“On Sunday 3rd of May, 2015, Precious started vomiting and had diarrhoea. He had a high temperature and within a short time became very weak. I had to rush him to the hospital. I was so afraid that I left him in God’s and the doctors’ hands,” said Mrs Bosede Adebayo, whose son, 11-month-old Precious, was admitted to the General Hospital Okeho, Ibadan, Oyo State, Nigeria, on confirmation of severe malaria.

The first dose of injectable artesunate (Artesun® 60 mg, manufactured by Guilin Pharmaceutical) was immediately administered and after 3 days Precious was well enough to be discharged.

“The response to treatment was very encouraging and amazing,” said Dr Olusola Ayeleke the treating physician. “Precious responded quickly. Following the first dose there was significant improvement and by the time the second and third doses had been administered, he began eating well, taking oral medications and was good to go.”

Dr Ayeleke attributed the positive outcome to the use of injectable artesunate provided to the hospital through the Improving Severe Malaria Outcomes (ISMO) project, supported by UNITAID, MMV and the Malaria Consortium in collaboration with the Oyo State Government. “Before the MMV-led ISMO project, treating severe malaria was really challenging because we were using intravenous quinine,” said Dr Ayeleke. “There was increased mortality due to malaria. Intravenous quinine is associated with side effects and must be administered more frequently. Injectable artesunate makes the management of severe malaria easier and more fruitful.”

“After the ISMO training, health workers can use injectable artesunate to treat severe malaria patients,” said Dr Campbell Ibiokpe Oluonymi (pictured on the left), the Consultant Paediatrician in charge of Oni Memorial Children’s Hospital. “It is very fast acting and so patients recover from the condition faster and are no longer dying from severe malaria.”
Supporting the switch, saving more lives

**Injectable artemisinin**

WHO prequalified product
(manufactured by Guilin Pharmaceutical)

**Indication:** Severe malaria  
**Potential impact:** 22.5% reduction in mortality in Africa and a 34.7% reduction in Asia compared to previous standard of care (quinine)  
**Implementing partners:** Clinton Health Access Initiative (CHAI), Malaria Consortium (MC) and Swiss Tropical and Public Health Institute (Swiss TPH)  
**MMV Project Director:** Pierre Hugo

Since Guilin Pharmaceutical became the first company to receive WHO prequalification for their injectable artemisinin, Artesun®, in 2010, over 36 million vials of the medicine have been delivered to malaria-endemic countries (as of May 2015). Given that artemisinin injection offers a 22% reduction in mortality compared to the alternative, injectable quinine, an estimated 200,000–240,000 additional lives have been saved during that time.

While uncomplicated malaria is debilitating, when it progresses to severe malaria it becomes deadly. Around 584,000 people die each year of severe malaria, 75% of whom are under the age of 5. Since 2011, WHO recommends injectable artemisinin as first-line treatment for severe malaria, as it saves more lives than quinine.2

To improve access and increase use of the medicine across the malaria-endemic world, MMV joined forces with two partners with global reach: first with CHAI in Nigeria to support the introduction of the medicine and then Swiss TPH in the DRC to gather evidence to support the switch. These two countries together represent around 30% of the global population at risk of malaria.

The DRC has the highest burden of severe malaria in the world. In 2013 and 2014, MMV, Swiss TPH and the Kinshasa School of Public Health collaborated with the National Malaria Control Programme to undertake a study comparing injectable artemisinin with quinine in four districts in and around Kinshasa. The study reported 3.8% case fatalities with quinine and 1.7% with artemisinin, with a median time to discharge of 3 versus 2 days, respectively.6,7

These findings supported the inclusion of injectable artemisinin into the DRC’s strategic plan and a request for funding to the Global Fund. As a result, national deployment of injectable artemisinin will take place in the DRC over the coming years. The target is for all reported severe malaria cases to be treated with the medicine by 2016–2017.

Based on the knowledge and experience gained in Nigeria and the DRC, MMV established a severe malaria consortium with CHAI and MC. In 2013, this MMV-led Improving Severe Malaria Outcomes (ISMO) project was awarded a UNITAID grant of USD 34 million to continue the scale-up of injectable artemisinin in 13 of the 36 states in Nigeria and in five other high-burden African countries (Cameroon, Ethiopia, Kenya, Malawi and Uganda).

