Outcome of the WHO Evidence Review Group on malaria low density infections

Dr A. Bosman

Malaria Policy Advisory Committee (MPAC) Meeting
17-19 October 2017
Chateau de Penthes, Pregny-Chambésy, Switzerland
Outline of the presentation

• WHO process for developing malaria policies
• ERG objectives, participants and method of work
• Conclusions of WHO ERG
• Draft recommendations for MPAC consideration
WHO policy-making process for malaria

Evidence Review Groups

- A
- B
- C

Technical Expert Groups

- Vector Control
- Surveillance monitoring evaluation
- Chemotherapy
- Drug Resistance & Containment

WHO GMP Secretariat

MPAC

VCAG (with NTD)

WHO DG

WHO policy recommendations

Evidence Review Group on submicroscopic falciparum and vivax infections
Background of the ERG meeting

- In recent years, the application of nucleic acid amplification (NAA)-based diagnostic tools in epidemiological surveys and research has continued to expand.
- WHO reviewed the evidence in 2013 and issued recommendation on the use of malaria diagnostics in low transmission settings.
- A WHO evidence review group on MDA, MSAT and FSAT concluded in 2015 that using current point of care (POC) diagnostic tests, MSAT and FSAT are not suitable as interventions to interrupt malaria transmission.
- More recently, funding agencies, manufacturers and researchers have been working towards developing ultra-sensitive RDTs with limits of detection similar to those of NAA-based methods. One highly-sensitive RDT is now commercially available (Alere™ Malaria Ag P.f RDT, http://www.alere.com), with manufacturer claims of ten-fold higher sensitivity compared with conventional RDTs.
- The concept note, objectives and plan of convening a Evidence Review Group on submicroscopic falciparum and vivax infections were presented to the WHO Malaria Policy Advisory Committee in March 2017 and widely supported.
Objectives of the meeting

• To review data on the natural history of submicroscopic *P. falciparum* and *P. vivax* infections in different epidemiological settings, to evaluate implications for detectability, duration of infection, and infectivity, and to assess the relationship with symptoms of clinical malaria.

• To describe at population level the contribution of submicroscopic *P. falciparum* and *P. vivax* infections to transmission with respect to different levels of vectorial capacity and immunity in the population.

• To define procedures for the case management and reporting of submicroscopic *P. falciparum* and *P. vivax* infections identified through multiple means, e.g., reactive case detection, surveys, research, etc.

• To review and update the WHO recommendations on the diagnosis of *P. falciparum* and *P. vivax* malaria in low transmission settings, which were endorsed by the Malaria Policy Advisory Committee in March 2014, based on the report of the 2013 ERG meeting.

• To establish a set of research priorities and study design characteristics to address knowledge gaps on the relative importance of submicroscopic infections and the public health impact of detecting them using highly sensitive diagnostic tests.
Preparations for the meeting

The GMP/PDT unit collaborated with Dr Teun Bousema, Radboud University Medical Center of The Netherlands, and Professor Chris Drakeley, London School of Tropical Medicine and Hygiene, in the planning of the ERG meeting, selection of studies and experts to prepare the literature reviews.

Pre-reads of the meeting:

1. Hannah Slater & Lucy Okell: Systematic literature review on the density, temporal dynamics and infectiousness of submicroscopic *P. falciparum* infections

2. Leanne Robinson, Natalie Hofmann and Stephan Karl: The detectability and infectivity of submicroscopic *P. vivax* infections

3. Patrick Kachur: Clinical consequences of submicroscopic vivax and falciparum malaria infections

List of participants

**ERG Panel Members**
- Graham BROWN (Chairperson)
- Sócrates HERRERA
- Patrick KACHUR
- Richard MAUDE
- Kamini MENDIS
- André Lin OUEDRAOGO
- Robert SINDEN
- Hannah SLATER
- Fitsum TADESSE

