Children and malaria: treating and protecting the most vulnerable

Of all the causes of childhood mortality, malaria is among the top killers, and in 2017, 61% of the estimated 435,000 lives lost to malaria were those of children under 5.[1] The disease continues to take the life of a young child every 2 minutes.

Children are particularly vulnerable to malaria as, unlike adults that have grown up in endemic regions, they have yet to develop the necessary immunity to defend themselves against the disease. The malaria parasite, once it has infected a child, multiplies exponentially, destroying red blood cells, leading to fever, vomiting, diarrhoea and anaemia. If not treated within 24 hours, malaria can progress to severe illness, including convulsions and coma, and can result in death.

Repeated infections lead to impacts beyond health

Children who do survive an episode of *Plasmodium falciparum* malaria in some parts of Africa can go on to suffer up to 13 episodes of malaria a year.[2] The other main species of malaria, *Plasmodium vivax*, can remain dormant in the liver only to reawaken even in the absence of a new mosquito bite. This species is prevalent in South America and Southeast Asia, and causes relapsing malaria which, contributes significantly to global malaria morbidity. Each malarial episode keeps a child from school for 3 or more days, placing an economic burden on families and health systems. Evidence from across the three continents also shows that malaria significantly impedes physical and cognitive development of the young, likely leading to impaired economic productivity later in life.[3–7].

Need for child-friendly formulations: children are not just little adults

Severe anaemia, hypoglycaemia and cerebral malaria are features of severe malaria more commonly seen in children than in adults. Although children are the main victims of malaria, historically, few antimalarial medicines have been developed with their needs in mind. They are often given adult tablets crushed into powder and added to water. This is an issue, because children are not simply little adults; they absorb and metabolize medicines differently. Additionally, most antimalarial medicines are bitter; a child already nauseous from malaria may vomit the medicine and not receive a complete curative dose. Children need palatable, easy-to-take medicines adapted to their weight and age.

The global health community recognised this. In 2007, the World Health Assembly issued a resolution on Better Medicines for Children, which promoted child-friendly medicines that meet requirements for dosing, tolerability and ease-of-administration.[8] In 2009, the World Health Organization (WHO) developed its first Essential Medicines List for children, in recognition of the fact that children must be treated with medicines adapted to their needs.

> “If not treated within 24 hours, malaria can progress to severe illness.”

MMV – addressing the unmet need

Medicines for Malaria Venture (MMV), a not-for-profit organization, joined the global fight against malaria in 1999, partnering with academic and commercial groups to reduce the burden of malaria by discovering, developing and driving access to new medicines. Our vision is a world in which innovative medicines cure and protect the vulnerable and under-served populations at risk of malaria.

Above all, children are our priority. MMV recognizes the urgent unmet need for child-friendly medicines and have found several ways to ensure that the best science is devoted to developing medicines to meet their needs. As a product development partnership, our partners are our strength. By joining forces with organizations involved in different aspects of malaria eradication, we explore every possible avenue to advance the development of much-needed medicines.

1. WHO’s World Malaria Report 2018: https://www.who.int/malaria/publications/world_malaria_report/en/
2. Yeka A *et al.* Efficacy and safety of fixed-dose artesunate-amodiaquine vs. artemether-lumefantrine for repeated treatment of uncomplicated malaria in Ugandan children. *PLoS One.* 1;9(12):e113311 (2014).
3. Price RN *et al.* Vivax malaria: neglected and not benign. *Am J Trop Med Hyg* 77:79–87 (2007).
4. Vorasan N *et al.* Long-term impact of childhood malaria infection on school performance among school children in a malaria endemic area along the Thai-Myanmar border. *Malar J.* 14:401 (2015).
5. Fernando D *et al.* Short-term impact of an acute attack of malaria on the cognitive performance of school children living in a malaria-endemic area of Sri Lanka. *Trans R Soc Trop Med Hyg.* 97(6):633-9 (2003).
6. Bangirana P *et al.* Malaria with neurological involvement in Ugandan children: effect on cognitive ability, academic achievement and behaviour. *Malar J.* 10:334 (2013).
7. Brasil LMBF *et al.* Cognitive performance of children living in endemic areas for *Plasmodium vivax. Malar J.* 2017; 16: 370.
8. WHA60.20 - Better Medicines for Children. WHA Resolution; Sixtieth World Health Assembly, 2007: http://apps.who.int/medicinedocs/en/m/abstract/Js21455en/