To ensure injectable artemisinin is used correctly, appropriate and timely training is critical. Through the ISMO project, MMV and partners have benefited from the experience of Médecins Sans Frontières to train health-care workers in the use of the drug. To date, health-care workers in 1,175 facilities (as of 31 December 2014) in the six countries have been trained – exceeding the total target number for the project (1,039).

To continue the scale-up we must also ensure supply can meet demand. Working with the President’s Malaria Initiative and the Global Fund is critical to ensuring accurate quantification and forecasts. Should all reported cases of severe malaria be treated, it is predicted that 40–60 million vials of injectable artemisinin will be needed worldwide each year. Yet, today only 11–12 million vials are manufactured annually. The ISMO project seeks to reduce this supply gap by helping to introduce new manufacturers. This will help secure uninterrupted access to high-quality and affordable supplies.

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1. Late onset haemolysis has been reported with the use of injectable artemisinin. Published reports recommend that treatment with injectable artemisinin should be limited to the required period and followed by a full course of an oral antimalarial, in line with WHO recommendations. Monitoring for late haemolytic anaemia should occur in all cases of severe malaria, irrespective of treatment.
Buying time for severe malaria treatment

Rectal artesunate
Preparing for WHO prequalification

Target indication: Pre-referral treatment for severe malaria
Potential impact: A single suppository substantially reduces the risk of death and permanent disability in children when the time for referral exceeds 6 hours

MMV Project Director: Pierre Hugo

WHO Standard Treatment Guidelines for Malaria include the use of rectal artesunate for pre-referral treatment for severe malaria. However, no WHO-prequalified product exists.

With early collaboration from WHO-TDR, define requirements for WHO-prequalification of rectal artesunate; work with pharmaceutical partners, Cipla and Strides Arcolab, to obtain a prequalified product and optimize its use in low-resource settings.

The first point-of-care for many patients with severe malaria is a community-level health-care worker (CHW) or primary care facility. These critically ill patients should be treated as quickly as possible with injectable artesunate; however, local health posts may not have this drug or trained personnel to administer it. In such cases, WHO recommends the use of rectal artesunate (RAS) as a pre-referral treatment; this option can substantially reduce the risk of death or disability, buying time for patients to be referred to centres that can provide recommended treatment. However, no WHO-prequalified version of RAS exists, leaving malaria-control programmes and donors without a quality-assured option.

With funding from UNITAID, MMV is working with two Indian pharmaceutical companies, Cipla Limited and Strides Arcolab Limited, to develop RAS for submission to WHO prequalification by the end of 2015 and market introduction in 2016. This process will build on clinical studies led by WHO-TDR, which demonstrated the benefits of RAS.

MMV has also conducted qualitative research in 20 high-burden malaria countries in sub-Saharan Africa to understand the need, barriers to use and potential market demand for a pre-referral severe malaria treatment. The research revealed which countries are best placed to integrate the product after its prequalification.

Dr Yusuf Hamied
CEO of Cipla Limited, talks about getting involved in developing an RAS product and why they chose to work with MMV.

Cipla has been manufacturing antimalarial drugs since its inception in 1935. We believe that we are among the largest producers in the world of artesunate and artemether, two of the key medicines to treat malaria today. We are also in the process of producing injectable artesunate. Two years ago, we were asked to consider making rectal artesunate as well. We already have an approved facility for making rectocaps and as they have been shown to save lives, for us this project is a priority.

Mr Mohan Kumar
CEO of Strides Arcolab Limited, explains how Strides will make a prequalified product widely available and what it is like to work with MMV.

Strides has a distribution network in 25 countries across the African region. We have 250 medical representatives and field staff overseeing operations in these countries. Our established presence will accelerate access to the product for patients, once it is prequalified.

UNITAID

Action by MMV and Partners

ARTSININ-BASED COMBINATION THERAPIES (ACTs) REMAIN THE STANDARD OF CARE FOR UNCOMPROMPLICATED MALARIA. IN ARTESININ-SENSITIVE REGIONS, THESE THERAPIES ARE HIGHLY EFFICACIOUS (WITH CURE RATES BETWEEN 94–99%).

Today, WHO recommends five different combinations. Since 2008, these have provided countries with a greater selection of treatments to develop national guidelines for first-line, alternative first-line and second-line treatments for malaria. But how well do they work and what is their safety profile in a real world setting? How well are they addressing the unmet medical needs of patients?