**ERG Participants**
- David BELL
- Teun BOUSEMA
- Gonzalo DOMINGO
- Chris DRAKELEY
- Jessica LIN
- Ivo MUELLER
- Lucy OKELL
- Leanne ROBINSON
- Thomas SMITH

According to WHO’s Guidelines for Declaration of Interests (WHO expert), an interest is considered “personal” if it generates financial or non-financial gain to the expert, such as consulting income or a patent. “Specificity” states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has “financial significance” if the honoraria, consultancy fee or other received funding, including those received by experts organization, from any single malaria-related company exceeds 10,000 USD in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

Global Malaria Programme

World Health Organization
List of participants (continued)

Rapporteur
- Natalie HOFMANN

Observers
- Jonathan COX
- Iveth GONZALEZ JIMENEZ

WHO Secretariat
- Pedro ALONSO
- Andrea BOSMAN
- Jane CUNNINGHAM
- Kimberly Ann LINDBLADE
- Abdisalan NOOR
- Peter OLUHEME
- David SCHELLENBERG
- P. Silvia SCHWARTE
1. A high proportion of *P. falciparum* and *P. vivax* infections identified in cross-sectional surveys are characterized by low parasite densities undetectable by conventional RDT and microscopy. Although limited by small sample sizes, the relative frequency of low-density infections appears to be higher in low transmission settings than in high transmission ones. The presence of such infections is likely influenced by many factors, including the recent history of transmission, rates of superinfection, genetic diversity of parasites, treatment and immunity. More detailed analyses of existing data and larger datasets from low to very low transmission settings are required in order to improve estimates of the proportion and distribution of low-density infections. Data are limited, and there is great uncertainty regarding estimates in very low transmission settings. More studies are required that also consider the recent history of transmission and potential impact of residual immunity in the population.
Table 1. The proportion of *P. falciparum* and *P. vivax* infections that are submicroscopic at different levels of transmission. Transmission intensity is classified by malaria prevalence assessed using NAA-based techniques. Data taken from published and unpublished studies that assessed *P. falciparum* and *P. vivax* parasitemia using NAA-based methods (Slater & Okell, Robinson, meeting pre-reads).

<table>
<thead>
<tr>
<th></th>
<th>Low transmission</th>
<th>Moderate transmission</th>
<th>High transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-10%</td>
<td>10-20%</td>
<td>&gt;20%</td>
</tr>
<tr>
<td><strong>P. falciparum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies</td>
<td>n = 9</td>
<td>n = 1</td>
<td>n = 8</td>
</tr>
<tr>
<td>Unweighted Mean(^1) (IQR)</td>
<td>75.0% (77.3 - 90.4)</td>
<td>not applicable</td>
<td>56.7% (51.4 - 63.6)</td>
</tr>
<tr>
<td>Weighted Mean(^2) (Cl(_{95}))</td>
<td>85.4% (81.5-88.7)</td>
<td>72.2 (67.4-76.6)</td>
<td>51.1% (48.7-53.5)</td>
</tr>
<tr>
<td><strong>P. vivax</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies</td>
<td>n = 29</td>
<td>n = 20</td>
<td>n = 15</td>
</tr>
<tr>
<td>Unweighted Mean(^1) (IQR)</td>
<td>82.5% (68.0-100)</td>
<td>72.6% (59.2-90.7)</td>
<td>57.2% (50.0-73.8)</td>
</tr>
<tr>
<td>Weighted Mean(^2) (Cl(_{95}))</td>
<td>70.7% (67.5-73.8)</td>
<td>72.0% (70.2-73.7)</td>
<td>58.1% (56.3-59.8)</td>
</tr>
</tbody>
</table>

\(^1\) The unweighted mean is calculated by taking the raw average over all studies, by transmission level, of the proportion of submicroscopic infections observed in each study (independent of study size). The interquartile range is given as measure of variability in the proportion of submicroscopic infections between studies. For *P. falciparum* only one study was characterized as “moderate transmission” and the unweighted mean is thus not applicable.