Each partner brings technical know-how, enabling technologies, research facilities and funding. MMV brings not only funding but a wealth of malaria and R&D knowledge together with industry-standard portfolio management. Guided by globally agreed 'Target Product Profiles'[9] for new malaria medicines, we have a clear picture of our goals from the outset. Flexible support is provided for the most promising drug candidates, while those that do not meet the Target Product Profile are quickly terminated. This rigorous compound selection and management enables us to maximize the impact of donor funding while accelerating the progress of compounds through the pipeline.

> "MMV recognizes the urgent unmet need for child-friendly medicines and have found several ways to ensure that the best science is devoted to developing medicines to meet their needs."

Building a portfolio of child-friendly antimalarials

Health workers and caregivers often struggle to get sick children to take medicine. As mentioned, antimalarial medicines present the additional challenge of their bitter taste, which can cause children to vomit and thereby impact effectiveness of the treatment.

Furthermore, only the first dose is given by a healthcare worker under direct observation. Parents or caregivers must continue to treat their sick children at home. This makes it hard to guarantee that children will complete their treatment course, which is critical to ensure a complete and efficacious cure. Incomplete dosing can also contribute to a larger problem – the development of drug resistance.

After several years in clinical development with Novartis and MMV, the first high-quality artemisinin combination therapy (ACT) developed especially for children, *Coartem*® *Dispersible* (artemether-lumefantrine), broke through the wall of neglect that denied sick children in the developing world access to malaria treatment tailored to their needs. This sweet-tasting medicine is both highly effective and easy to give to children, thus helping to improve compliance and dosing accuracy. Since its launch in 2009, over 385 million treatments of *Coartem Dispersible* have been delivered to children suffering from malaria in 50 countries, saving an estimated 825,000 young lives. Furthermore, four other artemether-lumefantrine dispersible products have since been prequalified by the WHO, helping to strengthen the supply of child-friendly medicines.

Since the launch of *Coartem Dispersible* in 2009, MMV and partners have developed and brought forward ten more new medicines, which together have saved an estimated 1.9 million lives from malaria. This includes two additional ACTs: Eurartesim® (dihydroartemisinin-piperaquine) developed with partner Alfasigma, and Pyramax® (pyronaridine-artesunate) developed with Shin Poong. A paediatric formulation of *Pyramax*, Pyramax® granules, has also been developed and approved, while a paediatric formulation of *Eurartesim* is currently in development. The list also includes the first new medicine for relapsing malaria in more than 60 years developed with GSK, *Krintafel/Kozenis*[10] (tafenoquine). A paediatric formulation of this medicine is also being developed.

Historically, and in the case of these four paediatric formulations, new medicines are first developed for adults before child-friendly versions are pursued. MMV and partners are working to change that. If the safety profile in adults allows it, we have begun to run studies to find the right dose for children during the early development phase. As soon as efficacy has been evaluated in a first cohort in adults, we move judiciously and progressively down the age scale ensuring tolerability in the oldest children, before moving to younger groups. The aim of the approach is to enable simultaneous registration of new medicines for adults and children, and without the need for separate and costly paediatric development programmes.

To continue innovating in this area, in October 2018, MMV hosted a Forum on Paediatric Drug Development bringing together formulation, drug development and regulatory experts from the public and private sectors. The objective of the forum was to discuss current gaps in paediatric medicines for the treatment of malaria and to identify best practices and considerations for R&D to ensure acceptability of the formulations intended for children. MMV is now working on documenting the outcomes to help guide best practice for future R&D efforts for children.

9. A Target Product Profile describes the desired R&D outcome for each medicine. Each R&D project in the portfolio is selected, progressed, and managed according to well-defined decision matrices based on these TPPs.
10. Trademarks owned or licensed by GSKTrademarks owned or licensed by GSK

Treated with child-friendly medicine

Rose and Shanrol's story

"My name is Rose Aluoch Ngala and this place is called Ombeyi, Kamagaga, Kenya. I work in the farm and I have three children, Shanrol, Robata, Ngala. Shanrol is 2 years old and 1 month.

