Facilitating equitable access to quality antimalarials

Accelerating access to treatment options for children

**ISSUE**  
Children are the hardest hit by malaria – around 70% of all those that die are under 5 years of age.¹

**ACTION**  
MMV and partners are developing and improving access to child-friendly formulations of existing antimalarial therapies (artemisinin-based combination therapies, ACTs).

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**MMV** has long recognized that developing better medicines for children is vital, as this most vulnerable patient population is at the greatest risk of dying from malaria. The first MMV co-developed product to be launched, **Coartem® Dispersible** (artemether-lumefantrine), was a child-friendly formulation co-developed with Novartis. Since its launch in 2009, over 300 million treatments have been distributed across 50 countries, making it the most widely used quality ACT for children. It has saved an estimated 750,000 young lives.

In 2015, **Pyramax®** granules (pyronaridine-artesunate), developed by Shin Poong Pharmaceutical and MMV, received a positive scientific opinion under Article 58 from the European Medicines Agency (EMA). After its subsequent cross-listing on WHO’s prequalified drugs list and the Global Fund’s Quality Assured Medicines list, it became the second quality child-friendly ACT available to malaria-endemic countries.

**Eurartesim®** (dihydroartemisinin-piperaquine), an ACT co-developed by Sigma-Tau and MMV, was approved by the EMA in 2011 and received WHO prequalification in 2015. Sigma-Tau has completed formulation work on a child-friendly version of this medicine and is submitting results to the EMA in 2017.

All of these medicines represent real progress in the treatment of the most vulnerable. To support their optimal use in the real world, MMV has been working with partners to generate and disseminate post-approval evidence on their safety and efficacy in the real world.

**Dr Issaka Sagara** was one of the investigators for a large phase IIIb/IV multicentre clinical study designed to evaluate the safety and efficacy of ACTs over a 2-year follow-up period led by the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM). He talks us through the study results (published at the end of 2015),² how WANECAM supported the approval of the new child-friendly antimalarial, **Pyramax** granules, and his experience of working with MMV.

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**What did the WANECAM study look at, particularly for Pyramax?**

One of the objectives of the WANECAM study was to collect the data necessary to enable repeat use of **Pyramax** in malaria-endemic countries. In this 2-year follow-up study, patients from Mali, Burkina Faso and Guinea were re-treated with either **Pyramax** or **Eurartesim** each time they had a malaria episode, and the results were compared with the standard treatments available in the region (**Coartem** and **ASAQ Winthrop®**), both of which are already approved for repeated use.

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**What did the WANECAM study tell us about Pyramax?**

Importantly, our analysis revealed that the efficacy and safety of **Pyramax** after multiple re-treatments remained consistent with a single administration. These findings, based on an interim analysis of the data published online in the *Lancet Infectious Diseases* journal in October 2015,² informed the EMA’s decision to issue an updated positive scientific opinion for **Pyramax** tablets, supporting repeated use. That revision also removed requirements for liver-function monitoring and geographic restrictions on its use.

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At the same time, the results helped support the EMA’s decision to issue a positive scientific opinion for Pyramax granules. In the WANECAM study, we noticed improved adherence to treatment with Pyramax granules – the drug is taste masked, so easier to administer to children and only needs to be dosed once-daily. We hope this will facilitate wider use of Pyramax as a well-tolerated, alternative ACT for children, especially in those malaria-endemic countries where paediatric antimalarial treatments are limited. In addition, broadening treatment options might delay or even prevent resistance to the currently available antimalarials in the region.

The next step is to partner with national malaria control and elimination programmes in endemic countries to implement pilot schemes aimed at reducing the disease burden and slowing development of resistance to existing treatments. In parallel, new studies, such as a phase IIIb/IV to be carried out by the Central African Network on TB, HIV/AIDS and Malaria (CANTAM) in five African countries, will help us to continue monitoring the safety and the impact of Pyramax in real-world settings.

Next-generation medicines for children

Traditionally in drug development, medicines are developed for adults before child-friendly versions are pursued. At MMV, we are working to bring the development of paediatric formulations forward (pages 12–21). Provided the safety profile in adults allows, we are running studies to find the right dose in children during phase II development. This will allow us to register new medicines for children sooner and without the need for separate development programmes.

What was it like to work with MMV on the WANECAM study? What are the next steps?

Speaking on behalf of all three countries involved in the WANECAM study, we would like to thank MMV for all its support and guidance. Our resources on the ground are relatively limited, so we benefited enormously from MMV’s technical expertise and advice. Malaria is the number one public health concern here in West Africa. Based on the success of this study and the approval of Pyramax for multiple-course administration, we now have a powerful new weapon in the fight against malaria.

