Accelerating access to severe malaria interventions

In 2017, an estimated 435,000 people lost their lives to malaria.[1] The overwhelming majority of these deaths (93%) occurred in Africa,[2] mostly in children aged under 5 years (61%). Severe malaria is one of the biggest killers of young children. The condition can develop from uncomplicated malaria within a matter of hours, with symptoms including, but not limited to anaemia, hypoglycaemia, respiratory distress, convulsions and coma.

The World Health Organization (WHO) recommends injectable artesunate (Inj AS), in preference to quinine or artemether, for the treatment of severe malaria – due to its superior efficacy. The WHO also recommends rectal artesunate (RAS) for "pre-referral treatment of severe malaria in children under 6 years of age in remote areas […] pending immediate transfer to a higher-level facility where comprehensive care can be given."[3] MMV and its partners are working to improve access to quality-assured versions of these medicines and help improve overall case management of severe malaria.

Injectable artesunate: improving outcomes for children and pregnant women

Since WHO prequalification (WHO-PQ) of Artesun®, Fosun Pharma's Inj AS product, in 2010, more than 128 million vials have been dispatched worldwide, sufficient to treat an estimated 21 million children. Given that Inj AS offers a 22–35% reduction in mortality compared to the alternative treatment for severe malaria, quinine,[4,5] it is estimated that more than 840,000 additional lives have been saved by Inj AS since its launch, compared with the number that would have been saved by quinine.[6] As the first WHO-prequalified Inj AS treatment on the market, *Artesun* is now in widespread use – approved in 35 countries worldwide.

To ensure a sustainable global supply of quality-assured Inj AS, MMV is supporting additional manufacturers in their efforts to achieve WHO-PQ. In December 2018, Ipca Laboratories achieved prequalification of its Inj AS product Larinate® 60. In 2019, MMV will continue to support the introduction and scale-up of both quality-assured Inj AS products, collaborating with malaria-endemic countries and stakeholders to support improved severe malaria case management. In addition, MMV is working with manufacturers to simplify the administration of Inj AS by reducing the number of vials required.[7]

MMV has also worked closely with public health partners to develop training materials for healthcare workers on Inj AS (now available in four languages), aimed at giving clear and easy-to-understand information on product dosing. Nearly two dozen countries have adopted these materials, incorporating them into their national training programmes. MMV consistently seeks feedback on its training materials to make sure that healthcare workers have the information they need to deliver the right standard of care.

Management of severe malaria in pregnant women is an additional challenge. To improve outcomes for this vulnerable group, MMV is collaborating with countries to align with WHO guidelines for the management of severe malaria during pregnancy. By mapping out the capacity gaps in endemic-country healthcare systems, MMV is working with National Malaria Control Programmes (NMCPs) in five countries[8] to develop a plan for improving severe malaria case management in pregnant women.

1 WHO World Malaria Report 2018: https://www.who.int/malaria/publications/world-malaria-report-2018/en 9789241565653-eng.pdf?ua=1
2 Although the WHO African Region had the highest number of malaria deaths in 2017, it also accounted for 88% of the 172,000 fewer global malaria deaths reported in 2017 compared with 2010.
3 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;jsessionid=3136AF1F06AEB71D7937ECE08D1C719D?sequence=1
4 Dondorp AM *et al*. "Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial." *Lancet*. 13;376(9753):1647-57 (2010).
5 Dondorp A *et al*. "Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial." *Lancet*. 366(9487):717-25 (2005).
6 Calculated by applying superior mortality reduction for Inj AS vs IV quinine to an estimate of six vials per patient.
7 The current administration protocol requires three vials; it is hoped this can be reduced to two vials.
8 Niger, Nigeria, Liberia, Uganda and Democratic Republic of the Congo.

Rectal artesunate: buying time to save lives

In 2005, the WHO recommended the use of RAS for the pre-referral management of severe malaria in young children, and in 2017, RAS (100 mg) was added to the WHO Essential Medicines List and Essential Medicines List for Children.[9] Despite these guidelines, no WHO-prequalified, quality-assured RAS product was, until very recently, available – severely limiting its use and denying millions of children access to its benefits.

