

# High-quality, safe antimalarials for all

Dr Stephan Duparc on the importance of quality and pharmacovigilance in antimalarial drug development



The Medicines for Malaria Venture (MMV) believes that a mother seeking antimalarial treatment at a healthcare centre in a disease-endemic country in Africa, Asia, or South America, deserves the same standard of treatment for her child as a mother in Europe or the USA.

To make this belief a reality, all medicines co-developed by MMV meet high international regulatory standards, as endorsed by the International Conference of Harmonization (ICH) or the Pharmaceutical Inspection Cooperation Scheme (PIC/S), which ensures consistent quality standards. MMV also seeks high standards of approval from the World Health Organization's prequalification programme, which is a prerequisite for the procurement of antimalarials using public funding. The goal is to develop drugs that meet the international standards required to facilitate their widespread usage and to ensure quality, safety, and efficacy.

Even once MMV and a partner have developed a medicine and it is treating patients, the team's work is not yet complete. To continue to maximise the safe use of medicines post-approval, it is important to monitor drug safety in larger cohorts of patients in real-life settings, a process known as pharmacovigilance. In this interview, MMV's Chief Medical Officer, Dr Stephan Duparc explains why both quality control and pharmacovigilance is vital in the development and use of medicines for malaria.

## Why is it important that medicines meet international quality standards?

Low-quality medicines might have high levels of impurities, which can have a negative effect on the health of the person taking the medicine. Also, a drug with a sub-therapeutic level of active ingredient could result in treatment failures, which in the case of malaria could be fatal. Additionally, a partially effective dose can accelerate the development of drug resistance in the community.

Low-quality or fake antimalarials are being bought and sold in disease-endemic countries, but to what extent and what have been the repercussions for patients?

A recent review article published in the *Lancet* found that up to 35% of antimalarials collected in Southeast Asia and 20% in Africa were falsified.<sup>1</sup> This is a very serious issue. In fact, the global trade in fake medicines potentially kills up to 100 000 people every

year<sup>2</sup> while also putting effective treatments at risk of drug resistance.

The WHO also takes the issue very seriously and is working to tackle it together with Interpol – an intergovernmental organisation facilitating international police cooperation. In 2006 the WHO established the International Medical Products Anti-Counterfeiting Taskforce to halt the production, trading and selling of fake medicines around the globe.

Unfortunately, at the moment the consequences for those that produce and distribute fake medicines are not nearly as severe as they are for the patients that might use them. For example, the punishment for trafficking narcotics is much more severe than that for trafficking fake medicine. The production and distribution of counterfeit antimalarial drugs, or indeed any drug, should be deemed a serious crime against humanity and punished as such.

## Quality versus affordability

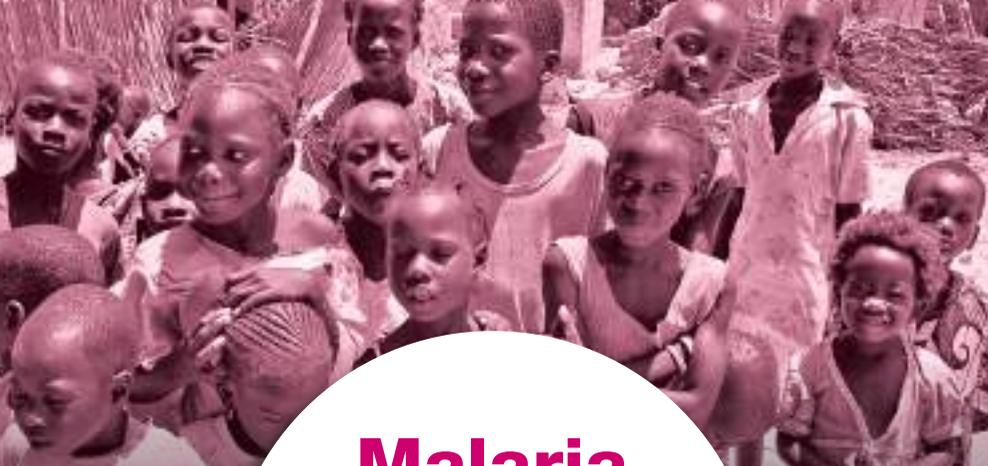
Pursuing quality takes time and money. How do you balance the need to develop affordable medicines and get them to patients quickly with ensuring the medicines are of high quality? Today, high-quality medicines for the treatment of malaria already exist and so there is no reason to accept a lower quality product in the name of urgency. Safety, efficacy, and quality must take priority.

