the proportion of cases due to *falciparum* increase with increasing incidence rate. The group agrees that the overall method is acceptable, and that data inputs need to be improved.

Discussion:

CM: For countries with no risk-based estimate (including in South Africa and some small countries with little malaria), instead of assuming 100% reporting completeness a value of e.g. 20-30%, analogous to the average in the region, might be more realistic.

RS+CM: For countries where the risk-based estimate was replaced by HIS case notification rate divided by a 1% reporting completeness, would it be possible to validate this assumption, e.g. against expert opinion? Or even better, for all countries with estimated or assumed reporting completeness below 5%? Expert opinion for any specific country should serve not to replace the assumed 1% reporting completeness (then the estimation method would become too subjective and too incomparable between countries!), but as a cross-check on to what extent the risk-based method does not hold up well. If needed, expert guesstimates of reporting completeness might be applied for several neighbouring countries together. However, we hope that improving the risk-based methods will reduce the number of countries needing an HIS-based estimates, but as an intermediate, the HIS triangulation seems to be acceptable.

JM: The estimation applies the proportion of cases due to *falciparum* from national HIS data to the overall country incidence estimate. For countries with few reported cases (e.g. below 4,000 per year), this may be an overestimate, because imported *falciparum* cases get a large share. CM: For these countries, the proportion *falciparum* might instead be derived from the regional average? RS: In PAHO, also imported *vivax* cases occur.

Urban versus rural malaria (SH)

As demonstrated above for outside Africa, the effect of urbanicity in lowering malaria incidence is important for country incidence estimations. The newly available Global Rural Urban Mapping Project (GRUMP)³ allows for a stricter and more standardized classification of country populations into urban and rural than countries' own definitions which UNDP uses. According to GRUMP, 0.8% of the African area is urban, but this is probably still an overestimate. Applying population-density criteria to GRUMP, we classified 0.6% of Africa's area as urban⁴. Since EIRs and parasite prevalences are lower in urban compared to rural areas, urbanicity decreases the population at malaria risk, and malaria mortality and incidence. In the near future it will be possible to link GRUMP to national population maps, making it possible to calculate country urban populations for the global malaria incidence estimations. For outside Africa, the population-density thresholds might have to be defined independently.

Discussion:

For analyzing the effect of urbanicity on malaria in the Oxford urban Africa paper⁴, categorization into 4 PR/EIR categories introduces arbitrariness and it may mask a possible rebound effect at highest PR. Analysis with PR and/or EIR as continuous variables is preferred.

The group agrees that the standardized urban definitions forthcoming from GRUMP should replace the current UNDP ones in the country incidence estimations. For consistency, it should then be verified that research studies used for inferring incidence rates in urban areas match the GRUMP urban definition. This is probably the case, because urban research studies are usually very clearly urban rather than peri-urban. This verification should be done at a 'back-prediction' of urban areas that accounts for smaller urban areas at the time of the research studies (typically late 1980s) than in GRUMP-2004.

IC: The approach in Simon's recent study might also serve to cross-check the estimated impact of urbanicity in reducing malaria incidence that we so far derived from incidence research studies. The reduction in EIR and PR in urban areas would then have to be assessed by principal anopheline vector.

Uncertainty bounds around country estimates (NW)

Given that the estimation is not a direct inference from data from population-based samples but a non-statistical synthesis of different methods, the uncertainty bound can only be estimated, not calculated precisely as a '95% confidence interval'. The approach taken for HIV/AIDS estimates by UNAIDS may be considered: first defining the uncertainty in subsequent steps, then summing all uncertainties by a Delta method, or by assuming normal distributions for each uncertainty, which yields much smaller resulting errors.