Supported by Unitaid grants, MMV has worked closely with two partners, Cipla Ltd and Strides Pharma Science Ltd, over the past 5 years, to bring to market quality-assured RAS (100 mg) products.[10] In February 2018, Cipla's product achieved WHO-PQ and is now approved for use in seven malaria-endemic countries in Africa. In June 2018, the Strides product also achieved WHO-PQ and is now approved in eleven countries. RAS has been enthusiastically welcomed by African countries: in Zambia, for example, the National Malaria Elimination Centre (NMEC) and Ministry of Health have already agreed to scale up RAS at the community level, with the aim of making it available nationwide.

WHO-PQ of the Cipla and Strides products has accelerated procurement of RAS in endemic countries, with the latest data showing an upward trend in its use. In 2018, an estimated 1.7 million RAS products were ordered by endemic countries – a substantial increase compared with 2017, and of those orders, 1.5 million were for WHO-prequalified quality-assured RAS 100 mg.[11] As such, over 85% of RAS procured in 2018 by the three largest international buyers – The Global Fund, President's Malaria Initiative and UNICEF – was quality-assured.

With funding from Unitaid, MMV is working to support improved introduction and scale-up of RAS. This work is further supported by the community access to rectal artesunate for malaria (CARAMAL) project, led by the Clinton Health Access Initiative. The project is focused on three high-burden countries – Democratic Republic of the Congo, Nigeria and Uganda – and is currently piloting community case-management schemes and multi-country observational research to identify the operational and health system-related factors affecting the introduction of RAS.

9 The WHO followed this up with an 'information note' in October 2017, describing when, and how, to administer the treatment.
10 Building on work initiated by the WHO's Special Programme for Research and Training in Tropical Diseases (TDR), not funded by Unitaid.
11 Instead of alternative, non-WHO-approved 50 mg and 200 mg formulations.

Severe Malaria Observatory: sharing best practice

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 gives stakeholders a chance to share knowledge, experience and treatment guidance relating to severe malaria (the site houses numerous reports and surveys), thereby deepening global understanding of, and expertise in, the disease.

Specifically, the SMO 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 January 2019, the SMO was, on average, receiving more than 5,000 hits per month, with the majority of visits coming from African stakeholders. In just 1 year since the SMO was launched, the number of site visits has increased five-fold, demonstrating the value of this resource for the global community.

www.severemalaria.org

MAM initiative: increasing access to rectal artesunate in rural communities

In July 2017, MMV joined forces with an international development orgnaization, Transaid, as well as Development Data, DAI Global Health, Disacare and the NMEC of Zambia, to implement a pilot access project that reduced malaria case fatality by a dramatic 96%.

The project, known as MAMaZ[12] Against Malaria (MAM), introduced the use of RAS at the community level, and used locally operated bicycle ambulances to improve the transport of sick children to health centres, as well as community theatre, song and dance to raise awareness of malaria danger signs. The project was conducted in the Serenje district of Zambia's central province, and reached 54,000 people across 45 communities, served by a total of eight health facilities.

In every suspected case of severe malaria, children were given quality-assured 100 mg RAS (by one of 447 trained community health volunteers – CHVs) before being transferred to a health facility, where they received Inj AS followed by a 3-day oral course of artemisinin-based combination therapy (ACT). The project's bicycle-based emergency transport system (ETS) was involved in more than 70% of these cases, making a total of 1,066 health facility transfers.

Over the 12-month pilot period (August 2017 to July 2018), only three deaths (0.25%) were recorded for 1,215 cases of severe malaria, compared with 97 deaths (8%) that would otherwise have been expected to occur in this timeframe. This represents a dramatic overall reduction in the case fatality rate of 96%.[13] The success of the MAM pilot provides undeniable evidence that through targeted interventions (e.g., providing RAS and ETS in tandem), it is possible to save the lives of vulnerable children with severe malaria – even in access-challenged rural settings.

