Lifting the burden of severe malaria: studying existing and novel therapies

Saving more lives from severe malaria

Severe malaria occurs as a result of complications during malaria infection, including multiple organ failure or abnormalities in a patient’s blood or metabolism. Symptoms may include anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which can progress rapidly and result in death within hours or days.1 In 2019, an estimated 409,000 lives were lost to malaria, 67% (274,000) of which were children under five years of age.2 If development of severe malaria is suspected, patients must be treated immediately, however, access to appropriate diagnostics and medicines can be limited in endemic areas, making assessment and treatment of patients challenging. MMV and its partners are working hard to optimize access to currently available treatments and expand the range of novel antimalarial medicines available for the treatment of severe malaria.

Rectal artesunate

When treating cases of severe malaria, every minute counts. This is particularly true in young children. In their latest guidance (2017–2018), the World Health Organization (WHO) recommends the use of artesunate rectal capsules to help manage the complications of severe malaria in children.3 The administration of artesunate rectal capsules can reduce malaria progression in patients, giving them more time to seek more advanced care at a healthcare facility. For example, improved access to artesunate rectal capsules in rural Zambia through the Mobilizing Access to Maternal Health Services in Zambia (MAMaZ) Against Malaria (MAM) project contributed to a 96% reduction in reported malaria case fatality rates in children under six years of age in intervention sites.4 This illustrates the value of such treatments in remote settings where the burden of malaria often falls heaviest.

In remote settings, community healthcare workers provide an initial diagnosis, prescribe basic medications and, if necessary, refer patients to more advanced facilities. As part of efforts by MMV and partners to support the continuum of care from the community level to referred health centres, the Rectal Artesunate Information Education and Communication (RASIEC) study was conducted in Malawi.5 The overall goal of this cohort case control study was to evaluate the introduction of the RASIEC toolkit (consists of information pamphlet, poster, indication and step-by-step administration of artesunate rectal capsules) alongside appropriate training. The study investigated whether these measures could increase early presentation at village clinics for pre-referral administration of artesunate rectal capsules. Additional metrics investigated include increased acceptability of artesunate rectal capsules by caregivers, improvement in community healthcare worker diagnosis and treatment, as well as enhanced, prompt compliance with referral instructions by caregivers.

After completion of the study in 2020, findings indicated that providing healthcare workers with RASIEC toolkits and a formalized referral slip protocol successfully increased the likelihood of a positive treatment outcome for patients. These findings have now been disseminated to key stakeholders in

References:
5. Partners include University of Malawi College of Medicine and Malawi Ministry of Health with funding by Unitaid.
Injectable artesunate

Artesun®, developed by Fosun Pharma at Guilin Pharmaceutical Co. Ltd., was the first injectable artesunate product to receive WHO prequalification. The milestone was achieved in 2010 with the support of MMV, and 34 million vials were distributed in 2020 alone. As part of ongoing efforts, MMV supported the refurbishment of Guilin’s manufacturing site, ensuring uninterrupted supplies via the US President’s Malaria Initiative and The Global Fund. To help maintain supply security, MMV supported the WHO prequalification of a second drug called Larinate® 60mg, which was developed by Ipca Laboratories. Cumulatively, 209 million vials of Artesun and Larinate 60 have been distributed to 37 million people, saving an estimated 1.36 million additional lives compared with quinine (assuming patients would have received injectable quinine in the absence of injectable artesunate). As COVID-19 creates numerous risks for malaria efforts, MMV has worked closely with partners to help address bottlenecks and to secure global supply of injectable artesunate with limited disruptions.

In 2020, MMV continued supporting the upscaling of the MAM project in collaboration with an international consortium and Zambian partners, with support from the FIA Foundation for the Automobile and Society (FIA Foundation), Grand Challenges Canada® and match-funding partners. The pilot project in Serenje District increased rural access to commodities such as artesunate rectal capsules for the case management of severe malaria, helping to reduce the reported malaria case fatality rate in children under six years of age in intervention sites. Based on its success, the MAM@Scale project expanded to five districts in Zambia, with the aim of increasing access to artesunate rectal capsules in areas of high disease burden. Importantly, the National Malaria Elimination Centre within the Zambian Ministry of Health have agreed to scale up artesunate rectal capsules at the community level, with a goal to cover 10 districts in 2021.

Rapid assessments of severe malaria case-management practices were completed in Angola and Mali, supporting the National Malaria Control Programmes by addressing areas for improvement, based on recommendations.
Dr Michael Kayange discusses severe malaria in Malawi and the RASIEC cohort case control study.

**What is the burden of malaria and, in particular, severe malaria in Malawi and what impact does the disease have on individuals, communities, and the country as a whole?**

Each year there are about six million cases of malaria (one third of the total population) in Malawi, resulting in approximately 2,300 deaths. Patients tend to travel to hospital with at least one guardian, meaning at least 12 million people could be attending hospital due to malaria each year. This keeps adults away from work and children away from school, sometimes for days at a time, which leads to economic and educational impacts on local communities and the country as a whole.