In this case, uncertainty intervals would have to be estimated for:

- Population size by country and urban/rural division: could be guesstimated based on the timing of the most recent census.
- National population sizes by endemicity level: could be done by calculating the length of endemicity class boundaries in each country compared to the national surface area and population distribution.
- Basic incidence rates, by endemicity, age group and urban/rural division: from sensitivity analyses, not directly from the statistical models, because the model input data are not a representative sample and are likely to have systematic biases.
- Coverage of ITNs and IRS: For ITNs, 95% confidence intervals follow directly from survey data.
- Impact of ITNs and IRS: from Cochrane review of short-term trials, ignoring for simplicity possible non-representativeness of these results for longer time periods, other age groups and other endemicity levels.
- Triangulation against HIS data for non-African countries: unclear whether this increases or reduces the error, because we don't know whether reporting competenss in HIS might truly be below 1%.

The above approach will not give precise uncertainty bounds for all steps and all countries. As a simplification, for a given step in the estimation we could divide the countries into low/moderate/large uncertainty and assume e.g. $\pm 5\%$, $\pm 10\%$ and $\pm 25\%$ uncertainty for these respective categories. Or the overall level of uncertainty might be pinned at the order of magnitude typically arrived at for other diseases. For example, for HIV incidence, uncertainty has been estimated at $\pm 50\%$ for countries with high prevalence and good surveillance systems and $\pm 100\%$ for most countries with low prevalence⁵. The proposed uncertainty bounds for malaria incidence for Africa should be compared with those estimated recently for mortality in African under-5s by Alex Rowe for CHERG.

To get comparable uncertainty bounds for all countries, it is preferable to standardize the estimation method as much as possible, e.g. for Southern Africa do a risk-based estimation rather than an HIS-based one, by constructing a risk map that is valid for Southern Africa. Uncertainty will be smaller for regional estimates than for country estimates, and will in any country be smaller for the time trend than for the absolute level.

Case fatality rates resulting from proposed incidence estimates (EK)

Compared to existing estimates of malaria mortality globally, the proposed incidence estimates would generally be consistent with plausible case fatality rates (CFRs), ranging between 0.06% and 0.85% for different world regions and age groups. Since CFRs are so variable between settings and over time, however, this only means that the proposed incidence estimates are not implausible. Moreover, the triangulation is probably circular, because consensus on realistic CFRs is in part based on earlier comparisons between incidence and mortality estimates.

Discussion:

IC: Could CFRs be estimated independently from demographic surveillance sites (DSS)? BN: probably not, since DSS do not usually monitor morbidity on a continual basis, and if they monitor fever incidence, this is usually without slide confirmation of malaria. CM: Could CFRs be estimated independently based on vital registration data? BN: In African settings, vital registration systems are

prone to misclassification, such as misclassifying AIDS deaths in adults as malaria, thus compromising the validity of this method.

CM: Lacking an alternative method for malaria mortality estimation in all countries for all age groups, might the incidence estimates also be used as the basis for new mortality estimates, by applying fixed case fatality rates? EK: The same problem with estimating and assuming fixed CFRs as for EIP's past back-calculation of incidence from mortality would apply: in reality, CFRs vary considerably between settings and over time, depending on quality of and access to care.

How to update country estimates for future MDG reporting rounds (EK)

In the proposed method, risk-based country estimates change with changing population size, with changing ITN or IRS coverage and with changing proportion of population that is urban. For HIS-based estimates, in addition to population size only the trend in case notifications would apply.

For Africa, it was proposed to additionally apply the trend in the proportion of outpatient visits due to malaria and/or proportion of hospital deaths due to malaria. The rationale is that African incidence estimates correlate better with these HIS outcomes than with absolute malaria case notifications. Since the proportional outcomes are also influenced by time trends in other disease (such as HIV!) and the correlation is not too high (around 25%), however, the group feels that that this should not be done. This is despite the observation that some ITN trials demonstrated that ITN use decreased sick-child clinic visits for malarial illness. The influence of non-malarial intervention on the proportion of outpatient visits and other proportional HIS outcomes attributed to malaria in African countries might be explored as follow-up to planned measles vaccination campaigns.

Discussion:

NW/IC: When the method changes, e.g. for defining population at risk, new incidence estimates should always be presented alongside updated estimates for older years (i.e. as a time trend), to avoid suggesting spurious changes over time.

