

4 Scaling up access to life-saving interventions for severe malaria

In 2018, there were an estimated 405,000 deaths from malaria worldwide, the overwhelming majority of which occurred in Africa.¹ Although the risk of death due to mild, uncomplicated malaria is low,² if left untreated or inadequately treated in individuals with insufficient immunity, the disease can progress within a few hours to severe malaria – a life-threatening condition characterized by high levels of parasitaemia and vital organ dysfunction. The symptoms of severe malaria include anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which present significant challenges for physicians and healthcare systems. Urgent and aggressive treatment is critical if severe malaria is confirmed, yet in many endemic areas, access to diagnostic and therapeutic tools is limited.

Since 2011, the World Health Organization (WHO) has recommended injectable artesunate for the treatment of severe malaria in preference to quinine or artemether, due to its superior efficacy.³ The WHO also recommends the use of artesunate rectal capsules as a pre-referral emergency intervention in children under 6 years of age presenting with severe malaria symptoms, in remote areas where comprehensive treatment and care cannot immediately be provided.⁴ MMV and partners are working hard to increase access to quality-assured versions of these medicines to help improve the case management of severe malaria, and ultimately reduce mortality rates.

Injectable artesunate: improving treatment outcomes

Artesun[®], developed by Fosun Pharma, was the first injectable artesunate product to receive WHO-prequalification (PQ),⁵ with the support of MMV. Since its approval in 2010, the use of *Artesun* has been widespread, having been approved in 33 malaria-endemic countries. To increase the security and stability of global supply over the long term, MMV is supporting additional manufacturers to seek WHO-PQ for their injectable artesunate products. In December 2018, Ipca Laboratories achieved WHO-PQ for its product, *Larinate*[®] 60 mg. With MMV's support, *Larinate* 60 has now been registered and launched in 12 countries. As a result, a total of 168 million vials of injectable artesunate have been distributed to date, estimated to have saved the lives of more than one million additional children compared with quinine (assuming that patients would have received injectable quinine in the absence of injectable artesunate). In addition, MMV and partners are looking at ways to simplify the administration of injectable artesunate, by reducing the number of vials required from three to two.

Alongside securing a quality-assured supply of injectable artesunate, MMV is taking steps to increase uptake in endemic countries. Given the importance of providing healthcare workers with easy-to-understand information on product administration, MMV has worked closely with public health partners to develop training materials for healthcare

workers (now available in four languages). Nearly two dozen countries have adopted these materials, incorporating them into their national training programmes. Managing severe malaria during pregnancy is particularly challenging, so MMV is working with National Malaria Control Programmes (NMCPs) in five countries⁶ to identify and help address gaps in the management of severe malaria during pregnancy. In 2017, MMV launched the 'Severe Malaria Observatory', a knowledge-sharing platform and repository of information on severe malaria for the global community, which is currently receiving over 8,000 hits per month (p. 25).

In October 2019, MMV and partners convened a global stakeholder meeting to share experiences and improve the 'continuum of care' for severe malaria – artesunate rectal capsules, injectable artesunate, followed by a full course of artemisinin-based combination therapy (ACT) – from the community to a referral healthcare facility. One of the challenges discussed was the WHO guidance to replace artesunate rectal capsules after 4–6 months in areas where the ambient temperature is usually above 30°C. As this represents an additional logistical burden for countries, MMV and partners are exploring options to generate real-world data on the condition of artesunate rectal capsules returned from the field, which may support an amendment of the current guidance.

1 WHO World Malaria Report 2019: <https://www.who.int/publications-detail/world-malaria-report-2019>
2 Olliaro P. "Mortality Associated with Severe *Plasmodium falciparum* Malaria Increases with Age." *Clin Infect Dis.* 47(2): 158-160 (2008).
3 WHO. Guidelines for the treatment of malaria. Third edition. April 2015: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>
4 WHO Global Malaria Programme. Information Note: Rectal artesunate for pre-referral treatment of severe malaria (October 2017, rev. October 2018): <http://apps.who.int/iris/bitstream/handle/10665/259356/WHO-HTM-GMP-2017.19-eng.pdf>
5 Set up in 2001, the WHO's prequalification programme is designed to "facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis".
6 Niger, Nigeria, Liberia, Uganda and Democratic Republic of the Congo.

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Artesunate rectal capsules: the pre-referral intervention that buys time to save lives

Time is of the essence when treating severe malaria, as complications can develop rapidly and progress to death within a matter of hours. For children aged 6 months to 6 years living in remote settings, pre-referral administration of artesunate rectal capsules can buy valuable time until injectable artesunate can be administered at the nearest healthcare facility. Although the WHO has recommended the use of artesunate rectal capsules for the management of severe malaria since 2005,³ until recently, no WHO-prequalified product has been available, limiting its use and denying millions of children access to its benefits.