Her body was hot… she was not eating or playing and crying all the time. It was then that I decided to take her to hospital at Ogra. At the hospital, she was taken to the lab and diagnosed with malaria. I was told that she would be admitted for 3 days.

This is the fourth time she has had malaria. The first time she was only 8 months, and I took her to the hospital where she received drip water and medicine. When your child is always sick you can hardly eat or work at all. The only work is to take care of the child, carry her around since she is always in pain. I fear that my child can die because of this disease, malaria.

This medicine is good because the child can swallow it fast. The fever also goes down very fast. Now as you can see she can speak and play and truly, I have seen a big difference."

Ensuring access to quality-assured paediatric medicines remains a challenge

Despite progress against malaria between 2000 and 2015, ACT treatment for children with malaria remains unacceptably low. While there are six ACTs prequalified by the WHO, only two of these are available in a child-friendly formulation. It was estimated that in 2015, only one in five children younger than 5 years old with *P. falciparum* malaria infection and fever was treated with an ACT.[11] Most likely, even fewer received a child-friendly version of WHO prequalified ACTs.

One of the key issues is cost – paediatric formulations typically cost more than adult tablets. The MMV-supported introduction of multiple, quality-assured manufacturers is one way to help reduce price differentials between adult and paediatric formulations. Another is the Global Fund's pooled procurement mechanism; by drawing on their significant purchasing power in health solutions for HIV, tuberculosis and malaria, over the past few years the Global Fund has successfully negotiated down the cost of paediatric formulations to almost that of adult formulations. The Global Fund has also begun to reallocate orders of antimalarials for children from the hard tablet to dispersible forms.

In addition to cost, another key issue is the prevalence of substandard and falsified medicines. Estimates indicate that in low- and middle-income countries, almost one in five antimalarials is substandard or falsified.[12] Fake medicines put patients and the public at risk. Patients believe they are receiving genuine treatment, but instead they are getting potentially dangerous products that could increase resistance to real treatments, and cause further illness, disability or even death. For sub-Saharan Africa alone, it was estimated that more than 120,000 children under 5 die annually from treatment with poor-quality antimalarials.[13] MMV is a signatory to the Fight the Fakes campaign aiming at raising awareness about the dangers of fake medicines.

> "In 2015, only one in five children younger than 5 years old with *P. falciparum* malaria infection and fever was treated with an ACT."

11. Bennett A *et al.* Population coverage of artemisinin-based combination treatment in children younger than 5 years with fever and *Plasmodium falciparum* infection in Africa, 2003-2015: a modelling study using data from national surveys. *Lancet Glob Health*. 5(4):e418-e427 (2017).
12. Ozawa S *et al.* Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries A Systematic Review and Meta-analysis. *JAMA Netw Open*. 1(4):e181662 (2018).
13. Renschler JP *et al.* Estimated under-five deaths associated with poor-quality antimalarials in sub-Saharan Africa. *Am J Trop Med Hyg*. 92: 119–126 (2015).

Procurement of high-quality ACTs has increased from 187 million in 2010 to 409 million in 2016.[14] Yet, more work is clearly needed at the country level to understand how health-care access, service delivery, and high-quality ACT supply and surveillance might be improved to help flush out the fakes and ensure that appropriate treatment is available for all children with malaria.

Accelerating access to severe malaria interventions

When malaria escalates to its severe form, again it is children who are the main victims. Without treatment, severe malaria can rapidly become fatal. In 2011, the WHO strongly recommended injectable artesunate (Inj AS) as the first-line treatment for severe malaria, given its ability to reduce malaria mortality by 22.5% in Africa compared to quinine.[15] In anticipation of this policy change and to help improve its access, MMV worked with a Chinese company, Fosun Pharma, to enable it to obtain WHO prequalification in 2010 for its Inj AS product – Artesun®. This approval represented a critical turning point, making it possible, for the first time, for donor funds to support procurement of this preferred treatment for severe malaria.

14. WHO Q&A on artemisinin resistance: https://www.who.int/malaria/media/artemisinin_resistance_qa/en/

15. 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).

Recovering from severe malaria

Desmond's story

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 8 million estimated cases of malaria in 2017 alone.[1] 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.

Desmond received his first dose of injectable artesunate soon after being admitted and then every 12 hours until he was able to take oral treatment. After 3 days in hospital, Desmond recovered and was able to return home.