As for affordability, this remains critical. At MMV we recognise that unless medicines are affordable, access is extremely problematic. The cost of goods is considered



Healthcare worker administering a dispensible ACT to a child in a clinic in Kenya

Stephan Duparc, MD, is the Chief Medical Officer with the Medicines for Malaria Venture, based in Geneva, Switzerland.



**Malaria**  
kills one child  
every minute

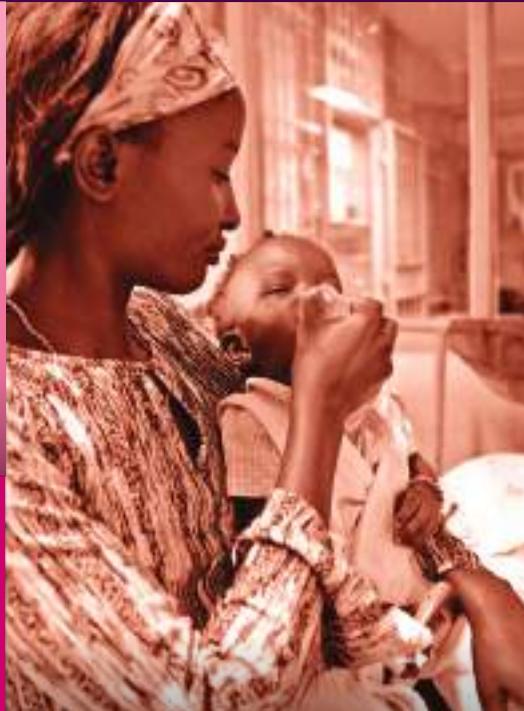
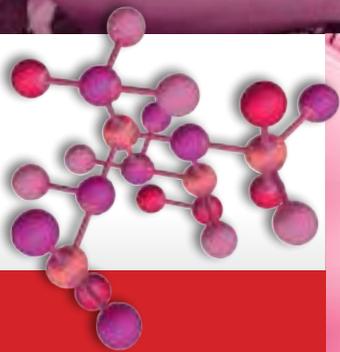
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MMV has brought forward four new antimalarials:

- **Coartem® Dispersible**, for young children  
– with Novartis
- **Artesun®** injection for severe malaria  
– with Guilin Pharmaceutical
- **Eurartesim®** tablets for uncomplicated malaria  
– with Sigma-Tau
- **Pyramax®** tablets for uncomplicated *P. falciparum*  
and *P. vivax* malaria – with Shin Poong

We will continue to develop new medicines until malaria is defeated.



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right from the outset of drug discovery and is one of the key components of our target product profiles for drug development. Additionally, all MMV partnering agreements include price targets. The goal is to ensure that an adult treatment course for malaria will be sold at a price that will maximise its uptake (around US\$1 today).

On the access side, we are working with partners to help design ways to make effective antimalarials affordable to the most vulnerable populations. One such initiative is known as CAPSS (Consortium for ACT private sector subsidy) – a private sector subsidy scheme designed to lower the costs of quality malaria medicines. The early evidence generated by the initiative helped shape the design of the international global subsidy mechanism AMFm, which seeks to lower patient prices for ACTs and thereby increase timely access to quality treatments.

### Medicine safety

Once a medicine has been developed and is in use for treating patients, how do you continue to ensure it is safe and effective in the real world?

