Meeting the challenge of artemisinin resistance

The malaria parasite and man have coexisted for millions of years – each influencing the other in their fight for survival. Historically, the parasite has become resistant to each medicine developed to kill it. One of the main reasons for the failure of the first global malaria eradication campaign, initiated in 1955, was the development of widespread resistance to chloroquine. Now, at the Thai–Cambodian border, the first signs of resistance to artemisinin, the key component of the current treatment of choice, have begun to emerge.1 In conversation with MMV’s Tim Wells, Chief Scientific Officer, and George Jagoe, Executive Vice-President, Global Access, we explore the real significance of this issue and what it means for antimalarial drug development.

What is drug resistance and why does it occur?

Tim: Drug resistance is a fact of life. When any species reproduces, random genetic mutations occur. The malaria parasite can replicate extremely rapidly, with up to a trillion parasites in a severely ill patient. If a parasite generates a mutation that aids its survival, such as preventing a drug target being attacked, or pumping the drug out from its system, these will be selected for and potentially passed on to the next generation. Should the drug in question be unable to stop transmission, such a parasite will survive, and, via the mosquito, go on to infect new people. Often more than one mutation is needed to render a drug useless. As artemisinin is most likely to have many targets in the cell, many mutations are needed to protect the parasite.

George: From the scientific perspective we acknowledge that resistance is inevitable – the result of a constantly evolving “enemy”.2 That said, the use of single-agent drugs (monotherapy), low-quality medicines and inadequate dosing are partly responsible for accelerating its onset. Many patients stop taking their medication as soon as they feel better. Some patients receiving co-blistered combinations only take the artemisinin tablet – as this has a reputation for being fast-acting – and discard the slower-acting partner drug, thus effectively taking artemisinin monotherapy.

Recognizing the correlation between suboptimal monotherapy use and the onset of resistance, the WHO urged governments to ban the use of artemisinin monotherapy in 2006 and adopt Artemisinin-based Combination Therapy (ACT) as first-line treatment.3 Nevertheless, while an increasing number of countries including Cambodia have followed WHO’s advice and taken significant steps to remove monotherapies from circulation, they can still be purchased in some malaria-endemic countries.

How is resistance measured?

Tim: To identify resistance you have to have evidence of three things: first, patients not responding to therapy, second, the parasites taken from these patients are less responsive to the drug, and third, the drug is present in the patients who are not responding.

The Thai–Cambodian border region has been the epicentre of malaria drug resistance since the 1970s.
In the case of artemisinin, the first clinical sign that ACTs might be at risk was a change in parasite clearance time (PCT) – or the time taken to reduce the number of parasites in an infected patient to below the level of detection. This is normally around 24 hours, but a 2–4 fold increase in this time has been reported and independently confirmed on the Thai–Cambodian border. This means that patients are suffering with fever or other symptoms more than twice as long as they would have in the past with the same treatment. The long-term risk is a resulting decrease in the percentage actually cured at Day 28.

Why is monotherapy such a problem?

**Tim:** The incorrect use of monotherapy can lead to the development of resistance. A complete 7-day course of monotherapy completely cures most people. However, the probability of generating a mutation that will protect the parasite against the drug is unknown. Given that there are a trillion parasites in a severely infected patient, and over 250 million patients each year, even if it were extremely rare, a mutation could still happen.

The idea of a combination therapy is always to have a second drug present – one with a different mechanism of action that will kill any remaining parasites. But this does highlight a second danger: since artemisinin is fast-acting, the longer-acting partner drug is actually at risk – effectively monotherapy after 3 days of treatment. Thus, artemisinin resistance can also accelerate the development of resistance against the partner drugs – producing a double whammy.

We have heard the warnings against the use of monotherapy but what is the reality on the ground?

**George:** The reality is quite harsh. The good news is that in recent years there has been a shift towards the use of ACTs in the public sector. But in the private sector, where many people in disease-endemic countries have to buy their medicines, the range of non-quality, untested and often legally registered yet unsafe medicines is overwhelming.