Supported by grants from Unitaid, MMV has worked with two industry partners since 2013 to bring 100 mg artesunate rectal capsules to market.⁷ Both manufacturers' products achieved WHO-PQ in 2018, enabling countries to procure these life-saving products – Artecip™ (Strides Pharma Science Ltd) and Artesunate Rectocaps (Cipla Ltd) – using donor funds. These products are currently registered in 16 countries in sub-Saharan Africa, and a total of 3.2 million capsules have been delivered to date. Importantly, more than 90% of the capsules procured by the three largest international buyers – The Global Fund, US President's Malaria Initiative and UNICEF – are now sourced from both MMV-supported manufacturers that supply these WHO-prequalified products.

MMV is continuing its efforts to achieve new country registrations, expand the delivery of artesunate rectal capsules and provide community-level education to increase uptake. For example, MMV and partners have initiated the RASIEC⁸ study in Malawi to evaluate the impact of introducing an information, education and communication toolkit to train community health workers on the use of artesunate rectal capsules. In 2019, MMV continued implementation of the MAMaZ⁹ Against Malaria (MAM) project to increase access to the capsules in rural areas of Zambia. In the pilot, the project had a great impact in this highly malaria-prevalent region, reducing malaria mortality in children under 6 years by 96%.¹⁰ Based on the success of the pilot, this project has been scaled up with support from MMV and expanded to five districts in Zambia. Furthermore, the National Malaria Elimination Centre and Zambian Ministry of Health have agreed to scale-up use of artesunate rectal capsules at the community level, with the aim of making it available nationwide.

As part of the Community Access to Rectal Artesunate for Malaria (CARAMAL) project, funded by Unitaid and led by the Clinton Health Access Initiative (CHAI),¹¹ MMV is supporting the introduction of quality-assured rectal artesunate capsules and ensuring community training on their correct use, as part of a continuum of care for severe malaria. The project is focused on three high-burden countries – Democratic Republic of the Congo (DRC), Nigeria and Uganda – and is currently piloting community case management initiatives (see N'Simba's story, p. 27). In addition, multi-country observational research is being conducted to identify the operational and health system-related factors affecting the introduction of artesunate rectal capsules. During a Global Severe Malaria Stakeholder meeting held in Abuja, Nigeria in October 2019, 19 countries shared their experience of rolling out artesunate rectal capsules within their health systems to improve the continuum of severe malaria care from community to referral facility levels. This was the first meeting convened on severe malaria case management, building on stakeholder meetings focused on injectable artesunate and artesunate rectal capsules in 2011 and 2016, respectively.

7 Building on work initiated by the WHO's Special Programme for Research and Training in Tropical Diseases (TDR), not funded by Unitaid.

8 Rectal Artesunate Information Education and Communication.

9 MAMaZ: Mobilizing Access to Maternal Health Services in Zambia.

10 Bulletin of the WHO, 2019;97:810-817: <https://www.who.int/bulletin/volumes/97/12/19-231506/en/>

11 Implemented by CHAI, UNICEF, the Swiss Tropical and Public Health Institute (Swiss TPH) and in-country research partners.



Severe Malaria Observatory

In May 2017, MMV launched the Severe Malaria Observatory (SMO) – a repository of information on severe malaria and its management. Created by and for the global malaria community, the platform shares knowledge, experiences and treatment guidance relating to severe malaria (the site houses numerous reports and surveys), thereby deepening global understanding of, and expertise in, the disease.

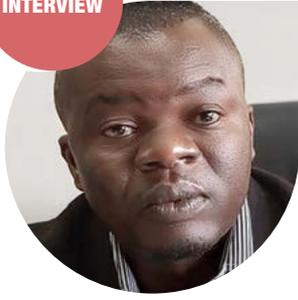
In particular, the observatory aims to:

- disseminate best practices, toolkits, market information, guidelines, projects, outcomes, etc.;
- highlight the need for continuous research and capacity building;
- increase visibility and coordination of ongoing initiatives to address severe malaria.

As of late 2019, the platform was, on average, receiving more than 8,000 visits per month with the majority from African stakeholders. Peer-reviewed articles, new reports and surveys are regularly uploaded to the site (most recently, from Liberia and DRC), making SMO a widely recognized source of information on severe malaria.

www.severemalaria.org

“These products are currently registered in 16 countries in sub-Saharan Africa.”



Prof. Eric Sompwe Mukomena

Head of DRC's National Malaria Control Programme (NMCP)

Prof. Eric Sompwe Mukomena tells us about some of the challenges of severe malaria case management in his country.

Could you tell us about your national strategy for improving the case management of severe malaria in DRC?

■ DRC has a high burden of malaria, with over 95% of the population living in areas of high transmission. Following on from its 2013–2015 strategy, the NMCP developed a new National Malaria Control Strategic Plan (NSP) for 2016 to 2020. The overall objective of this new strategy is to reduce malaria morbidity and mortality in the DRC by 40% compared with 2015; we are, however, unlikely to reach this ambitious target. For the treatment of severe malaria, the NSP recommends injectable artesunate or, if unavailable, intramuscular artemether or intravenous quinine. Pre-referral intervention with artesunate rectal capsules at a peripheral level¹² is national policy, although roll-out of training for health workers¹³ and commodities is still ongoing.