In 2011 and 2012, two MMV co-developed ACTs, Eurartesim® (dihydroartemisinin-piperaquine) and Pyramax® (pyronaridine-artesunate), were approved and granted positive scientific opinion by stringent regulatory authorities. A pediatric formula of Pyramax is currently undergoing regulatory approval and one for Eurartesim will be submitted in 2016. To help guide best treatment practice, MMV is working with partners to study how these medicines may be best used in the real world.

First, MMV and Sigma-Tau provided Eurartesim for the INESS® phase IV platform to gather real-life safety and effectiveness data. In clinical trials, the piperaquine component of Eurartesim was shown to transiently lengthen the heart’s electrical activity. Although this was shown not to have a clinical effect in the trial population, INESS enabled this to be explored in a real-life setting. INESS is a four-country (Ghana, Burkina Faso, Mozambique, Tanzania) research programme to assess ACTs, supported by the Bill & Melinda Gates Foundation. In 2014, INESS evaluated the use of Eurartesim in almost 10,000 patients and concluded that it is well-tolerated, and that transient prolongation of the electrical activity of the heart, occurring in some patients, did not appear to be associated with any clinical symptoms.

Second, with EDCTP’s support, MMV is working with Shin Poong Pharmaceutical and WANECAM® on a longitudinal phase IIIb/IV trial comparing the safety and efficacy of repeated use of Eurartesim and Pyramax with that of currently used ACTs (artemether-lumefantrine [AL] or artesunate-amodiaquine [ASAQ]). This research is particularly important for Pyramax, as it was initially given an Article 58 positive opinion from the European Medicines Agency (EMA) in 2012 for one-time-only use. WANECAM is generating new data on the repeated use of Pyramax in adults and children. Interim data from the trial shows that Pyramax is equally well tolerated and efficacious for repeat dosing as for initial dosing. This data has now been submitted to the EMA to support a change in Pyramax’s label to permit retreatment.

MMV has also collaborated with the Drugs for Neglected Diseases initiative (DNDi) and Sanofi in evaluating Coarsucam®/ASAQ Winthrop®. In Côte d’Ivoire, over 15,000 patients have been treated with ASAQ and closely monitored for rare adverse events (defined as occurring in 1-in-5000 patients). This study is helping to build a more robust safety record to inform national stakeholders about the real-life experience they can anticipate with ASAQ.

Lastly, in May 2015, artesunate-mefloquine (ASMQ), a DNDi-Cipla prequalified product, entered the MMV portfolio. Disseminating the results of recently completed safety and tolerability studies using ASMQ will be a new area of work for MMV.

MMV is proud to generate and disseminate scientific evidence about these important new treatments to help NMCPs decide which ACTs they should use for their populations.
Protecting pregnant women

ISSUE

125 million pregnant women are at risk of malaria each year and up to 200,000 babies and 10,000 mothers die as a consequence. To protect them, WHO recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP). Today, IPTp coverage is very low – only 24% of pregnant women in sub-Saharan Africa receive the minimum dosing. In addition, SP might one day lose its chemopreventive efficacy to drug resistance.

ACTION BY MMV AND PARTNERS

MMV and the London School of Hygiene & Tropical Medicine (LSHTM) will undertake a safety study in Tanzania testing DHA-PQP as a possible alternative to SP for IPTp. In addition, MMV sponsored the inaugural meeting of the Call to Action for the Scale-up of IPTp in 2014 and is working with partners to advocate for better IPTp coverage.

I need more protection from malaria: Angela’s story

Angela Kangulumais is a primary school teacher in Zambia. When we met her she was 6 months pregnant with her second child and no stranger to malaria. Just before her first pregnancy, she had nursed a headache for over a week and woke up one morning unable to see properly and walk unaided. With the help of her husband, she went to the local clinic where she was diagnosed with malaria and prescribed artemisinin combination therapy (ACT). Within a day, she felt much better.

For Angela, the need to protect herself from malaria becomes an even greater priority when she is pregnant. Bed nets are one solution. However, Angela explained. “This method alone is inadequate as I can’t always be under the net”.

Pregnant women at risk of malaria like Angela benefit from IPTp. According to WHO, this highly cost-effective intervention reduces the chances they will contract malaria and their unborn babies will die. With low coverage levels today, IPTp with SP must be rolled out more broadly in regions where it is effective.

