ERG on multidrug-resistant *P. falciparum* in the GMS

Minutes of ERG meeting
Presented by D. Wirth, Chair of the ERG

Geneva, 22-24 March 2017
MPAC meeting
Background

• At the Malaria Policy Advisory Committee (MPAC) meeting, 14–16 September 2016, Professor N. White (Mahidol Oxford Tropical Medicine Research Unit) cited new evidence of a multidrug-resistant *P. falciparum* parasite lineage;

• MPAC requested that an Evidence Review Group (ERG) assess the relevance of the information and report the potential implications to MPAC at the next meeting in March 2017.

• Meeting was organized 20-21 December in Geneva
Situation of drug resistance in the greater Mekong

• Artemisinin resistance in *P. falciparum* has emerged independently and evolved in the GMS over the past decade;

• Even in the presence of artemisinin resistance, efficacy rates of ACTs may still be adequate. It is only once resistance to the partner drug emerges that treatment failure rates increase significantly;

• Resistance to artemisinin-based combination therapy (ACT) partner drugs, including piperaquine and mefloquine, has been detected in the GMS resulting in the declining efficacy of some of the recommended ACTs;

• In response to the drug resistance situation and the declining number of malaria cases, in May 2015, GMS Ministers of Health adopted the *Strategy for malaria elimination in the Greater Mekong subregion 2015–2030*. 
Objectives of the meeting

General Objective
• To discuss the emergence and spread of multidrug-resistant *P. falciparum* lineages in the GMS.

Specific Objectives
• To review new evidence on the emergence and spread of multidrug-resistant *P. falciparum* lineages with the *PfKelch13* C580Y mutation and the *Pfplasmepsin* 2-3 gene amplification in the GMS;
• To assess the risk posed by these parasites in terms of malaria control and elimination in the GMS and in other parts of the world;
• To identify evidence gaps and provide recommendations for further research.
Percentage of samples with C580Y mutation

Studies done with start-year **2008-2011** and n ≥ 15

Studies done with start-year **2013-2015** and n ≥ 15

**Percentage of parasites with C580Y**

- 0
- 0.01 - 5
- 5.01 - 20
- 20.01 - 50
- 50.01 - 90
- 90.01 - 100
• Three manuscripts were shared and presented by the relevant research groups:
  
  
  

• The ERG panel addressed the following key questions:
Is there new evidence of selection and spread of specific artemisinin-resistant genotype(s) in the GMS?

- PfKelch13 C580Y mutation can be found in several genetic backgrounds (at least 3 haplotypes) throughout the GMS;
- The prevalence of one specific PfKelch13 C580Y haplotype is increasing, replacing other haplotypes in an area that includes sites in western Cambodia, north-eastern Thailand and southern Lao PDR;
- This lineage is also resistant to piperaquine in western Cambodia and north-eastern Thailand;
- However, the frequencies of different PfKelch13 C580Y haplotypes vary by region, and no single haplotype is dominant throughout the GMS.
What would be the consequences of the selection and spread of specific artemisinin-resistant genotype(s)?

- Partial or total loss of efficacy with respect to artemisinin treatments;
- Global spread of a dominant haplotype encoding that would increase levels of resistance;
- A common genetic background could accumulate mutations that might encode potential compensatory factors, such as ACT partner drug resistance, fitness or transmissibility;
- Alternatively, the spread of *PfKelch13 C580Y* haplotypes could result in a loss of within-population genetic diversity (fitness disadvantage).
Is there evidence that artemisinin resistance has facilitated the emergence of partner drug resistance in the GMS?

- There is evidence of parasites with resistance to both artemisinin and piperaquine in Cambodia and areas of Thailand bordering Cambodia;
- Piperaquine resistance has occurred in the past in China and Cambodia independently of artemisinin resistance;
- Therefore, artemisinin resistance is not a prerequisite for the initial appearance of piperaquine resistance;
- It is not possible to determine the temporal relationship between the emergence of either resistance;
- There is no evidence that *PfKelch13* C580Y confers any resistance to piperaquine.
As the resistance mechanism is not understood, it is difficult to understand the spread of resistance in the different genetic backgrounds;

Different factors affect the selection and spread of piperaquine resistance:

- Artemisinin resistance may increase the exposure of the parasite population to piperaquine;
- Piperaquine long half-life (present as a monotherapy for about 1 month);
- Conversely, it is possible that the reduced efficacy of piperaquine has facilitated the selection of artemisinin-resistant mutations.