What are some of the challenges for case management of severe malaria, especially in rural settings?

■ Despite improved coverage of malaria interventions in recent years, access to medicines, lack of funding and infrastructure challenges continue to be major obstacles for the case management of severe malaria in rural settings. As quinine is cheaper and has been the treatment of choice for many decades, it is still being used to treat severe malaria in certain parts of the country – even though it is less effective than injectable artesunate. For artesunate rectal capsules, there are knowledge gaps that prevent effective administration of the intervention, and sometimes there is just not enough supply of medicines. In some areas, patients aged 6 years and above are receiving artesunate rectal capsules, although WHO and national guidelines do not recommend them for this age group. Lastly, seeking treatment in the private sector is common in the DRC, and we cannot always ensure that private facilities are adhering to our national policies and prescribing quality-assured medicines.

What more can be done to improve case management of severe malaria in DRC?

We need to advocate for more funding to ensure an adequate supply of quality-assured treatments for severe malaria (between 2016 and 2018, financial contributions from DRC's three biggest donors fell by 27%).¹⁴ Our current priorities are training and supervision of health workers, especially in regard to pre-referral intervention, and expanding referral centres and community care sites. Alongside donor funding, we also need to mobilize government funding for severe malaria care, especially for people that currently don't have access, and improve the integration of public-private health services to streamline care aligned to national and international guidelines. In particular, we need to do much more to improve malaria outcomes in pregnancy.

What is your experience of working with MMV?

■ MMV-supported products have made a major contribution in terms of reducing the burden of severe malaria in DRC, and we welcome the diversified supply base of both injectable and rectal artesunate. Through the CARAMAL project, we are currently benefiting from the introduction of artesunate rectal capsules, made available by MMV-supported manufacturers, as well as community training on their correct use. We expect to identify the key gaps in our current system of integrated community case management,¹⁵ which in turn will help us ensure that artesunate rectal capsules are an effective part of a continuum of care – right from the community level up to a referral healthcare facility.

“We also need to mobilize government funding for severe malaria care, especially for people that currently don't have access.”

¹² The health system in DRC has three levels: central, intermediate, and peripheral. The peripheral level is comprised of communities, health facilities, general referral hospitals and health zones.

¹³ Health workers in DRC work at the community level and carry out health promotion and community mobilization, and they also provide diagnosis, treatment and referral services for selected conditions, which includes administration of artesunate rectal capsules.

¹⁴ WHO World Malaria Report 2019: <https://www.who.int/publications-detail/world-malaria-report-2019>

¹⁵ Integrated Community Case Management (ICCM) aims to provide timely and effective treatment of malaria, pneumonia and diarrhoea to populations with limited access to facility-based healthcare providers, and especially to children under 5. Source: WHO (2016) 'Integrated community case management of malaria': https://www.who.int/malaria/areas/community_case_management/overview/en/



Mother and father, Anette and Noel with their children N'Simba, left and Mbangi right and two healthcare workers.



N'Simba's story



N'Simba is a bright-eyed toddler growing up with his sister Mbangi and parents Noel and Anette in the village of Katenda, in the south of DRC. The country carries one of the heaviest malaria burdens in the world.

During a follow-up visit at their home by healthcare workers from Katenda's community health centre, Noel and Anette recall the stressful experience when N'Simba first contracted malaria. Noel remembers clearly the morning he woke up to find N'Simba burning with fever. "N'Simba started to vomit, the fever persisted, and he refused to be breast-fed," said Noel. They rushed N'Simba to the community health centre by motorbike. Time was precious and N'Simba's condition seemed to get worse with each passing minute.

On arriving at the community health centre, the nurses quickly tended to N'Simba. After some initial tests, they administered a dose of artesunate rectal capsules and urged Noel and Anette to take N'Simba to the nearest general hospital 50 kilometres away.

With no public transport and a poorly constructed road, the only option for Noel and Anette was to drive N'Simba to hospital by motorbike. On the way, Anette noticed that N'Simba's fever was starting to drop. Soon after, he even wanted to be fed.

"I stopped my bike in the middle of forestland and Anette was able to breastfeed N'Simba," said Noel. "We were relieved! This was a good sign already."

After the long ride, they arrived at the hospital, where the doctor applauded the quick reaction on the part of N'Simba's parents and the nurses at the health centre. N'Simba was prescribed injectable artesunate and ACT to ensure a complete recovery.

In remote parts of DRC where small villages do not have fully functional hospitals, initiatives like Community Access to Rectal Artesunate for Malaria (CARAMAL) play an important role in helping people access artesunate rectal capsules and therefore buy time to access full treatment for severe malaria.

Anette concluded by saying, "I really appreciate the efficiency with which my son was treated, and I am also impressed by the routine follow-up checks done through the initiative to ensure that N'Simba completely recovered."

Source: Diaka T Jules/Alain Mugoto, CARAMAL project

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