The further one gets from urban areas the harder it becomes to buy an ACT, because the cost of transport increases and availability decreases. Patients have no choice but to buy cheaper, ineffective drugs such as sulfadoxine-pyrimethamine or chloroquine monotherapy or even incomplete doses of ACTs. This creates a breeding ground for resistance.

How is MMV working to make effective antimalarials affordable?

**Tim:** Right from the outset we work on the basis that a new treatment must not cost more than $1 for adults and $0.25 for the smallest children. We work constantly throughout development to make production more efficient, and with the help of numerous experts from both the pharmaceutical sector and contract manufacturing we try to bring down the price of the final medicine. This is a struggle, but one in which we can really have an impact.

**George:** We are also helping to bridge the affordability gap by supporting the work of a new financial initiative – the Affordable Medicines Facility, malaria (AMFm), which will radically subsidize the cost of ACTs to the price of chloroquine. MMV helped design the AMFm, primarily by managing a “proof-of-concept” study in Uganda with the Ministry of Health. The study demonstrated that a properly managed subsidy scheme, supported by effective social marketing, can enable patients to switch from ineffective drugs and opt for high quality, affordable ACTs. We continue to be closely aligned with the design and roll out of the AMFm.

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In spite of such innovative initiatives, how likely is it that artemisinin resistance will become widespread?

**Tim:** What we need to be prepared for is not if resistance to artemisinin will become widespread, but when. The new medicines in discovery will take 10 years to bring to the market, so we must take a really long-term view. It is most likely that artemisinin has several targets within the parasite, and so is protected against simple methods of resistance generation. Nonetheless, it is highly probable that it will be weakened as a viable treatment option, given the hundreds of millions of patients being treated and that every anti-infective therapy eventually falls prey to resistance.

**Figure 1:** The peroxide bridge – the link between current and in-development artemisinin-related compounds

Antimalarial endoperoxide compounds, including the artemisins, are a group of chemically related compounds that all possess a peroxide bridge. It is this bridge that is believed to confer the antimalarial activity. The compounds in development are hoped to be structurally distinct enough that artemisinin resistance will not jeopardize their efficacy.

Currently available compounds

- **Artemisinin**
- **Dihydroartemisinin**
- **Artemotil/Arteether**
- **Artesunate**

- **O-O** = Peroxide bridge

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The early warning signs of resistance are already present, e.g., increases in PCT. What concerns us all is when will this start to translate into a decrease in the effectiveness of ACTs in terms of preventing the disease relapsing within the first 28 days. Also of concern are the confirmed reports of resistance outside the epicentre in the Mekong area. There are already early unconfirmed reports of what is believed to be artemisinin resistance outside Cambodia, and it’s important that these are followed up rapidly.

On the more optimistic side, we have completed a clinical trial of a new ACT, Pyramax® (pyronaridine-artesunate), in Cambodia, in the area of reported resistance, and the medicine attained a 99.2% cure rate at day 28. Therefore, patients are still being cured by ACTs, but the increased PCT is a warning of what is to come.

Chloroquine resistance took 15 years to spread from the original source to Africa. Although there are many reasons why artemisinin resistance might spread more slowly, transport and migration are more efficient than 40 years ago. Bearing in mind it takes 10–15 years to develop a new drug, it is clear that the time to develop new medicines is now. We cannot wait until we lose artemisinin to resistance. By then, it will be too late.

Could resistance to artemisinin jeopardize other antimalarials in development?

Tim: Normally when resistance emerges it is specific to a particular medicine, and not to the entire class, e.g., chloroquine resistance did not compromise the activity of all related antimalarials. There are a number of peroxide-containing molecules in development – based on the same mechanism of action as artemisinin, but with very different chemical structures (Fig. 1). The most promising compounds we have are the ozonides: OZ 439 is in Phase II of clinical trials and also holds promise as a one-dose cure, while OZ 277, (in development with Ranbaxy and MMV) is in Phase III. In parallel, we need to test these medicines in patients from the areas of reported artemisinin resistance. If they are active when artemisinin is not, we have a solution to the problem. The difficulty so far has been getting enough patients to be able to test the medicines. These data are critical, as it is possible that we might lose all endoperoxide compounds to resistance.

