Technical Consultation on the role of parasite and anopheline genetics in malaria surveillance

Surveillance Unit
Laura Anderson
Abdisalan Noor
Dyann Wirth
Malaria Policy Advisory Committee, 2019
Background

• Emerging evidence shows that genetic epidemiology can create new opportunities for malaria surveillance, prevention and control
  • Mosquito genotyping for improved mechanisms for speciation, better understanding of vectorial capacity and monitoring of spread of insecticide resistance
  • Parasite genotyping for understanding of transmission intensity and gene flow, including drug resistance, Pfhrp2/3 deletions and facilitating quantification of malaria importation risk

• Most work to date has been carried out in research settings with few examples on how malaria genetic epidemiology can be used to improve operational decisions made by NMCPs
Three day Technical Consultation 5 to 7 June

Approved by MPAC in October 2018

**Main objectives**

- To understand the role of genetic epidemiology (specifically parasite and anopheline genetic signals and gene flow) in malaria surveillance and control
- To define priority research questions that are relevant to policy and operational activities of national programmes

**Other objectives**

- Review existing evidence across the use cases of genetic epidemiology in malaria surveillance
- Identify key research questions relevant to policy and operational activities of national programmes for each use case
- Discuss appropriate study protocols and issues related to ethics, data sharing and coordination mechanisms

**Deliverables**

- A meeting report summarizing the content of the presentations, discussions and outcomes of the meeting
- A list of key research questions relevant to policy and operational activities of national programmes for each use case
- A work plan to implement the key action points of the meeting
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<tr>
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<th>Presenters</th>
<th>Rapporteur</th>
<th>WHO GMP</th>
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<td>Dyann WIRTH</td>
<td>Junhu CHEN</td>
<td>Koya ALLEN</td>
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<td>Members</td>
<td>Dominic KWIAKTOWSKI</td>
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<td>Prevention, Diagnostic and Treatment</td>
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<td>Junhu CHEN</td>
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<td>Elimination</td>
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<tr>
<td>Bryan GREENHOUSE</td>
<td>Alistair MILES</td>
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<td>Drugs, Efficacy and Resistance</td>
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<td>Alfredo MAYOR</td>
<td>Olivo MIOTTO</td>
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<td>Didier MENARD</td>
<td>Daouda NDIAYE</td>
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<td>Alvaro MOLINA-CRUZ</td>
<td>Daniel NEAFSEY</td>
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<td>Global TB Programme</td>
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<td>Infectious Hazard Management</td>
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<td>Kumar V. UDHYAKUMAR</td>
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<td>Sarah VOLKMAN</td>
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Global Malaria Programme
Meeting process

5 sessions

1. Experience from other diseases
   - Polio: Elimination setting
   - Ebola: Outbreak setting
   - TB: Ongoing transmission setting

2. Malaria parasite, anopheline gene flow, modelling

3. Parasite gene flow and spread of drug resistance

4. Parasite and mosquito genetics to understand transmission intensity

5. Parasite and anopheline gene flows to understand importation and identify foci of transmission
Meeting process

Group work

Group 1: Surveillance of *pfhrp* 2/3 deletions and drug resistance

Group 2: Transmission and elimination

- What are the use cases where genetic data will be most useful for national malaria programme strategy and operations?

- Do we have adequate information to make policy recommendations?

- How best do we collect the required data (SoPs, coordination, timelines, data sharing, analysis)
# Meeting process

