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The rapid and aggressive spread of artemisinin-resistant *Plasmodium falciparum* carrying the *kelch13* C580Y mutation is a growing threat to malaria elimination in Southeast Asia, but there is no evidence of their spread to other regions. We conducted cross-sectional surveys in 2016 and 2017 at two clinics in Wewak, Papua New Guinea (PNG) where, among 239 genotyped clinical samples, we identified three infections caused by C580Y mutants. Ring-stage survival assays (RSA) for artemisinin showed that these mutants exhibited the highest survival rate (6.8%) among the parasites surveyed. Analyses of *kelch13* flanking regions by microsatellite markers did not suggest a common origin of mutants in PNG and Cambodia. Comparative analyses based on deep sequencing data from 389 clinical samples from PNG, Papua Indonesia and Western Cambodia supported an independent origin of the Wewak C580Y mutation, showing that the mutants possess several distinctive genetic features. Identity by descent (IBD) showed that multiple portions of the mutants' genomes share a common origin with parasites found in Papua Indonesia. Within these shared haplotypes, a number of alleles differentiate Wewak C580Y mutants from other PNG samples, including several within genes previously associated with drug resistance, such as *mdr1*, *ferredoxin*, *atg18* and *pnp*. These findings suggest that *P. falciparum* lineages are spreading across New Guinea, gradually acquiring a complex ensemble of variants, including *kelch13* C580Y, which may affect their drug sensitivity. This worrying development reinforces the need for increased genetic surveillance of the evolving parasite populations on the island, to contain the spread of resistance.

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A LONG-LASTING PROTECTION OF CHEMOPROPHYLAXIS IMPLANT AGAINST MALARIAL INFECTION

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Liver stage *Plasmodium* control is essential to decrease new malaria infection and to prevent relapsing malaria. One of the approaches is to parenterally administer an implant to provide a slow and long-acting release of antimalarial agent for causal prophylaxis. In the recent study, we have created a series of formulations for intramuscular or subcutaneous depot of decoquinate (DQ) by using hot melt extrusion (HME) or co-solvency methods. Compared to classic co-solvency method using synthetic polymers typical for controlled drug release, the implants prepared by the HME technique at doses of DQ 50-200 mg/kg provide much better efficacy in preventing *Plasmodium* infection in mice. A single intramuscular injection of an optimized, HME made, cholesterol-based composition, provides a DQ release at a slow rate and maintains a sufficient level of the desired drug active in mice for preventing *Plasmodium* infection for up to 4 months with a single inoculation of *Plasmodium* parasite sporozoites (50,000) by tail vein. To reflect real-world endemic exposure, repeated inoculations of the same number of parasites (sporozoites) were given each time at an interval of each month to mice with initial one time intramuscular injection of the implant. Surprisingly in this case, the mice remained free of the disease for as long as 7 months. The implants made by HME also demonstrated far better protection for the same period of time than the simple physical mixing of the same formulation components, indicating that the mechanic process and the validated parameters for the HME play an important role in making desired implants. Our innovative, safe and controlled-released intramuscular implants utilize naturally available materials that are easily metabolized or degraded or excreted by animals or humans. The implant in the aqueous suspension (saline) for intramuscular placement results in limited pain or distress and the surgical removal rarely is needed. Furthermore, the HME process is environmentally clean, and the product quality and the massive production can also be quarantined. More studies using primates will be needed to further evaluate the implants.

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TRIPLE ARTEMISININ COMBINATION THERAPIES: A NEW PARADIGM FOR THE TREATMENT OF MALARIA?

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Artemisinin Combination Therapies (ACT) are first-line treatments for malaria. The Tracking Resistance to Artemisinin Collaboration (TRAC) mapped the spread of artemisinin resistance in 10 countries in Asia (7) and Africa (3) and described artemisinin resistance in Southeast Asia (SEA). In Cambodia, Thailand, and Vietnam, artemisinin resistance is compounded by partner drug resistance resulting in dihydroartemisinin-piperaquine (DHA-PPQ) treatment failure rates of >60%. The TRACII study conducted in 8 countries in Asia (7) and Africa (1) explored the concept of combining an ACT with a third antimalarial drug and assessed efficacy, safety and tolerability of two Triple ACT (TACT): DHA-PPQ+mefloquine (DHA-PPQ+MQ) and artemether-lumefantrine+amodiaquine (AL+AQ). Both TACT were safe, well tolerated and highly efficacious against ACT-resistant parasites in SEA. TACT could become standard treatment for malaria worldwide as part of strategies to prevent or delay emergence of drug resistant malaria in regions outside of SEA. A new project titled Development of Triple Artemisinin Combination Therapies (DeTACT) will take a multifaceted approach to assess potential benefits and disadvantages of deploying TACT as first-line antimalarial treatments. In a randomized, controlled, non-inferiority trial, we will compare safety, tolerability and efficacy of dose-optimised artesunate-PPQ+MQ and AL+AQ TACT in blistered co-packages versus ACT+placebo in 13 countries in Asia (5) and Africa (8). The potential of TACT to delay emergence and spread of antimalarial resistance and cost-effectiveness of deploying TACT will be assessed through mathematical modelling. We will address ethical issues such as balancing individual and community disadvantages versus public benefits of introducing TACT in regions where ACT are still efficacious. Market and demand related issues involved in development, implementation and deployment of TACT will be studied to guide future introduction in the global marketplace and communicated to stakeholders via a strategic engagement plan. Development of the project and progress to date will be presented.

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EFFECT OF ARTEMISININ ON THE SEXUAL CONVERSION OF *PLASMODIUM FALCIPARUM*

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Artemisinin-based combination therapies (ACTs) remain the frontline treatment for malaria. However, ACTs show limited efficacy against the transmissible sexual forms of the parasite, termed gametocytes, and some reports suggest that drug treatment increases sexual conversion rates. Here we combined *in vitro* and field-based approaches to determine whether artemisinin affects the production of *Plasmodium falciparum* sexual stages. We collected serial blood samples from 32 Vietnamese patients with uncomplicated falciparum malaria enrolled in an artemisinin clinical