First, to ensure safety, it is important that we develop a post-marketing Risk Management Plan (RMP) and a risk/benefit analysis of the drug. This analysis, while developed at the same time as the drug, is continually updated with any new adverse reaction reported throughout the lifespan of the drug. Stringent regulatory authorities and WHO request the RMP before they will endorse a new medicine. (At the moment this is not requested by the regulatory authorities in

malaria-endemic countries). The RMP lists all the pharmacovigilance studies that must be conducted post-registration in order to detect any new potential safety signals<sup>3</sup> or to follow-up on any potential safety signals previously detected during the development of the drug. The companies who own the drug must commit to a date when the report of the studies will be made available to the regulatory authorities. The WHO pharmacovigilance group has also published a detailed manual explaining how to undertake these studies for antimalarial drugs.<sup>4</sup>

To ensure efficacy/effectiveness, the WHO–Global Malaria Programme has developed a standard protocol<sup>5</sup> to determine if an antimalarial's efficacy has decreased. The protocol is for use in malaria-endemic countries to detect emerging drug resistance; there are also studies that are conducted by local key opinion leaders. The efficacy/effectiveness results of these studies now must be sent to the WorldWide Antimalarial Resistance Network (WWARN), which is working to gather all the data related to efficacy/resistance of the antimalarial drugs.

### Pharmacovigilance studies

Post-launch safety data on a new medicine can be collected either passively or actively. In an ideal world all patients experiencing an adverse reaction to a drug would report it to their physician, who in turn would report it to the pharmaceutical company, who would report it to the regulatory authority. This is known as passive reporting. In the real world, however, this process does not work optimally, particularly in malaria-endemic



Market stall in Cameroon selling a range of medicinal products

countries. Often patients and physicians simply don't report these events.

Alternatively, pharmacovigilance data can be collected actively, via Phase IV studies such as cohort event monitoring studies. These studies can be designed to detect adverse events classified as 'rare', which occur in between one in 3000 and one in 5000 patients. To detect such events, between 10 000 and 15 000 patients, respectively, must be followed. Patients take the first course of treatment at the clinic and then go home. A healthcare worker visits the patient during the following week to see if there are any problems. In addition, a subset of patients can be followed more closely if there are any specific concerns already detected with the medicine.

### Why is pharmacovigilance a priority for MMV now?

Our pipeline is maturing and we have co-developed three ACTs that have been approved by stringent regulatory organisations: Coartem®-Dispersible (artemether-lumefantrine developed with Novartis), Eurartesim® (dihydroartemisinin-piperaquine with Sigma-Tau), and Pyramax® (pyronaridine-artesunate with Shin Poong). While the toxicity profiles of artemisinin-based medicines have been well defined, we nonetheless must follow these medicines to be sure that they are as well-tolerated in the real world as in clinical trials. Additionally, we have new medicines in the pipeline with completely novel mechanisms of action, whose profiles are not yet as well defined. These will require even closer follow-up. We do not want to put patients at risk.

### Key pharmacovigilance projects

Sanofi, Drugs for Neglected Diseases initiative (DNDi), and MMV are undertaking a Phase IV field cohort event monitoring study to assess the real-life safety and effec-

tiveness of the fixed-dose ACT, artesunate-amodiaquine (AS-AQ), developed by DNDi, Sanofi, and partners. The study has now recruited two-thirds of the necessary patients in the health district of Agboville, Côte d'Ivoire, where AS-AQ is used as first-line treatment.

We are also planning a pharmacovigilance study of the recently approved Eurartesim with the INDEPTH Effectiveness and Safety Studies of Anti-malarial Drugs in Africa (INESS) in four African countries: Ghana, Tanzania, Burkina Faso, and Mozambique. The studies will begin once registration has been obtained in each of the countries. There are also plans to conduct similar studies with Pyramax in the Mekong Delta region, and with other ACTs in northern India together with DNDi.

Once completed, what implications might these studies have for the use of the medicines? To reiterate, these studies are critical. Sufficient evidence from pharmacovigilance studies, be it positive or negative, can have the potential to change the recommendations in the drug label, and therefore impact how the medicine can ultimately be prescribed and used in the future. It is all about ensuring that people receive the safest, most effective medicines possible.

### References

1. Nayyar GM et al. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis* 2012; 12: 488–96.
2. Bate R. *Phake: the deadly world of falsified and substandard pharmaceuticals*. AEI Press, Washington, DC, 2012.
3. A signal is defined by the Council for International Organizations of Medical Sciences (CIOMS) as "information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."
4. World Health Organization website: [www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/handbook\\_antimalarialpharmvigilance.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/handbook_antimalarialpharmvigilance.pdf)
5. World Health Organization website: [whqlibdoc.who.int/publications/2009/9789241597531\\_eng.pdf](http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf).

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