Genetic surveillance and why it's critical in the fight against antimalarial drug resistance

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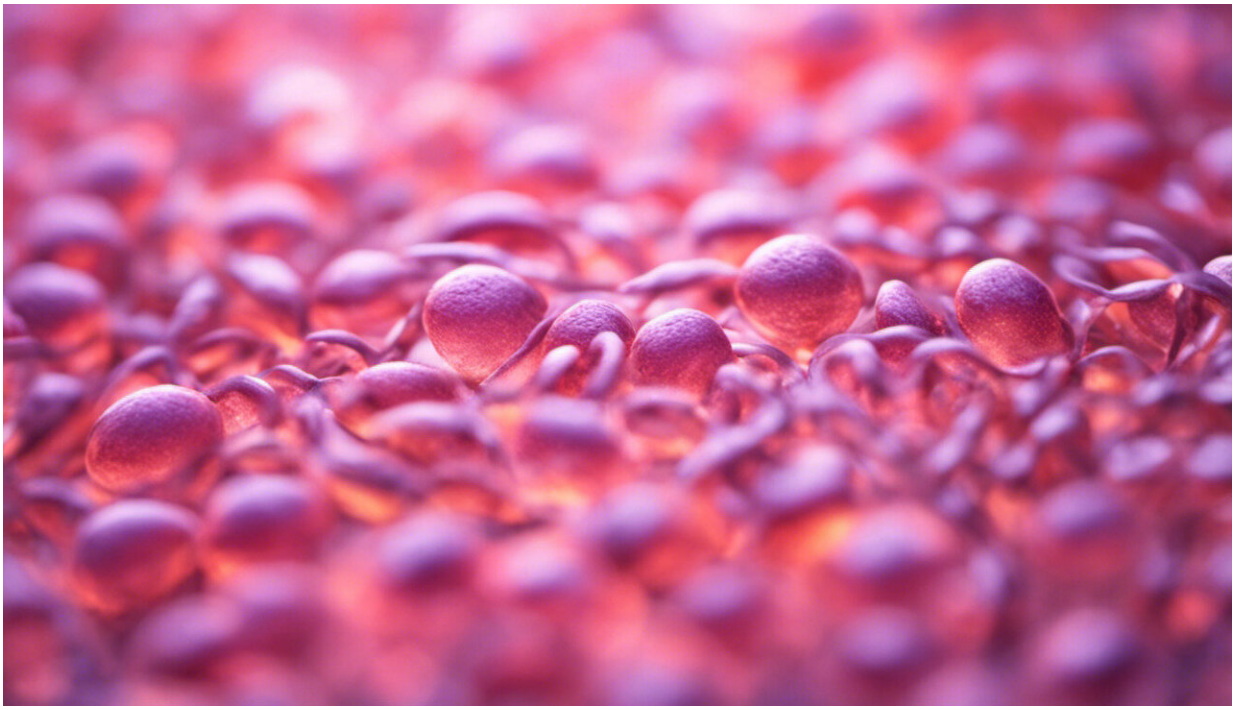

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Efforts to tackle malaria infections over the past decades have yielded impressive results across the tropics, so much so that full elimination is now a public health priority for many malaria endemic countries.

However, resistance to frontline treatments against malaria has emerged

and spread across South-East Asia, which is proving a major challenge for elimination efforts. To achieve malaria elimination and contain multidrug antimalarial resistance, strong surveillance systems are essential.

With widespread resistance to older drugs, artemisinin-based combination therapy (ACT) is now recommended for the treatment of uncomplicated malaria caused by the *Plasmodium falciparum* parasite in nearly all areas of the world. ACT contains potent artemisinin – derived from the sweet wormwood plant and known to quickly clear malaria parasites from a patient's blood – plus a second, longer-acting drug, which eliminates the remainder and limits resistance to artemisinin. The WHO currently recommends five ACTs that can be used depending on efficacy against local strains of this type of malaria.

A small set of tools are available to assess resistance to antimalarial drugs, with varying costs. These range from clinical trials that compare the efficacies of different drugs, to lab-based methods that assess the growth of the parasites in the presence of particular doses of drugs.

Genetic analysis

As the cost of genetic analysis decreases, a relatively low-cost option for surveillance is to collect samples of parasites from small volumes of blood taken by a finger-prick from a malaria patient. These blood spots can then be looked at in the laboratory to determine the genetic sequence of the parasite DNA. Particular mutations in the DNA have been clearly associated with resistance to certain drugs. In fact, we now have a whole collection of genetic alterations that are markers of resistance (www.wwarn.org/tracking-resistance) to almost all the currently used drugs.

In the past, molecular markers of resistance to antimalarials were

identified long after the resistant parasites had emerged and spread throughout the world. However, with the advancements of molecular tracking and surveillance technology, we have the unusual opportunity to monitor the prevalence of mutations in the kelch gene (K13), which is associated with artemisinin resistance, as they evolve in time and across different locations.

This early phase molecular information is allowing us to support elimination or containment of the resistant parasites in South-East Asia, before they spread elsewhere. Monitoring the potential emergence, spread and prevalence of K13 mutations in other regions can provide us with an early warning system to trigger rapid public health mobilisation to drive elimination. The WHO's latest recommendations include extending surveillance outside this region.

In Africa, where there is the greatest global burden of malaria morbidity and mortality, a global collaboration effort is mounting to monitor mutations associated with ACT resistance. To date, numerous mutations associated with artemisinin resistance in Asia have been found in low frequencies in sub-Saharan Africa, but they are not yet clearly associated with reduced drug efficacy in patients.

In West Africa, antimalarial drugs in treatment and prevention of malaria are key tools of the strategy to control malaria. However, this success is highly dependent on the continuing efficacy of the drugs. Efforts to identify and monitor any drug resistance in the malaria parasites at molecular level is essential.

The additional cost of collecting blood spots on filter papers, however, can be prohibitive in sub-Saharan Africa. But there is work being done into the reuse of positive diagnostic tests that are widely available in health centres across sub-Saharan Africa. The idea is that the tests – which work like a pregnancy dip-stick – could be used to extract parasite

DNA and their genetic profiles used to provide a picture of the resistance pattern in the parasite population. Reusing these malaria positive diagnostic tests could prove a more cost-effective of carrying out large-scale surveillance of antimalarial drug resistance.

With reducing costs and increasing speed possible from taking a patient sample to receiving a result, it is possible to envisage real-time molecular marker evidence contributing to evidence based decision making. Genetic information is a valuable tool to monitor the occurrence or spread of drug resistance and agreeing standards of reporting and pooling of results is critical in the fight against this deadly disease.

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