MMV has now secured matched funding from Grand Challenges Canada (a non-profit organization) and the Government of Canada to expand the MAM initiative in Zambia from one to two districts, followed by a further three-district expansion, enabling the project to reach four times as many people. Further funding will need to be sought to enable the project to reach all vulnerable children in Zambia.

12 MAMaZ: Mobilizing Access to Maternal Health Services in Zambia programme: led by Health Partners International (2010–2013, funded by DFID) and MORE MAMaZ, led by Transaid (2014-2016, funded by Comic Relief).

13 Calculated by applying the case fatality rate at baseline (8%) to the number of suspected severe malaria cases (1,215 cases) vs baseline (224 cases).

INTERVIEW

Dr Elizabeth Chizema
NMCP Manager, Zambia, explains the approaches taken by Zambia and the role of MAM as it works towards eliminating malaria.

Zambia has set itself the ambitious goal to eliminate malaria by 2021. How did this goal come about and how will it be achieved?

➔ Despite our best efforts, Zambia continues to experience spikes of malaria. Because of this, we have decided that control is no longer enough – we need to eliminate malaria for good. So, between 2017 and 2021, we are implementing a new strategic plan designed to eliminate local transmission of malaria and, critically, prevent re-introduction of the disease. One important aspect of this is ensuring prompt and effective case management of malaria to reduce the pool of individuals who can contribute to malaria transmission.

What is Zambia's approach to the case management of severe malaria?

➔ We have revised our national policy to align it with WHO recommendations, that is, replacing quinine with more effective treatments, such as Inj AS. And, having trained up CHVs through the MAM initiative, we can now proactively diagnose and manage cases of severe malaria – using RAS – at the community, pre-referral level, rather than waiting for cases to present at district health facilities.

How can the MAM project be scaled up to close the coverage gaps?

➔ The pilot initiative focused on one district only (Serenje). In the next phase of the project, we will expand into one new implementation district in Central Province (Chitambo) and three national scale-up districts, before scaling up even further. Training is a key part of this expansion. So far, we have trained up to 7,500 CHVs, and we aim to have trained a further 7,500 by the end of 2019. Ultimately, for maximum coverage, we hope that initiatives similar to MAM will one day be present in all 114 districts of Zambia.

How have you benefited from working with MMV and Transaid?

➔ By working with multiple partners, our approach to the management of severe malaria has been comprehensive and well-integrated. Supported by MMV, we were able to introduce and increase access to quality-assured RAS and, supported by Transaid, we were able to scale up and strengthen existing services, such as the bicycle ambulances. Almost 100% of the children treated for suspected severe malaria in the pilot reached a health facility in good time – all thanks to this team approach. I hope that our experience in Zambia will inspire other African countries to consider similar projects and forge new collaborations.

Mervis' story
Surviving severe malaria

One night in May 2018, 3-year-old Mervis from Kebumba, Serenje District, Zambia, began to show signs of being unwell. She had a high fever and had lost her appetite. By the next morning, the situation had taken a dramatic turn for the worse; little Mervis had begun convulsing.

Priscilla Chibuye, Mervis' mother, rushed her to the nearest community health volunteer, Idess. Thanks to the training Idess had received through the MAM project, she quickly suspected severe malaria and administered two artesunate suppositories. These helped to stabilize Mervis until she could get to a health facility.

Meanwhile, Justina, an ETS bicycle rider, was called. The journey to Mulilima Rural Health Centre took an hour and a half. On arrival, it was confirmed that Mervis was suffering from severe malaria.

She was promptly given Inj AS. Later that evening, following her second dose of treatment, Mervis was already starting to show signs of improvement. She began to show interest in her surroundings and ask for food again. The next morning, Mervis received her third and final dose of Inj AS and was soon discharged. Mum Priscilla was given further oral medication to complete Mervis' malaria treatment at home.

During a follow-up visit Idess made to the family, Priscilla remarked that, before the MAM project came to her community, many children used to die from severe malaria. She was grateful the situation today had changed, and that her own daughter had made a full recovery.