\(^2\) The weighted mean is calculated as an overall proportion of submicroscopic infections from accumulated data by transmission level and reported with a binomial 95% confidence interval.
2. Evidence from several reports using mosquito-feeding experiments indicates that mosquitoes can be infected with low-density *P. falciparum* and *P. vivax* infections, although less efficiently than with high-density infections. For *P. vivax*, gametocyte densities closely follow those of asexual parasite stages. Transmission to mosquitoes becomes less efficient at *P. vivax* densities below the limit of detection (LOD) of expert microscopy (estimated at >10 parasites/µl), but can readily occur with infections below the LOD of field microscopy (estimated at >100 parasites/µl). For *P. falciparum*, the relation between gametocyte density transmissibility and the density of asexual parasitaemia is less predictable, and low-density infections below the detection level of expert microscopy can frequently result in mosquito infection. The outcome of experimental mosquito feeds is influenced by a variety of host, vector and parasite factors in addition to methodological factors, but their dynamic interactions are poorly understood.
3. Depending on the relative proportions of low- and high-density infections in a particular location, the role of each in overall transmission may vary considerably. Mosquito feeding experiments help to measure the infectiousness of low- and high-density infections for mosquitoes. However, there are limited data on the relative contributions of low- and high-density *P. falciparum* and *P. vivax* infections to the onward transmission to human populations at the community level. It is critically important to understand the contribution of low-density infections to malaria transmission in order to inform effective malaria control strategies.

4. Conclusive data on the natural history of low-density *P. falciparum* and *P. vivax* infections in different endemic settings remain elusive. Knowledge gaps exist in understanding the longitudinal dynamics of parasite density and infectivity in untreated chronic natural infections; identifying risk factors for carriage of low-density infections; and understanding the prospective clinical and pathological impacts of untreated low-density infections. Available evidence related to the different parasite biology of *P. falciparum* and *P. vivax* suggests that chronicity of infection is achieved through different mechanisms for the two species: antigenic variation and persistence in the blood stream for *P. falciparum*, and periodical relapses for *P. vivax*. 
Figure 2. Models of the average pattern of *P. falciparum* and *P. vivax* blood-stage infection dynamics. Blood stage parasitemia is depicted in the absence of super-infections. Within individual infections, there is fluctuation in density. Figure taken from the ERG presentation by Ivo Mueller.
5. With the available evidence, it is difficult to accurately predict how the identification and treatment of low-density *P. falciparum* and *P. vivax* infections through active screen-and-treat based interventions in different endemic settings would impact transmission. Moreover, it is not possible to predict the proportion of the total infectious reservoir that would need to be detected and eliminated in order to accelerate the reduction of transmission. **Intervention trials** in different epidemiological settings using appropriate control interventions are warranted in order to evaluate the impact on transmission and cost–benefit of applying highly sensitive diagnostics for targeting low-density infections. Until the outcomes of such trials are available, highly sensitive diagnostics should not be part of any routine malaria control or elimination programme; their use should be limited to research purposes.
Detectability of low parasite infections

Figure 3. Parasite density distributions by quantitative NAA methods of individuals from Burkina Faso that are detectable (red) and undetectable (blue) by microscopy (left panel); and the proportion of infected individuals (middle panel) and of the infectious reservoir (right panel) that is detected with different diagnostic sensitivity thresholds (1, 10 and 100 parasites/μL). Figure from Slater & Okell, meeting pre-read, unpublished data.
6. To improve comparability of results, better harmonization and standardization is required in the reporting of the molecular methods used for the detection, identification and quantification of malaria parasites in epidemiological surveys and research studies. Adherence to the Minimum Information for Publication of Quantitative Real-time PCR Experiments (MIQE) guidelines for reporting quantitative PCR results, as well as the validation of nucleic acid-based amplification assays using standardized and quality controlled material (such as the WHO International Standard for P. falciparum DNA NAA Assays) is strongly encouraged. Until standardization is achieved, all reports should include a detailed description of the precise methods used to obtain the data being reported, including the analytical sensitivity and specificity of tests.
Additional ERG expected outcome

- Agreement on **term** = submicroscopic infection or low density parasitemia or subpatent infection or ...
  