<table>
<thead>
<tr>
<th>Use case/application</th>
<th>Operational component</th>
<th>Field sampling (methods, data source, spatial scale, frequency)</th>
<th>Laboratory (methods, standardization, expected advances)</th>
<th>Ethics and data sharing</th>
<th>Added value</th>
<th>Challenges for implementation</th>
<th>Immediate, medium- or long-term action</th>
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<tr>
<td>1) Monitoring changes in frequencies of molecular markers of drug resistance over time and space</td>
<td>First-line drug policy decisions</td>
<td>Passive case detection</td>
<td>Amplicon sequencing or other genotyping methods</td>
<td>Data ownership: country owns primary data</td>
<td>Less expensive than TES</td>
<td>Unbiased population sampling – including establishment of appropriate spatial sampling strategy</td>
<td>Immediate</td>
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<td>Identify populations at risk of treatment failure</td>
<td>Active sampling desirable</td>
<td>Aggregate data shared with the malaria community</td>
<td></td>
<td>Early warning of clinical failure</td>
<td>Nagoya protocol</td>
<td>Evidence ready for submission to WHO for review within six months to one year</td>
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<td>Desired frequency: annual or semi-annual</td>
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<td>Ability to genotype from dried blood spots</td>
<td>Countries need technical support and capacity-building to generate, store and analyse the data.</td>
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<td>Dried blood spots</td>
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<td>Allows more dense sampling in time and space and at epidemiological scales</td>
<td>Procurement and access to reagents. May need to rely on regional reference laboratories</td>
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<td>Spatial sampling strategy should be relevant to implementation of national drug policies (e.g., district,</td>
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**Global Malaria Programme**

**World Health Organization**
What we expect from MPAC

- Review and improve priority questions and next steps.

- Discuss and agree on the lead and coordinating roles of WHO in each of the next steps.

- Advise on proposals to use existing sentinel sites and passive case detection systems for sampling.
Priority Questions- *pfhrp2/3* deletions

**Surveillance for *pfhrp2/3* deletions**

- Sufficient evidence from several countries to show that deletions of *pfhrp2 +/- pfhrp3* can cause false-negative HRP2-RDTs.

- WHO has developed recommendations on investigating suspected false negative RDTs due to *pfhrp2/3* deletions as well as indications for when countries should switch to non-HRP2-exclusive RDTs.

- WHO has established a network of reference laboratories experienced in *pfhrp2/3* genotyping and a proficiency testing scheme for malaria NAAT that includes *pfhrp2/3* deleted parasites.

- Surveillance for *pfhrp2/3* deletions across all epidemiological settings is essential for maintaining confidence in HRP2-RDT results and detecting areas where RDTs are failing.
Monitoring changes in frequencies of molecular markers of drug resistance over time and space

- Sufficient evidence to show that molecular markers can be used to monitor changes in drug resistance in parasite populations over space and time.

- Essential for detecting populations at risk of treatment failure in order to subsequently inform first-line drug policy decisions (ensuring that effective treatment is given to patients).

- **Routine monitoring** should be implemented at the appropriate administrative level, which is relevant for the implementation of national drug policies.
Determining the origins of drug resistance

- Determining the origins of drug resistance can facilitate the monitoring of the spread of resistance within and between countries.

- By monitoring haplotypes associated with drug resistance mutations from samples on a routine basis and comparing them over time and across regions, it is possible to determine if drug resistance is emerging locally or spreading.

- Identifying populations at risk can inform regional drug policies and ensure interventions are targeted to contain resistance.

Detecting changes in parasite population structure or signatures of positive selection

- Detecting changes in parasite population structure to determine whether there is anthropogenic impact from interventions or other selective pressures can help to identify populations at risk for emergence of resistance.

- Early detection of emergence of new resistance mechanisms through identification of new resistance markers.
Monitoring local species composition and changes over time

• Improved understanding of local species composition and changes over time (gene flow within countries and between countries) can i) inform selection of vector control tools by identifying key vectors responsible for transmission, and ii) aid in assessing residual transmission and its implications for the effectiveness of interventions.

Insecticide resistance surveillance

• Monitoring insecticide resistance allows for the targeting of specific interventions (e.g., pyrethroid-PBO nets) and resistance mechanisms (e.g., mixed-function oxidase (MFO) resistance mechanisms) over time. Such monitoring also enables programmes to assess the value of different insecticide resistance management strategies (e.g., IRS rotation, new types of ITNs, attractive toxic sugar baits).
Priority Questions - Transmission

Vector species dynamics

• Understanding **vectorial capacity** and **vector competence** to inform surveillance and control measures surrounding imported cases.