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Based on the success of this study and the approval of Pyramax for multiple-course administration, we now have a powerful new weapon in the fight against malaria.”
Rectal artesunate: buying time to save lives

**ISSUE**

World Health Organization (WHO) Guidelines for the treatment of malaria\(^1\) recommend the use of rectal artesunate (RAS) for pre-referral management of severe malaria. A single dose reduces the risk of death and permanent disability significantly.\(^2,3\) Despite this recommendation, no WHO-prequalified product currently exists.

**ACTION BY MMV AND PARTNERS**

- Build on the earlier work of WHO-TDR\(^4\) in RAS product development, to define requirements for WHO prequalification of RAS.
- Select and work with pharmaceutical partners, Cipla and Strides Shasun, to develop and submit products for WHO prequalification.
- Optimize use of RAS in low-resource settings.

If left untreated, uncomplicated malaria can quickly progress to severe malaria — a life-threatening condition that can kill within a few hours. The first point-of-care for many patients with severe malaria is a community-level health-care worker or a primary care facility. Those presenting with severe malaria should be treated as quickly as possible with injectable artesunate (Inj AS), followed by oral treatment with an ACT when the patient is sufficiently well; however, most local health posts do not have the Inj AS or personnel trained in its administration. As a result, patients need to be referred to higher-level facilities, creating delays in access to critically-needed treatment. In such cases, WHO recommends the use of RAS as a pre-referral intervention.\(^3\) RAS buys time until Inj AS can be administered — and can mean the difference between life and death.\(^3,5\)

With funding from UNITAID, MMV has been working with two Indian pharmaceutical companies, Cipla and Strides Shasun, to obtain WHO prequalification for their RAS products. Both companies submitted their dossiers to the WHO Prequalification of Medicines Programme in 2015.

In 2016, the Expert Review Panel (ERP) of the Global Fund issued a 12-month authorization for procurement of Cipla’s product. The authorization allows RAS to be procured while awaiting WHO prequalification, and offers a landmark opportunity for donor financing to support broad uptake of this critically-needed medicine.

Through renewed UNITAID funding, MMV will support the registration of RAS in several high-burden African countries. In parallel, MMV will be working with implementing partners and host countries to design pilot introduction programmes for RAS. These will develop and test tool kits to help reinforce correct use of RAS and referral of patients to health-care facilities for treatment with Inj AS followed by an oral ACT. This will form part of an integrated severe malaria management approach.

Prof. Christian Lengeler explains the importance of RAS and MMV’s role in introducing the first quality-assured version of the product.

**How is RAS being used today?**

Unfortunately, today, the use is minimal. There are very few countries that have policies in place and even fewer countries implementing its use.*

**Why is RAS an important tool in the management of severe malaria?**

The reality is that more than 400,000 people, mostly children, die each year from malaria. Most of these children live in remote areas far from health-care services. RAS has the potential to help address a substantial part of this mortality burden. It’s a drug that is easy to administer and so can be used in very remote settings. It’s the most important new intervention for severe malaria management since the WHO prequalification of Inj AS.*

**What is the implication of the Global Fund’s authorization of a RAS product?**

It’s an absolutely essential first step in a relatively long chain of events that will help RAS achieve maximum impact. The Global Fund is the main funder supporting procurement of malaria medicines in endemic countries but it can only purchase ERP-authorized or WHO-prequalified medicines. ERP authorization will allow immediate and time-limited procurement by the Global Fund. The next step will be WHO prequalification of the drug, which will allow its continued purchase with donor funds beyond the ERP-time limit and therefore further expand its access. Meanwhile, we must refine the strategy of how RAS will be used in the field. We must not forget it will be used to address severe disease far away from health systems – one of the most difficult tasks in malaria control.*

**How do you see MMV’s role in this process?**

The granting of the ERP authorization for an RAS product is the latest important step in a process to ensure widespread availability of a quality RAS product initiated over 20 years ago. In 2013–2014, building on the earlier work of WHO-TDR, MMV engaged two companies to develop quality RAS products and worked to define requirements for WHO prequalification, thus helping put this tool back on the agenda.

Moving forward, MMV’s role is to continue to support the WHO prequalification of the product, to help better forecasting of RAS needs at country level and ensure a robust pipeline to secure its availability.*

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Scaling-up injectable artesunate to save more lives from severe malaria

**ISSUE**
Slow uptake of WHO-recommended treatment for severe malaria (injectable artesunate) costs lives.

**ACTION**
MMV led a multi-stakeholder project to undertake a 3-year scale-up of injectable artesunate in six African countries, while helping to mobilize financing and stabilize supply of the drug.