**What is Malawi’s national strategy to manage severe malaria? What is the role of injectable artesunate and rectal artesunate?**

Our policy for severe malaria includes entry at the health facility or community levels. At the health facility level, patients are assessed by a clinician or nurse and admitted for microscopy diagnosis and treatment if there are signs of severe malaria. Patients with a positive diagnosis receive intravenous artesunate for a minimum of three doses before switching to oral antimalarial drugs. Most patients improve within 24 hours after the first three doses, they are then given oral drugs and discharged. At the community level, health surveillance assistants manage mild malaria but are trained in detecting severe malaria and administering rectal artesunate. They then refer cases to the health facility. This means that severe malaria signs can be detected quickly and drugs can be given at the community level.

**What are the main challenges you face in the management of severe malaria?**

At the health facility level, delayed diagnosis is a challenge. Some patients admitted with signs of severe malaria do not get a diagnosis within 24 hours, however, this does not stop us managing cases by starting treatment with intravenous artesunate. If the result is positive, we continue with intravenous artesunate and, if not, we stop and move to other treatments. At the community level, compliance with pre-referral management is a challenge. We train health surveillance assistants in severe malaria management, but most cases are still referred without rectal artesunate administration.

**Last year, together with MMV you conducted the RASIEC study. What were the key findings?**

The greatest impact was observed in health surveillance assistants. The study showed that additional training of health surveillance assistants was needed to maintain correct administration of rectal artesunate. With the RASIEC toolkit, acceptability and use of rectal artesunate increased compared with the control district, and the capacity to identify symptoms of severe malaria also increased, leading to appropriate care. There was no difference in referrals compared with the control district, showing that health surveillance assistants referred patients appropriately. However, the introduction of a referral slip did improve the reception of patients and caregivers at the next healthcare level.

**What are the next steps to implement changes based on these findings?**

We plan to present study findings to the Case Management Technical Working Group and Malaria Social and Behaviour Change Communication Technical Working Group for possible inclusion in the upcoming community engagement campaign. Unfortunately, this has been delayed due to the COVID-19 pandemic.

**What has it been like to work with MMV on this study?**

We were privileged to work with MMV on this project and appreciate their support. We would like to engage with them again on future projects targeting the same or different malaria issues in Malawi.
Akullo Conny lives with her little daughter Aboli Patricia in Oyam, Northern Uganda. Mother and daughter love to be in each other’s company and often share domestic chores. However, it was not long ago that Akullo almost lost her only child to an episode of severe malaria.

One night, Akullo woke up to the cries of Aboli who was convulsing and had a burning fever. Akullo was overcome with fear and remembered thinking that her daughter might be dying. She rushed her to the community health worker, who quickly diagnosed that Aboli was suffering from severe malaria and administered artesunate rectal capsules. “The quick actions of the health worker helped lower the fever and the convulsions stopped soon after,” recalls Akullo.

Though the administration of artesunate rectal capsules brought immediate relief to Aboli, the community health worker urged Akullo to take her daughter to the nearest town hospital to ensure full treatment for severe malaria. Upon reaching the hospital, Aboli was taken to the children’s ward and started on IV treatment: over the course of her 24-hour stay, she received three doses of injectable artesunate followed by a three-day treatment with an oral artemisinin-based combination therapy. Soon after completion of the parenteral treatment, Aboli’s health improved significantly, and she was able to return home with her mother.

Akullo says, “These medicines saved my daughter’s life. After my experience, I am encouraging fellow mothers to take their children to the community health workers when they notice symptoms of severe malaria, and then follow the referral advice to go to a hospital for further treatment.”

Today, Aboli is a healthy and happy girl who continues to love playing outdoors and being in the company of her mother.

Cipargamin for severe malaria

Cipargamin (KAE609) was discovered and developed by Novartis in collaboration with MMV and the Swiss Tropical and Public Health Institute, together with Wellcome Trust funding. Cipargamin has the potential to become part of a fast-acting treatment in combination for uncomplicated malaria, or a next-generation parenteral treatment for severe malaria. Cipargamin targets a cell membrane channel in the parasite, the first validated new molecular target for malaria in more than 20 years. In a Phase II proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated Plasmodium falciparum or Plasmodium vivax malaria. The fast onset of effect was reconfirmed in a Phase II study in Africa of cipargamin monotherapy, which also demonstrated a good safety profile. Cipargamin will be further investigated in combination with other agents.

A new intravenous formulation is also being investigated by Novartis for the treatment of severe malaria, supported by funding from the Wellcome Trust. A Phase I study of the intravenous formulation was completed in 2020, which supported progression to a Phase II study that is expected to start in the third quarter of 2021. This study will be conducted by the PAMAfrica consortium® with funding from the Wellcome Trust and the MMV-led European and Developing Countries Clinical Trials Partnership.