Not enough data are available to draw any conclusions for other ACTs except that there was a background of mefloquine resistance in the GMS prior to the introduction of artemisinin drugs.
Is there evidence of the geographical extent of artemisinin resistance outside the GMS?

• There is evidence of multiple *PfKelch13* mutations in many geographic regions:
  • none of these are associated with a haplotypic expansion of *PfKelch13* C580Y;
  • no evidence to indicate artemisinin resistance outside the GMS (according to WHO definition);
• One exception is the possible independent emergence of *PfKelch13* C580Y in Guyana.
What is the risk of the spontaneous emergence, selection and spread of artemisinin resistance and/or resistance to ACT partner drugs outside the GMS? (1)

- Historically, chloroquine, sulfadoxine and pyrimethamine resistance emerged in South-East Asia and spread.
- Mefloquine resistance also emerged in the GMS, but it has not spread to other regions;
- PfKelch13 mutations and probably piperaquine-resistant parasites are present at low frequencies in P. falciparum outside the GMS including Africa and elsewhere;
What is the risk of the spontaneous emergence, selection and spread of artemisinin resistance and/or resistance to ACT partner drugs outside the GMS? (2)

- There is the potential that these variants may rapidly select and spread:
  - The massive and uncontrolled use of dihydroartemisinin-piperaquine in settings outside the GMS (Africa) may lead to resistance and loss of efficacy of this treatment;
  - The fact that the PfKelch13 C580Y mutation is not spreading suggests that additional mutations may be necessary; under drug pressure, however, the necessary compensatory mutations might be acquired;
- Overall, there is a significant risk of artemisinin and partner drug resistance outside the GMS – either via spontaneous emergence or importation, and spread.
Identify research questions that might improve our understanding of artemisinin resistance

- Biologically characterize artemisinin resistance mutations and mechanisms of artemisinin resistance;
- Investigate the impact of parasite population characteristics, such as population genetic structure, on the emergence and spread of drug resistance;
- Assess the role of human mobility and drug use in the emergence and spread of resistance;
- Explore alternative drug regimens;
- Determine the contribution of artemisinin resistance to the spread of multidrug-resistant malaria parasites;
- Investigate the contribution of partner drug resistance to the spread of multidrug-resistant parasites.
Conclusions (1)

• Independent emergence and transnational spread of different lineages of artemisinin-resistant parasites have occurred throughout the Greater Mekong subregion (GMS).
• These multidrug-resistant parasites have been responsible for increasing dihydroartemisinin-piperaquine failure rates across Cambodia over the last 5 years.
• Artesunate-mefloquine is currently efficacious in Cambodia, with cure rates >95%, and is being used as first-line treatment in Cambodia as an intermediate solution.
Conclusions (2)

• The risk of a highly fit multidrug-resistant lineage spreading widely in higher transmission settings cannot be discounted.
• This risk is mitigated by the likelihood that resistance and/or fitness mutations residing on different chromosomes would be rapidly broken up by recombination in multiclonal infections.
• Similar to the situation in South-East Asia, changing transmission dynamics in Africa have resulted in larger regions of lower malaria transmission intensity.
• The shift in Africa towards higher drug pressure and less outcrossing in Africa increases the potential for the selection and spread of locally generated resistant strains.
• There is also a possibility for parasites from GMS to potentially become established and spread following importation. Nevertheless, issues of fitness, genetic complexity of the multi-resistant parasites and reduced prevalence of malaria in the GMS mitigate this risk.
Recommendations

• The new data reaffirm the need for an urgent and continued intensive regional malaria elimination campaign in the GMS;
• Surveillance for artemisinin and partner drug resistance needs to be continued and strengthened in the GMS;
• There is a critical need for surveillance outside the GMS to detect potential de novo resistance or the potential introduction of resistant parasites;
• Where surveillance signals a potential threat to leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.
Thank you for your attention