In 2011, WHO-recommended injectable artesunate (Inj AS) as first-line treatment for severe malaria, as it saves more lives than quinine. In anticipation of this policy change and to help improve access, MMV worked with Guilin Pharmaceutical to enable them in 2010 to become the first company to achieve WHO prequalification for their Inj AS product – Artesun®.

MMV then established a consortium with the Clinton Health Access Initiative (CHAI) and the Malaria Consortium (MC) to implement the MMV-led Improving Severe Malaria Outcomes (ismo) project. The project was awarded UNITAID funding in 2013 to continue scale-up in six high-burden African countries (Cameroon, Ethiopia, Kenya, Malawi, Nigeria and Uganda).

In September 2016, the project came to a successful close having achieved the following:

- More than 90% of severe malaria cases across the six countries are now treated with Inj AS in preference to quinine;
- More than 18,000 health-care workers across 2,082 facilities were trained to administer Inj AS.

Furthermore, since prequalification of Guilin’s Artesun in 2010, 75 million vials have been dispatched, saving an estimated 450,000 to 500,000 additional young lives compared to treatment with quinine.

In parallel with the ISMO project, to ensure a sustainable global supply of Inj AS, MMV supported Ipca Laboratories, India, to enable submission of its dossier to WHO for prequalification review in 2016.

**Dr Jimmy Opigo provides his perspective on the impact of the ISMO project.**

**What is the burden of malaria in Uganda?**

Malaria is the number one health-care challenge in Uganda. We are the third most heavily burdened country in Africa following Nigeria and the Democratic Republic of Congo. In 2015, there were more than 7 million reported and confirmed cases of malaria. The real number of cases, however, is much higher, since this does not include those that seek treatment from the private sector, which is around half the population.

**How was severe malaria managed in Uganda before the start of the ISMO project in 2013?**

For a very long time, quinine was the mainstay. Managing the manual infusion process in a high number of patients, with our level of nursing care, was a huge challenge. Additionally, the curative effect was not as dramatic as with Inj AS. We really very urgently needed to transition to something more efficacious, but also operationally more feasible, given our resource constraints.

**What impact does this burden have on the people and country?**

The impact on the people is huge, particularly for children. In regions of very high transmission, children can get malaria up to 12 times a year and each time they are sick for 3 to 4 days, which leads to a significant amount of time missed from school. Malaria in children also affects adult workers who need to stay at home to look after them. That’s not to mention the adults that also fall sick. In the long-term, it can also cause physical and mental disability, which can have a lifelong effect on quality of life and productivity.

**How has changed in Uganda since the end of the ISMO project?**

In the public sector, close to 100% of severe malaria patients now receive Inj AS.

Four-year-old Desmond Oming from Awir in northern Uganda had “serious fever with a lot of diarrhoea and vomiting”, explained his mum, Jennifer Alwin, when she brought him to Apac District Hospital.

After a lengthy wait in the crowded outpatient department, Desmond was seen by Dr Josephine Apio who suspected malaria and sent him for a blood test. The results came back positive. It was the fourth time he had suffered from malaria in his young life and this time it was severe malaria.

Uganda is a very high burden country with more than 7 million confirmed cases of malaria in 2015 alone. Dr Apio explained that 50 cases of severe malaria had been diagnosed at the hospital in the week Desmond was admitted.

Fortunately, Apac’s hospital is one of the 339 health-care facilities in Uganda that now receive injectable artesunate (Inj AS) for the treatment of severe malaria, through the MMV-led Improving Severe Malaria Outcomes project funded by UNITAID. Inj AS is the WHO-preferred treatment for severe malaria. This life-saving medicine has been shown to reduce mortality by 22.5% in Africa compared to quinine.

Given Desmond’s critical condition, he is admitted to the children’s ward for treatment.

Desmond receives his first dose of injectable artesunate soon after being admitted. It is administered every 12 hours until he can take oral treatment.

Given Desmond’s critical condition, he is admitted to the children’s ward for treatment.

Injectable artesunate is easier to administer than quinine and we have seen fewer side effects. After the first 2 doses we see children improve, we see them walk around and laugh even before they receive the third and final dose.”

Dr Josephine Apio, Senior Clinical Officer Apac Hospital, Uganda
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Desmond is making a good recovery and today is ready to start taking oral treatment with an ACT for 3 days, to ensure any remaining parasites are cleared.

Desmond is happily playing outside the hospital with his mum and baby brother.

Dr Apio is pleased with Desmond’s progress. After 3 days in her care, Desmond is told he can go home. His mum helps him get dressed.