How is MMV’s antimalarial pipeline placed to tackle resistance and fill the gap as it becomes more widespread?

Tim: We have been working for a long time on alternatives to artemisinin. To counter resistance we need novel, high-quality antimalarials. Today, we have 11 new chemical entities in development and 23 across the entire portfolio. The key is to find new molecules that will kill the parasite as quickly as artemisinin.

Over the last 4 years, we have collaborated with pharmaceutical, biotech and academic partners to find promising new molecules that can do just that, as well as remain steadfast against the development of resistance. To date, our programmes have successfully screened more than five million compounds for antimalarial activity; over 20,000 compounds have shown significant activity against the malaria parasite. The most advanced of these are now entering preclinical studies and should undergo testing in humans within a year.

Crucially, MMV only supports the research and development of a potential new antimalarial if it is both active against the parasite and all known resistant forms.

If novelty is the key in the battle against resistance, why is MMV developing more ACTs?

Tim: It’s a good question. Our partners have two high-quality fixed-dose ACTs available at the moment, and we plan to launch another two over the next 18 months. These are all at risk if artemisinin resistance takes hold. However, the other possible threat is resistance arising to the partner drugs – lumefantrine, amodiaquine, piperaquine and pyronaridine. By developing more ACTs we provide a back-up option for if and when the partner drug fails. Also, we cannot assume that each medicine will be equally effective in
all countries. Effectiveness varies depending on nutrition, ethnicity and also the strain of the parasite. In the end, our goal is to give the National Malaria Control Programmes as much choice as possible in the weapons they can deploy against malaria.

Q When can we expect non-artemisinin medicines to be available and what will it cost to bring them to market?

Tim: There are two scenarios. If we assume the best-case scenario – that we lose only some of the artemisinin derivatives to resistance and not all the endoperoxides – the funding gap is simple to calculate. We will need to do four Phase III studies to bring forward the next-generation of non-artemisinin combination therapies. These medicines could be ready in the next 5–6 years. But to do so, we will require an additional USD 40–50 million for 2010–2012 that we have not yet budgeted for.

If we assume the worst-case scenario, that the whole endoperoxide family is wiped out – the funding gap is considerably greater. It will take 7–9 years to develop a new non-endoperoxide therapy and would cost an approximate additional USD 200 million over 5 years. As we are currently working with an R&D budget of around USD 200 million, we would need to double our funding. The faster we want to go, the more drugs we have to develop in parallel, and the more expensive it gets.

Q In addition to developing new medicines, MMV is also working on an artemisinin resistance testing network; could you explain what this is?

Tim: MMV established the network to investigate whether emerging artemisinin resistance would compromise just the artemisinin derivatives or all endoperoxide-containing molecules.

To find the answer, we have assembled a collection of nine representative artemisinin derivatives from various projects. The molecules have been tested in vitro against parasite samples from patients at three sites in Southeast Asia (including one where extended PCT has been reported) and one in east Africa. No clear signal of a differential effect has been found between the molecules across the sites. The real test will be when we can conduct clinical studies on patients in artemisinin resistant areas. Fortunately, so far, these studies have been difficult to set up, due to the lack of eligible patients. But this could change quite quickly.

In addition, our partners have generated drug-resistant mutant parasites in the laboratory to identify the mechanism by which resistance occurs in them. All data obtained will be shared with the global malaria community to help assure an appropriate global response.

Prof. Nick White has often said that “the last parasite standing will be the most resistant”. When the day comes that our clinicians are facing the last parasite, we have to be sure that they have the tools to deal with all the resistance mechanisms it can throw at us. It is a great challenge and one that will need sustained effort for years to come.

The WHO – together with Ministries of Health and partners – is doing its utmost to contain artemisinin resistance that has emerged on the Thai-Cambodian border. With continued commitment, we can contain this threat and greatly extend the useful lifespan of artemisinin-based combinations. Ultimately, however, the development of new antimalarial medicines is absolutely essential if we are to stay a step ahead of the malaria parasite and win the fight against this deadly disease.

Robert Newman, Director, Global Malaria Programme, World Health Organization