Malaria—a mapping of artemisinin resistance confirms that resistance is confined to Asia

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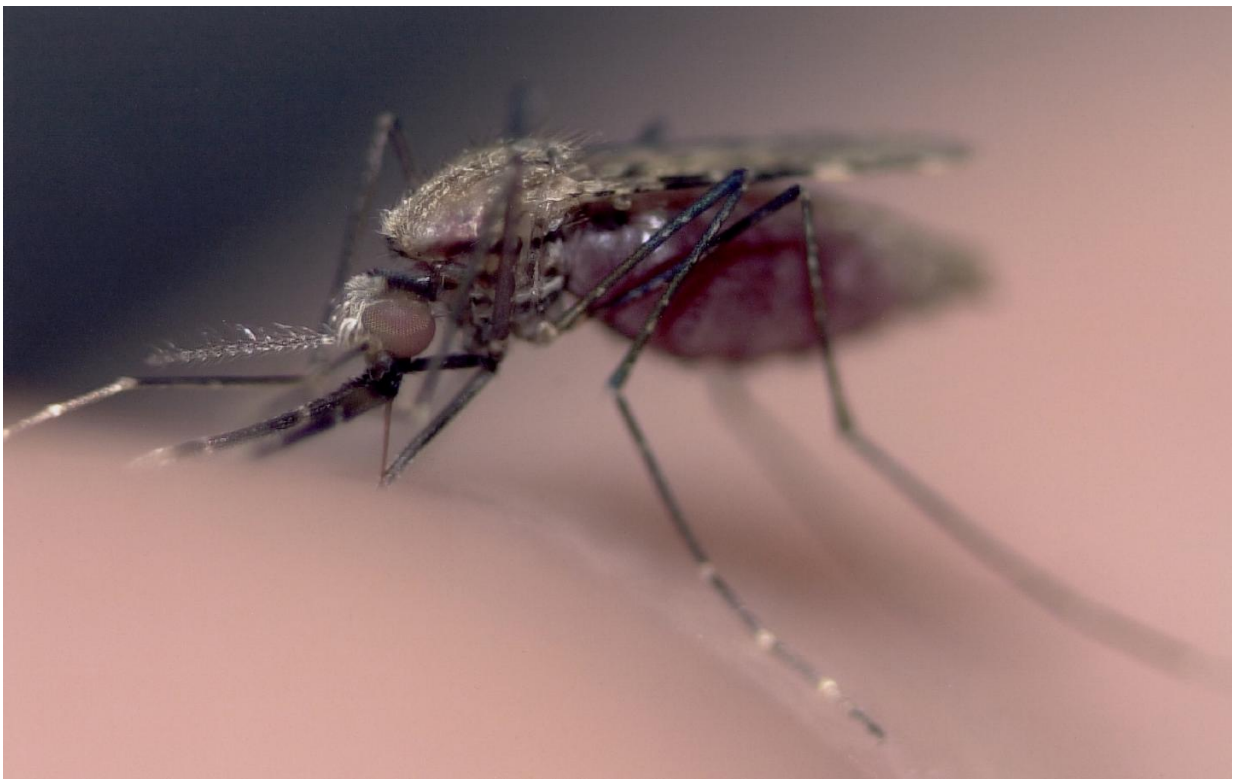

Anopheles gambiae mosquito. Credit:nstitut Pasteur/Paul Brey

The first global mapping of artemisinin resistance (the KARMA study) has definitively confirmed that resistance to the main drug currently used in the treatment of *Plasmodium falciparum* malaria is for the

moment confined to Southeast Asia and has not spread to sub-Saharan Africa. Led by researchers from both the Institut Pasteur in Paris and the Institut Pasteur in Cambodia, KARMA gathers a large consortium of institutions including 13 members of the Institut Pasteur International Network. The findings were published on the 22nd of June in the *New England Journal of Medicine*.

Since 2008, the emergence in Cambodia of *Plasmodium falciparum* strains resistant to artemisinin derivatives, the latest generation of anti-malarial drugs, has seriously threatened the global effort to fight malaria.

Over the past two years the Institut Pasteur researchers have been leading an international consortium KARMA (K13 Artemisinin Resistance Multicenter Assessment Consortium), supported by the World Health Organisation (WHO) and conducted with 41 partners, including 13 from the Institut Pasteur International Network, in 59 endemic countries. The KARMA study builds on the previous discovery in 2014 by scientists from the Malaria Molecular Epidemiology Unit at the Institut Pasteur in Cambodia and the Department of Parasites and Insects Vectors at the Institut Pasteur in Paris, identifying the K13 gene as the major determinant of artemisinin resistance of *P. falciparum* in 2014.

Between May and December 2014, they studied the diversity (polymorphism) of K13 gene on 14037 blood samples from patients infected with *P. falciparum* from 59 endemic countries (72 per cent in Africa, 19 per cent from Asia, 8 per cent from Latin America and one per cent from Oceania). The samples analyzed were all collected after 2012 in order to have the latest possible overview of the situation.

"Until now scientists have not had the tools to be properly informed about the nature of resistance to anti-malarial drugs in key affected regions such as sub-Saharan Africa," said Didier Ménard, head of the

Malaria Molecular Epidemiology Unit at the Institut Pasteur in Cambodia. "The KARMA study mapping results is the public health breakthrough so badly needed in the fight against Malaria."

The KARMA study results takes on added significance because it was in Southeast Asia that parasites resistant to chloroquine, the first generation of molecule used against malaria, first emerged in the late 1960s. Unfortunately, molecular markers for detecting this resistance were identified well after the resistant parasites had spread in Africa, causing millions of deaths.

"We now have the capacity, thanks to molecular markers, to be able to trace at a global level and virtually in real-time, resistance to antimalarial drugs" said Ménard. "We must ensure that we use this technology to keep us a step ahead of the parasite and prevent history from tragically repeat itself in Africa". According to the latest WHO estimates, there were 214 million cases of malaria and 438 000 deaths in 2015, mostly in sub-Saharan Africa.

While 103 K13 protein mutations were already known, including 4 conferring resistance to artemisinin (according to the WHO definition), the KARMA study identified 70 new mutations. "We suspect that only a small number of mutations appear to be associated with resistance, which should facilitate global monitoring of resistance to artemisinin" explained Odile Mercereau-Puijalon, from the Department of Parasites and Insect Vectors at the Institut Pasteur in Paris.

Indeed, KARMA shows that the most frequent mutation found in Africa (A578S) is not associated with resistance. "While previous studies showed the emergence of this mutation in Africa, we have gone further by observing and demonstrating biologically that this mutation does not spread."

The KARMA study also identified, two foci, each comprising multiple emergence events of artemisinin resistant parasites, in Cambodia-Vietnam-Laos and Myanmar- Western Thailand-South China. These foci were found to be independent from each other and tend to show that it is likely that international strategies were so far successful in containing the widespread dissemination of resistance.

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