It’s time to leave the hospital. Desmond is back to health and happy to go home.

Another life is saved; carrying the remaining doses of the oral treatment, Desmond and his mum begin their journey home.

DAY 3

It’s time to leave the hospital. Desmond is back to health and happy to go home.
Protecting children during the rainy season

ISSUE

Malaria is a major cause of childhood death in Africa, particularly in the Sahel sub-region of West Africa, where transmission of the disease is heavily concentrated in the 4-month rainy season. To protect these children, the World Health Organization (WHO) recommends Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) in regions where the combination remains effective. Ensuring sufficient high-quality medicines are available and correctly administered is a logistical challenge.

ACTION

As part of the UNITAID-funded ACCESS-SMC Consortium, MMV is continuing to support the scale-up of SMC in seven of the 12 countries where the intervention is being implemented, with a focus on strengthening drug supply and forecasting.

In the Sahel and sub-Saharan regions of Africa, SMC with SP+AQ is a cost-effective solution that has been shown to prevent up to 75% of malaria episodes in clinical trial settings: high-quality SMC costs less than USD 1 per season, while inpatient care for a case of severe malaria is estimated to cost USD 12–75.1,2,3,4

Thanks to the ACCESS-SMC project led by the Malaria Consortium, 73 million courses of SP+AQ were shipped to 12 countries in 2016, enough to protect 18 million children during the malaria season; the product is manufactured by MMV’s partner Guilin Pharmaceutical, currently the sole supplier of prequalified SP+AQ.

In 2016, Guilin Pharmaceutical’s SP+AQ product became the first taste-masked dispersible formulation validated by the Global Fund Expert Review Panel for purchase by international agencies. To ensure a sustainable supply of dispersible SP+AQ, MMV completed a partner selection process to identify a second manufacturer, S Kant Healthcare, India, and is supporting the company through WHO prequalification of its product.

Working closely with national authorities across the Sahel, MMV has developed a multi-country forecasting tool to improve stock management of SMC drugs, tracking key data by year, country, number of eligible children and drug volumes required. MMV is currently working to make the tool open-access for the entire malaria community and is adding a component that shows funding needs. In parallel, MMV is spearheading the collection of scientific and stakeholder input on the desired attributes of next-generation SMC drugs as alternatives to SP+AQ.

Dr Yacouba Sawadogo tells us about the SMC programme in his country.

What were the biggest challenges to the implementation of SMC and how did you overcome them?

First of all, there was a delay in the arrival of the commodities in some districts, which we overcame by redistributing stocks from other districts. Also, the child-friendly dispersible formulation wasn’t available in the quantities required and so we prioritized it for the 3 to 11-month-old children, while the tablets – which are more bitter – were administered to the older children. Even so, we needed to find and fund a supply of sugar to encourage them to take it.

Coordination of the implementation required continuous consultation with the partners.”

How was the dispersible formulation of SP+AQ received in practice?

“The dispersible formulation is a clear advantage with children as they willingly accept it, so it’s easier to administer and there is minimal wastage. Based on this we are considering adopting the dispersible formulation exclusively for SMC in Burkina Faso.”

What are the next steps for the implementation of SMC in Burkina Faso?

“With funding from the Malaria Consortium, UNICEF, PMI/USAID and the World Bank, we plan to implement SMC in a total of 58 districts in 2017. Eventually, we hope to achieve 100% coverage, as the whole country is eligible.”

What has been the impact of SMC in Burkina Faso to date?

In 2016, SMC was implemented in 54 health districts across 11 of the 13 regions in Burkina Faso. In these regions, it has decreased malaria cases by 45% in children below 5 years of age.”

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2 The UNITAID-funded ACCESS-SMC Consortium includes: the Malaria Consortium (prime recipient), Catholic Relief Services (joint lead), MMV, Management Sciences for Health, Speak Up Africa and the London School of Hygiene & Tropical Medicine.
6 Burkina Faso, Cameroon, Chad, Gambia, Guinea, Ghana, Guinea Bissau, Mali, Niger, Nigeria, Togo, Senegal.
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A mother gives her child the first dose of SP+AQ, Burkina Faso.
Lifting the burden of malaria in pregnancy

**ISSUES**

Coverage of the World Health Organization (WHO) recommended intervention to protect pregnant women from malaria (IPTp\(^1\)) with sulfadoxine-pyrimethamine; SP) is very low – only 31% of pregnant women in sub-Saharan Africa receive three or more doses during pregnancy.\(^3\) A further concern is the declining efficacy of SP in some parts of Africa.

