Technical consultation on the role of parasite & mosquito genetics in malaria surveillance to optimize response by national programmes

Malaria Policy Advisory Committee
17-19 October 2018
Abdisalan Noor on behalf of SUR, ELI, DER, EVC and PDT units
Malaria surveillance in GMP

GMP surveillance

- Epidemiology
- Drug efficacy & resistance
- hrp2 deletions
- Entomology, insecticide efficacy & resistance

GMP/SUR
- GMP/ELI
- GMP/DER
- GMP/PDT
- GMP/EVC

Parasite

Vector

Genetics and molecular epidemiology
## Malaria surveillance in GMP

### Malaria Threats Map

- **VECTOR INSECTICIDE RESISTANCE**
  - Resistance of malaria mosquitoes to insecticides used in core prevention tools of treated bed nets and indoor residual sprays threatens vector control effectiveness

- **PARASITE pFhrp2/3 GENE DELETIONS**
  - Gene deletions among some malaria parasites cause false negative diagnostic test results, complicating case management and control

- **PARASITE DRUG RESISTANCE**
  - Resistance of malaria parasites to artemisinin - the core compound of the best available antimalarial medicines - threatens antimalarial drug efficacy

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**Global Malaria Programme**

[World Health Organization](https://www.who.int)
Highly evolvable malaria vectors: The genomes of 16 Anopheles mosquitoes


**INTRODUCTION:** Control of mosquito vectors has historically proven to be an effective means of eliminating malaria. Human malaria is transmitted only by mosquitoes in the genus *Anopheles*, but not all species within the genus, or even all members of each vector species, are efficient malaria vectors. Variation in vectorial capacity for human malaria among *Anopheles* mosquito species is determined by many factors, including behavior, immunity, and life history.

**RESULTS:** We sequenced and assembled the genomes and transcriptomes of 16 anophelines from Africa, Asia, Europe, and Latin America, spanning ~100 million years of evolution and chosen to represent a range of comparisons to individual genes or sets of genomic markers with no genome-wide data to investigate attributes associated with vectorial capacity across the genus.
As the transmission intensity decreases from high to low levels, changes in mosquito (entomological inoculation rate [EIR]; human complexity of infection [COI]), and parasite (genotyping) indicators are anticipated to change. With relatively high transmission (e.g., EIR > 1), there are high COI levels and a predominance of polygenomic infections as assessed through genotyping methods.

As transmission decreases to more moderate (e.g., EIR from 0.1 to 1) or lower levels (e.g., EIR from 0.01 to 0.1), decreases in COI are detected and increases in the proportion of individuals harboring monogenomic infections.

Eventually as transmission intensity is very low (e.g., EIR from 0 to 0.01) evidence of COI = 1 and clonal parasite populations among monogenomic infections are detected using genotyping methods.
## Potential use cases

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<th>Use</th>
<th>Genetics</th>
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<td>8. Identification of imported cases</td>
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<td>9. Transmission chains</td>
<td>Parasite</td>
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</tbody>
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**Spread of dihydroartemisinin–piperaquine resistance to north Cambodia**

(A) Each point represents a sample from northern Cambodia.

(B) Genome-wide neighbour-joining tree of all samples from northern and western Cambodia in the dataset, with those carrying *plasmepsin 2-3* amplifications identified by black dots at the tip. The circular subpanels show a magnified view of parts of the tree containing samples from northern Cambodia carrying *plasmepsin 2–3*
Mapping transmission intensity

Mapping malaria by combining parasite genomic and epidemiologic data

Amy Wesolowski¹, Aimee R. Taylor²,³,⁴, Hsiao-Han Chang²,⁵, Robert Verity⁵, Sofonias Tessema⁶, Jeffrey Bailey⁷,⁸, T. Alex Perkins⁹, Daniel Neafsey⁴,¹⁰, Bryan Greenhouse⁶,¹¹, Caroline O. Buckee²,³
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Data

- Genetic data
  - SNP
  - Short haplotypes
  - Microsatellite
  - Whole genome

- Epidemiological data
  - Date and location of clinical cases
  - Population prevalence
  - History of travel

Methods

- Genetic measure of relatedness
  - Population: Fₚ, Jost’s D
  - Individual: IBS, IBD

- Connectivity between subpopulations
  - Travel survey
  - Gravity model
  - Mobile phone data

Translation

- Epidemiologically relevant metrics
  - Transmission intensity
  - Connectedness between populations
  - Rate of importation

- Impact on decision making
  - Effect of IRS on community A
  - Spatial scope of coordinated interventions
  - Where is local transmission interrupted?
Neighbour-joining tree of *Plasmodium falciparum* populations.

Prefixes of genomes indicate parasite origins: Green text indicates parasite populations from the Democratic Republic of the Congo (DRC); orange indicates parasite populations detected in soldiers who were returning from the DRC to Guatemala; red indicates parasite populations from Guatemala.
‘Variation in vectorial capacity for human malaria among Anopheles mosquito species is determined by many factors, including behavior, immunity, and life history.’

‘This variation in vectorial capacity suggests an underlying genetic/genomic plasticity that results in variation of key traits determining vectorial capacity within the genus.’
Multiple genetic origins of histidine-rich protein 2 gene deletion in *Plasmodium falciparum* parasites from Peru

Sheila Akinsi, Tonya Hayden, Dionicia Gamboa, Katherine Torres, Jorge Benclezú, Joseph F. Abdallah, Sean M. Griffing, Wilmer Marquiño Quezada, Nancy Arropide, Alexandre Macedo De Oliveira, Carmen Lucas, Alan J. Magill, David J. Boon, John W. Barnwell & Venkatachalam Udhayakumar

Major Threat to Malaria Control Programs by *Plasmodium falciparum* Lacking Histidine-Rich Protein 2, Eritrea

Araia Berhane, Karen Anderson, Selam Mhreteab, Karryn Gresty, Eric Rogier, Salih Mohamed, Filmon Hagos, Ghirmay Embaye, Anderson Chinorumba, Assefash Zehaie, Simone Dowd, Norman C. Waters, Michelle L. Gatton, Venkatachalam Udhayakumar, Qin Cheng, Jane Cunningham
Challenges

• Insufficient discourse between genomics researchers and policy making processes
• Few joint genetics and epidemiological analyses to ease translation of results to policy/operations
• Complex and diverse methods and limited national capacity, insufficient representative samples
• Unresolved ethical, regulatory issues in the collection, sharing and use of genetic materials
• Lack of clear guidance on priority policy relevant research questions
Opportunities

• Increasing number of demonstration studies
• Growing acceptance that genomics can play a role in policy and programme decisions
• Increasing investments in genomics epidemiology research
• Improving sampling and analysis methods and expanding regional capacity
• More clarity on the ethics of use of genetic materials
Drug resistance gene flow

Transmission intensity

Parasite gene flow

- Local transmission chains
- Identify foci of transmission
- Identify imported cases

Hrp2 & 3 deletions

Vectorial capacity

Insecticide resistance
Objectives of proposed technical consultation

1. Review existing evidence across the use cases
2. Refine the use cases to prioritize studies
3. Identify key research questions relevant to policy and operational national programme activities in each use case
4. Discuss the role of WHO in the legal, regulatory and ethics space to set standards for study designs and access to data
5. Explore possibility of a global WHO data portal
Reviews of existing literature on use cases

TC jointly convened by SUR, ELI, DER, EVC and PDT

Report submitted to MPAC

Nov 2018 – Feb 2019

March 2019

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