- Agreement on **definition** = blood stage parasitaemia below XX parasites/μL excluding isolated gametocytemia or ...

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**Diagram Description**

- **Desk Review** March - May
- **WHO Malaria Definitions**
- **WHO Departments (i.e. NTDs)**
- **Scientific Literature Terminology**
- **Priority Terms**
- **WHO Malaria Terminology Writing Committee** June - August
  - **New & Updated Definitions**
  - **Final List Terms & Definitions**
- **WHO Drafting Committee**
- **Web-based consultation**
- **MPAC Sept Review**

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**Global Malaria Programme**

**World Health Organization**
7. The terms “submicroscopic,” “asymptomatic,” and “low-density” infection are often used interchangeably in the literature, generating confusion. “Submicroscopic” generally implies parasitaemia that is below the LOD of microscopy or RDT, but detectable using molecular or other highly sensitive diagnostic methods. The use of the term “submicroscopic” for describing low-density malaria infections should be discouraged. The term “asymptomatic” is not based on parasite density and instead refers to the absence of signs and symptoms of malaria. Asymptomatic malaria should be defined with respect to the absence of specific clinical manifestations and the time period evaluated in relation to infection detection. In light of these definitions, the term “low-density” infection is considered most appropriate. When parasitaemia is quantified, a clear definition of “low-density infection” should be reported (suggested: <100 parasites/µl), accompanied by a description of the method of quantification. In studies that do not quantify parasitaemia, low-density infections can be defined as those identified through highly sensitive methods but not detected using conventional diagnostics (microscopy or RDT).
8. Updating the WHO recommendations on the diagnosis of *P. falciparum* and *P. vivax* malaria in low transmission settings is required in order to clarify that WHO does not currently recommend highly sensitive RDTs, other highly sensitive non-NAA-based methods, or NAA-based methods for parasite detection in the routine management of clinical malaria and surveillance. Research is needed to document the public health benefits and cost–effectiveness of detecting and treating low-density infections in low transmission areas and/or specific population groups. In particular, potential research objectives for highly sensitive diagnostics could include epidemiological research to understand the contribution of low-density infections to transmission, border screening of immigrants or migrant populations, foci investigations including the mapping of low-density infections, and use in pregnant women for the detection and treatment of low or sequestered parasite biomass.
To comply with the above conclusions, the WHO/GMP secretariat in consultation with the ERG Panel Members developed draft recommendations on the diagnosis of *P. falciparum* and *P. vivax* malaria in low transmission settings. These are listed below for consideration by the WHO MPAC.

8.1. Quality-assured conventional RDT and microscopy are the recommended diagnostic tools for the confirmation and management of malaria cases and malaria surveillance, including routine health information systems and household surveys, in all epidemiological situations. Malaria cases should be reported by type of diagnostic test used.
8.2. A number of highly sensitive techniques are available that detect low-density infections (below 100 parasites/µl). Until there is evidence that the detection of low-density infections using these tools will accelerate malaria elimination, in elimination settings, these tools should only be used for research purposes.

8.3. The majority of infections with asexual parasites have gametocytes detectable by NAA methods, and there is no known benefit of routine detection of low-density gametocytes by molecular methods. All malaria infections (including those infections with low-density parasitaemia) should be considered as potentially infectious.

8.4. Presentation of NAA results should include details of the methods used for sample collection and extraction, and the equivalent quantity of blood added for the PCR reaction, as well as details of outputs in DNA copies or parasite density.

8.5. Before the role of serological assays in malaria elimination programmes can be determined, there is a need for standardization and validation of reagents (antigens and controls), assay methodologies and analytical approaches.
Many thanks for your kind attention