HIV-positive pregnant women are particularly vulnerable because drug interactions with HIV treatment mean that no IPTp regimen is recommended for them.

There is also a need to expand on the limited safety data to support the use of ACTs for treatment during the first trimester of pregnancy.

**ACTION BY MMV AND PARTNERS**

- Work to improve coverage of IPTp with SP in areas where it remains effective, and increase the global supply of quality SP.
- Undertake a cardiac safety study in Tanzania evaluating dihydroartemisinin-piperaquine (DHA-PQP) as an alternative option for IPTp.
- Use modelling tools to better understand drug–drug interactions between widely used medicines for HIV-positive pregnant women and potential chemoprevention options.
- Gather additional data to demonstrate the safety of malaria treatment with ACTs, particularly during the first trimester of pregnancy.

Every year, up to 125 million pregnancies around the world are at risk from malaria,\(^4\) In Africa alone, approximately 10,000 women and 200,000 babies die annually as a consequence of malaria during pregnancy.\(^4\) Pregnant women have an increased risk of life-threatening outcomes, including cerebral malaria or severe anaemia, which put both mother and child at risk.\(^5\)

### Protection

With funding from UNITAID, MMV will work to strengthen the WHO-prequalified supplier base for SP and the active pharmaceutical ingredients for the medicine. This will support initiatives to expand IPTp-SP coverage, such as the UNITAID-funded Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP) project led by Jhpiego.\(^6\)

To address the need for more research on new IPTp options, MMV and the London School of Hygiene & Tropical Medicine are conducting a safety study of Eurartesim\(^7\) (DHA-PQP) in pregnant women in Handeni District, Tanzania. DHA-PQP is a medicine of interest for researchers as a potential IPTp alternative in part due to the half-life of the drug that confers a long window of protection against malaria infection. This specific study in Tanzania will closely evaluate the cardiac safety of DHA-PQP in pregnant women, building on phase IV safety research that MMV and partners have already conducted in other patient populations. The study addresses a key safety question that needs to be answered to build the case for DHA-PQP as an IPTp option.

An alternative to SP is urgently needed. A study published in 2015 by the London School found that two or more doses of IPTp-SP no longer adequately protects women against malaria infection and the associated incidence of low birth weight of their infants in areas where the prevalence of the 581 mutation in malaria parasites is greater than 10.1%. Research has shown that in the Handeni District, 55% of malaria parasites expressed this mutation, hence the selection of this location for the trial. These results are keenly awaited – this is not ‘a nice-to-know’ study; it’s a ‘need-to-know’ study.”

Matthew Chico,
London School of Hygiene & Tropical Medicine

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1. Intermittent Preventive Treatment in Pregnancy (IPTp) is the administration of a full course of an effective antimalarial treatment. It should only be administered to pregnant women living in areas of moderate-to-high malaria transmission after their first trimester and at a minimum of 1-month intervals.
6. TIPTOP is a 5-year project funded by UNITAID set to increase IPTp coverage and expand antenatal care attendance in four African countries – Democratic Republic of Congo, Madagascar, Mozambique and Nigeria.
7. DHA-PQP is a medicine of interest for researchers as a potential IPTp alternative in part due to the half-life of the drug that confers a long window of protection against malaria infection. This specific study in Tanzania will closely evaluate the cardiac safety of DHA-PQP in pregnant women, building on phase IV safety research that MMV and partners have already conducted in other patient populations. The study addresses a key safety question that needs to be answered to build the case for DHA-PQP as an IPTp option.
While WHO recommends ACTs to treat malaria in pregnant women during their second and third trimesters, additional data need to be assessed to confirm their safety and tolerability during the first trimester.

To expand on the evidence base for the safety of ACT treatment during pregnancy, MMV and partners are establishing a registry that tracks outcomes for pregnant women exposed to DHA-PQP. This research will be carried out in partnership with the Manhiça Foundation in Mozambique.

Women who receive DHA-PQP as part of a Mass Drug Administration programme and then become pregnant during the ensuing 2-month period will be followed-up. The data will allow better understanding of the tolerability of DHA-PQP during pregnancy as well as its impact on newborn health up to 1 year of age.

On the other side of the globe, the Liverpool School of Tropical Medicine supported by MMV will conduct a pharmacovigilance survey of DHA-PQP in Indonesia with a focus on first trimester pregnant women. Indonesia is one of the first countries to have made DHA-PQP first-line treatment for malaria during the second and third trimesters of pregnancy. This offers the opportunity to collect much-needed safety data to add to the growing body of evidence on pregnancy in general, and on possible first trimester exposure to DHA-PQP in particular.