Antimalarial drug resistance

Artemisinin resistance in *P. falciparum* has arisen in the Greater Mekong subregion (GMS) and evolved over the past decade. Artemisinin resistance is strongly associated with point mutations in the propeller region of the Pfkelch13 (K13) gene. There are other genetic changes associated with artemisinin resistance which may either contribute to resistance or compensate for the fitness disadvantage incurred. Initially many independently arising mutations in K13 were observed in the GMS, but over the nine years this has been studied, certain mutations have progressively dominated, and outcompeted others. Several mutations associated with delayed clearance in the GMS were reported in Africa. However, contrarily to what has been seen in the GMS, these specific mutations do not seem to affect parasite clearance time in Africa or to undergo clonal expansion.

Artemisinin resistance is defined as delayed parasite clearance; it represents a partial resistance. The effect of artemisinin resistance on the efficacy of artemisinin-based combination therapies (ACTs) is variable, depending on the efficacy of the ACT partner drug. The reduction in the artemisinins’ parasite clearance rate results in larger numbers of parasites being exposed only to the partner drug. This increases the probability that partner drug resistance will emerge or lead to expansion if resistance was already present.

Resistance to partner drugs has been detected in the GMS including resistance to piperaquine and mefloquine. This has resulted in falling efficacy of some of the recommended ACTs. In Cambodia, high treatment failure rates have been observed with dihydroartemisinin-piperaquine while artesunate-mefloquine is currently highly efficacious, In Viet Nam, dihydroartemisinin-piperaquine has started to show increasing failure rates. In Thailand, high number of treatment failures has been observed after treatment with artesunate-mefloquine. In areas of southern Lao PDR, therapeutic efficacy of artemether-lumefantrine has declined.

**Recent evidence of emergence of *P. falciparum* parasites resistant to artemisinin and piperaquine**

At the meeting of the WHO Malaria Policy Advisory Committee (MPAC), 14–16 September 2016, researchers cited new evidence of a few multidrug resistant *P. falciparum* parasite lineages having developed, and are spreading geographically and outcompeting other *P. falciparum* parasites in the process. WHO called for the submission of the new evidence for review. MPAC requested that an
assessment of the relevance of the information is made, and that the potential implications are reported to the MPAC at the next meeting in March 2017.

The evidence appears to show that on the Thailand-Myanmar border, against a backdrop of declining malaria prevalence, another lineage with the K13 C580Y mutation has steadily taken over and is now the dominant genotype (Anderson et al.). A similar pattern is evident in western Cambodia; a C580Y lineage which probably emerged in the Pailin area in Cambodia has spread to Thailand and then east to southern Lao PDR (Imwong et al.).

Piperaquine resistance in *P. falciparum* was reported as early as 2002. Piperaquine resistance is associated with amplification of the gene encoding *Pfplasmepsin* 2-3. In epidemiological studies conducted in western Cambodia, *Pfplasmepsin* 2-3 amplifications were found only in association with the K13 C580Y mutation. The diversity of parasites which were piperaquine resistant was significantly less than those which were not (Imwong et al). This indicates that they have arisen more recently within the K13 C580Y lineage.

Mefloquine resistance is associated with amplification of wild type *Pfmdr1*. Amplification of *Pfmdr1* occurs readily but is associated with a significant fitness disadvantage so parasite populations exist in an equilibrium determined by the selection pressure. On the Thailand-Myanmar border, the efficacy of artesunate-mefloquine has worsened in recent years. While mefloquine resistance is associated with amplification of wild type *Pfmdr1*, piperaquine resistance is associated with single copy *Pfmdr1*.

**Plan for an Evidence Review Group meeting**

The Global Malaria Programme is proposing to convene an Evidence Review Group meeting to review the evidence, and advise WHO on the risk posed by falciparum parasites resistant to artemisinin and piperaquine. In preparation to the meeting, WHO will collect relevant publications on the topic and include any data shared by the relevant research groups (Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand, and Southwest Foundation for Biomedical Research, Texas, USA) for an in-depth analysis.

The specific objective of the Evidence Review Group meeting will be:

- To review the new evidence on the emergence and spread of multidrug resistant *P. falciparum* lineages with the *PfKelch13* C580Y mutation and the *plasmepsin2/3* gene amplification in the GMS;
- To assess the risk that these parasites may pose for malaria control and elimination in the GMS, and in other parts of the world;
- To identify evidence gaps and provide recommendations for further research.

The conclusions of the Evidence Review Group will be presented to the MPAC in March 2017.

**References**