All: Applying the trend in case notifications for HIS-based estimates is unacceptable. This is too sensitive to changes in reporting completeness and health care access, and may for example change with increasing availability in the public sector of artemisinin-based combination therapy. Instead, fix the HIS-based country estimates at the average case notification rate over a few years, and apply the national trend in ITN coverage, population size and proportion urban to that, just as for risk-based estimates. If, however, for a country the case notification rate changes dramatically, this is a reason to flag that country for a more thorough re-estimation of malaria incidence, using preferably the risk-based method.

Changes in population at risk are the most problematic part of updating. It is conceivable that large-scale ITN or IRS programmes reduce population at risk, not only malaria incidence within at-risk populations. It is therefore preferable that new risk maps outside Africa allow for the concept of prevention impact, and be based on recent PR and EIR data, not data from the early 20th century. For middle Africa, however, the use of the climate-based MARA map while accounting for impact of ITN and IRS at the level of the incidence rate within fixed risk areas seems acceptable, at least in the short term until new and better data are available.

The period-prevalence of child fevers in DHS and MICS surveys might be explored as an additional time trend indicator. In the longer term, once more PR and anemia data become available from malaria surveys, the trend in these indicators might be considered to help updating incidence estimates.

ACTION POINTS

Planning and time line

The overall proposed planning for completing incidence estimations is:

- November 2004 - April 2005:
 - improving estimates, including an extended APW with Oxford on endemicity mapping outside Africa
 - circulating estimates with regional offices and country experts,.
- Spring 2005/summer 2005: country consultations for countries with most malaria and/or largest uncertainties.
- In the interim, use the draft estimates for the next MDG reporting round and GBD, at least at regional level.
- In the longer term:
 - distribute Excel spreadsheet to allow country estimations done in countries, for use in calculating expected impact of intervention programmes, GFATM applications, etc.
 - develop a system to export and use endemicity maps at country level.

Action points for improving overall estimation (EK):

1. For countries with no risk-based estimate, replace the assumed 100% reporting completeness by the median value for the surrounding region, e.g. 25%.
2. Calculate HIS 'reporting completeness' separately for the middle African countries with a risk-based estimate, excluding the small and low-malaria countries where reporting completeness was *assumed* to be 100%.
3. Check whether surveys measuring ITN coverage outside Africa were truly national, in order to avoid duplicate correction to arrive at a coverage estimate for the population at risk.
4. Replace UNDP urban populations by GRUMP urban populations, forthcoming from Columbia/Oxford.
5. For countries with few reported cases e.g. below 1000, check whether the proportion *falciparum* in HIS case notifications is possibly biased by imported cases.
6. Propose uncertainty ranges.
7. Improve the method for the updating of country estimates, as proposed above.
8. Trace the rationale for the 2-9 year age group for measuring PR as the criterion of endemicity category for the Lysenko map (Metselaar en Van Thiel 1959). This might also be relevant for the appropriate age range in DHS, MICS, MIS surveys with a malaria lab-component...
9. Include additional estimates of ITN coverage using survey data on alternative indicators, in particular household possession of nets (using a conversion factor between net possession and use), for countries with no data on child usage of ITNs.
10. Modify report section on cases prevented by ITN+IRS to state that the previous calculation referred only to the subset of countries with a risk-based estimate.
11. Add to the report a description of uncertainties and the effect of HIS triangulation separately for each of the big malarious countries outside Africa: India, Indonesia, Pakistan and Myanmar.
12. For these countries, refine the estimation to first sub-national level, and do country consultations on revised estimates.
13. Search for independent data or expert opinion on HIS reporting completeness (not within system, but compared to total burden in population), especially for countries with low estimated completeness and for the 5 non-African countries with most malaria cases. Probe in particular for whether the HIS is changing.
14. Prepare a presentation explaining the interregional distributions and their differences to previous GBD estimates.

Action points for endemicity mapping outside Africa (SH):

1. Standardize ITH 2004 description of transmission boundaries, using standard definitions of urbanicity and its impact on malaria, and standardized altitude thresholds.
2. Refine map using 1 km² resolution for population data (GRUMP?).
3. Thereby, solve the remaining 7% of population at undetermined risk.