In response, RBM’s Malaria in Pregnancy working group and WHO launched a Call to Action in 2014 advocating greater uptake. In parallel, the search continues for new regimens to replace SP in the future.

Q

Of all the ACTs, why was Eurartesim® selected for this study?

DHA-PQP is not only curative for malaria, but it also has a very long half-life. This means that it can clear malaria when administered and provide a long preventive window so that if a pregnant woman gets an infective bite a week after dosing, she will still be protected. POP has been shown to be protective for up to 63 days after dosing; but it could be longer.

In Africa, DHA-PQP has been shown to be superior to artemether-lumefantrine at preventing further parasitaemia, although both drugs have failure rates less than 5%.

Q

When will we have the answer the study seeks to find?

We should have the answer by June 2016, WHO is interested in the results. In July 2015, it will convene an Expert Review Group to discuss, among other topics, the safety of DHA-PQP in pregnancy. The Expert Review Group will make policy recommendations for consideration by WHO. But without the results of our study, it will be difficult to make an unequivocal endorsement of DHA-PQP for use in pregnancy. This is not ‘a-nice-to-know’ study; it’s a ‘need-to-know’ study.

Matthew Chico from LSHTM talks about why DHA-PQP (specifically, Eurartesim®, developed by Sigma-Tau and MMV) was chosen for this study and when the results are expected.

3 IPTp: administration of a full course of an antimalarial treatment to pregnant women living at risk of malaria after their first trimester and at a minimum of 1-month intervals.
Protecting children during the rainy season

Sulfadoxine-pyrimethamine + amodiaquine (SP+AQ)

Higher strength formulation (children aged 12–60 months) received WHO prequalification in October 2014; infant strength is currently under review and received Global Fund Expert Review Panel approval until November 2015, allowing procurement in the interim.

Indication: Seasonal Malaria Chemoprevention (SMC) for children in areas of highly seasonal transmission across the Sahel sub-region.

Potential impact:
- SMC with SP+AQ has been shown to be generally well-tolerated and efficacious, preventing around 75% of malaria episodes.
- Cost-effective: high-quality SMC drug costs ~USD 1 per season to protect a child from malaria. The cost of inpatient care for a case of severe malaria has been estimated at between USD 12–75.

Partners: Guilin Pharmaceutical Co. Ltd., China

MMV Project Director: Adam Aspinall

What is MMV’s role in the consortium?

In 2013, we began developing an SMC tool kit for countries interested in implementing this life-saving intervention. The tool kit is a training and communication aid. It assists people ‘at the sharp end’ with the implementation of SMC and has four sections: planning, training, monitoring and evaluation of results, and communicating the importance and implementation of SMC to people and health-care workers on the ground.

Today, we are participating in a major project funded by UNITAID and led by the Malaria Consortium and Catholic Relief Services to scale-up the intervention in the Sahel region. Our role is to make sure that a quality medicine is available, and that there is enough of it at the right time. First, we are working with Guilin Pharmaceutical to obtain WHO prequalification for both strengths of SP+AQ and develop a child-friendly formulation, which should significantly improve the ease of administering the treatment. Second, to secure the drug supply, we are identifying additional manufacturing capacity for prequalified SP+AQ.

What is the role of the implementing partners?

The implementation of SMC is a complicated logistical process. The implementing partners are working at the frontline to ensure the medicine is administered appropriately to the children that need it. They must work closely with national government partners to ensure that community-based delivery of monthly treatment can effectively be managed for up to 4 months in a row. They are also involved in quantifying the demand. It’s a critical role.

ACTION BY MMV AND PARTNERS

As part of the UNITAID-funded ACCESS-SMC consortium, MMV is supporting the scale-up of SMC in the Sahel sub-region by helping expand the global manufacturing capacity for quality SP+AQ and supporting the development of improved child-friendly formulations.

1 Seasonal Malaria Chemoprevention: previously termed intermittent preventive treatment in children, is the intermittent administration of full treatment courses of an effective antimalarial medicine during the malaria season to prevent malaria illness.
5 UNITAID-funded ACCESS-SMC consortium includes: Malaria Consortium (prime recipient), Catholic Relief Services (joint lead), MMV, Management Sciences for Health, Speak Up Africa, London School of Hygiene and Tropical Medicine