• Imported case management in countries with **low transmission** or in **malaria-free** countries with **high receptivity risk** for sustained introduced transmission.

• Understanding the **local vector competence** for **imported malaria species** can help to define risk and inform response strategies for outbreak prevention.
Priority Questions-Transmission

Changes in transmission

- Understanding changing transmission and being able to distinguish between natural fluctuations in parasite populations and the impact of interventions are important for future strategic planning.

Transmission intensity

- Understanding the levels of transmission intensity and transmission patterns with accuracy can inform stratification and malaria control strategies, detect persistent local transmission and help to establish a baseline of variation for future parasite population-genetics studies.

Gene drive

- With increasing research on gene drive as a control strategy, it is necessary to map implementation of research and assess impact on local mosquito and parasite populations.
Elimination and low transmission settings: case classification of local, introduced or imported cases

• In low transmission settings, accurate case classification is crucial to certify a country as malaria-free (certification).

• The use of genomic data can add precision to case classification (indigenous vs imported), providing a country with evidence demonstrating zero indigenous cases of malaria.
Elimination and low transmission settings: risk factors for local transmission and outbreak investigations

• In low transmission settings, genomics can also help to identify active foci, provide information on the origin of imported cases, identify high-risk groups for infection and for sustaining transmission (“hotpops”), and assess their contribution to onward transmission.

• Genomic data can help to determine how geographical areas may be linked through regular travel/importations. In considering progress towards elimination, it is important to generate data that help to elucidate parasite boundaries in a region, regardless of administrative borders, so that determination of origin and control measures can be implemented in relation to the parasite boundary rather than administrative borders.

• In outbreak investigations, genomic data can be used in conjunction with conventional epidemiology to confirm linkages between locally transmitted cases. This information can be used to direct public health resources appropriately and prevent unnecessary investigations or interventions.
Opportunities for which WHO should take a lead role

- WHO should develop and host a database of researchers and institutions involved in policy-relevant malaria genetic epidemiology studies, and this database should be updated annually.
- WHO should make the table of research priority areas identified during this meeting available online and update it on an annual basis with help from research networks and individuals.
- Evidence review groups should be convened in a timely manner as new evidence emerges.
- In addition to research studies, there are opportunities to explore drug and insecticide resistance monitoring sites, collecting genetic samples during case detection and investigations in elimination settings, and in burden reduction settings, passive case detection systems as well household surveys could become the mainstay for genomic surveillance. A structured approach that will not add unnecessary burden on health system is needed.
- Established global databases should be harnessed to develop information products relevant for policy and country operations.
Opportunities for which WHO should take a coordination role

• Investment in regional and national capacities for genetic epidemiology should be sought.
• WHO should work with researchers to ensure that study protocols are designed to generate evidence in formats relevant to policy and programmes. For example, studies exploring the relevance of genomic surveillance metrics must include a comparison to metrics currently recommended by WHO and used by countries in terms of their relevance, reliability, accuracy, precision, cost and sustainability.
• Use cases share several overlapping themes across the spectrum of transmission in terms of understanding gene flow in insecticide and drug resistance. Studies should maximize these linkages so that common data generation platforms and samples can be used, wherever possible.
Challenges

- Countries need technical support and capacity-building to generate, store and analyse the data.
- Lack of reference genomes; a global database of comparable sequences is required which should be accessible for submitting data, querying (useful outputs for public health) and analysis (research).
- Nagoya protocol- Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization.
- Robust regional reference laboratory networks and outsourcing of genotyping/bioinformatics.
- Standardization across data, genotyping and analysis types for comparison.
- Quality assurance and control.
- Translation of genetic data into information that can easily be used for control and elimination programmes.
Thank you