4. Define uncertainty bounds for country populations at risk, based on the number of borders between endemicity categories relative to the country surface area, and the population distribution over this surface and the endemicity borders. (and urban/rural distinction?)
5. Provide country endemicity distributions, population sizes and proportions urban at first subnational level for India, Indonesia, Pakistan and Myanmar.
6. Get a translation into English of the Lysenko book chapter (EK/RBM will do this.)

Possibly:

7. Refine map using HIS data at lowest administrative level? This is too ambitious to do for all countries, but might be done for 10 big countries - *if* JM can get the data from countries/regional offices.
8. Redoing Lysenko-like endemicity classification with recent PR survey data, from extensive literature review. Some data might come from the active case detection studies reviewed for the incidence rate estimation outside Africa. Especially for SEARO and WPRO: China, India and Indonesia, Pakistan, and Myanmar. Do a contingency table of the predicted PR from Lysenko against empirically observed PR. Use this to correct Lysenko-endemicity class for regions with a systematic mismatch, e.g. too high predicted PR across several neighbouring countries). Or to justify the simplistic Lysenko-updating approach of downscaling all non-Africa area by one endemicity class.

Action points for incidence rate estimation for African under-5s (IC):

1. Replace the SAMC-based rate estimate for Angola and Zambia by the middle African rate, or by an average of the two methods.
2. Estimate a rate for urban Africa, using existing research data (Ghana?) and a forthcoming 4-site study from Christian Lengeler on school children.
3. To improve geographical representativeness:
 - a. try relaxing the duration of 12-months multiple criterion, using MARA map of seasonality in malaria transmission.
 - b. try relaxing age criterion, e.g. including studies with slightly higher upper age bound (6-year olds are quite similar to 4-year olds).
4. Explore in the CHERG dataset the relationship between the incidence of acute malarial episodes and PR and anemia prevalence (need not necessarily apply strict age and seasonal criteria in this analysis, as long as the incidence and PR or anemia are from the same age group and season).
5. If there is a relationship under (4), try to impute incidence for Central Africa based on more abundant EIP/PR data points there.
6. Verify that urban studies were truly urban in the definition by GRUMP/Oxford, on a back-prediction of GRUMP for the time of the research studies.

Action points for Incidence rate estimation outside Africa (ARF/EK)

1. Verify that urban studies were truly urban in the definition by GRUMP/Oxford, on a back-prediction of GRUMP for the time of the research studies.
2. Try analysis for *vivax* and *falciparum* separately, preferably including additional studies which have been identified by Bob Snow.
3. Discuss with Bob Snow his reason for not including passive case detection studies for outside Africa, while relying on surveillance data for Southern Africa.
4. Try to adjust studies' results for oversampling the high-malaria season, to avoid overestimation of basic incidence rates.

Longer-term issues and beyond the incidence estimation

1. Promote standardization of the definitions of IRS coverage and its measurement (how?).
2. Promote measurement of parasite prevalence in surveys, including in MICS and DHS.
 - a. Make a list of priority countries for such surveys, including Central Africa (the MICS in DRC?) and African countries with planned measles vaccination+ITN distribution campaigns.

It is of note that for countries with perennial malaria transmission, such as in Central Africa, the timing of DHS and MICS surveys in the relatively 'dry' season does not render PR and anemia measurements useless; this is only an issue for countries with more strongly seasonal malaria.

3. Promote standardized assessment of national HIS reporting completeness, through standard reporting forms or surveys.
4. For consistency, not only RBM but also DHS, MICS and other international survey initiatives may wish to consider replacing countries' and UNDP definitions of urban versus rural by GRUMP, or presenting survey outcomes by urban/rural stratification in both definitions.
5. Reconsider terminology endemicity maps: 'holo-endemic/hyper-endemic/meso-endemic/hypo-endemic', as according to Lysenko, or 'very high/high/moderate/low'?

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