> "The proportion of Inj AS treatments procured in the public sector compared to quinine was 99.5% (versus 16% in 2013)"

Having worked successfully to improve access to Inj AS in Nigeria and Democratic Republic of Congo, in 2013, MMV received funding from Unitaid to continue this work in Nigeria and expand to five other high burden countries in Africa. As of December 2015, across these six countries, the proportion of Inj AS treatments procured in the public sector compared to quinine was 99.5% (versus 16% in 2013), and the average proportion of patients treated with Inj AS versus quinine was 85.5%. These figures alone confirm that during the project, a major shift to better treatment for severe malaria took place. To support this work, MMV established the Severe Malaria Observatory – an open, accessible, knowledge-sharing web platform that provides a repository of information and resources for the severe malaria community.

Overall, since the prequalification of *Artesun* in 2010, an estimated 127 million vials of Inj AS have been delivered, saving an estimated 800,000 additional lives compared to injectable quinine, the previous standard of care for severe malaria. In December 2018, with MMV support, Ipca Laboratories became the second manufacturer to obtain WHO prequalification for their injectable artesunate product thereby improving global supply chain security for this essential life-saving medicine.

Saving young lives in rural areas

Most of the children who lose their lives to malaria live in remote areas, many hours from healthcare services where treatment for severe malaria is unavailable. For those unable to access health facilities within 6 hours, immediate use of a pre-referral intervention with rectal artesunate suppositories (RAS) at the community level buys precious time and has been shown to save lives.[16] WHO guidelines recommend that once young patients have been admitted to a referral centre, they should receive injectable artesunate, followed by a full course of ACT.

Although the WHO Guidelines for the Treatment of Malaria have included recommendations for the use of RAS for over 10 years, until recently no quality-assured RAS product on the market could be purchased with donor funds. This situation hampered widespread availability and use of RAS, and forced malaria-endemic countries to choose from sources of drug supply which did not meet international quality standards.

Also with funding from Unitaid, MMV partnered with two pharmaceutical partners from India (Strides Pharma and Cipla) to enable development and WHO prequalification of RAS products. In 2016, Cipla received a temporary authorization for one year from the Global Fund Expert Review Panel, allowing its product to be procured with donor funds. Then in early 2018, the Cipla product received WHO prequalification – a landmark moment – making it the first RAS product to receive this international stamp of quality. Prequalification of the Strides product soon followed in June 2018. WHO prequalification enables countries to procure life-saving RAS, thus ensuring the product's greater uptake and distribution. MMV's work in severe malaria then extended to support the Indian manufacturers with the registration of RAS in several high-burden African countries. In parallel, in July 2017, MMV joined forces with the international development organization Transaid, in collaboration with the National Malaria Elimination Centre (NMEC) of Zambia on a project known as MAMaZ Against Malaria (MAM) to improve severe malaria case management, specifically by introducing RAS at the community level. Implemented with several partners, the MAM project adopts innovative approaches, including the use of bicycle ambulances, as well as community theatre, song and dance to create awareness of malaria danger signs. The 12-month pilot project came to an end in 2018 having successfully reduced severe malaria case fatality by 96% (from 96 anticipated deaths to three).

> "As of October 2018, just over half of the most affected countries in Africa have included the WHO-approved RAS in their national malaria treatment guidelines."

16. Gomes MF *et al.* Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*. 373(9663):557-66 (2009).

SMC in action

Fatou Touray's story

"During the rainy season my children usually suffer from malaria twice. When they suffer, or a close relative suffers from malaria, I have to stop everything to help care for him or her. That means all our farm and community activities are affected.

Children don't like medicines and are always afraid, but we still give them the SMC drugs. It has reduced the burden of malaria in my house and family at large. My children are not even suffering from malaria anymore thanks to the SMC medicines."

As of October 2018, just over half of the most affected countries in Africa have included the WHO-approved RAS in their national malaria treatment guidelines. Given this and the significant impact demonstrated by MAM, it is clear more needs to be done to roll-out these kinds of initiatives.

Treatment of severe malaria has a significant impact on the lives of young children. A recent article in *the Public Library of Science (PloS),*[17] ranked the cost effectiveness of 93 health interventions for low-income and middle-income countries and identified the MMV-supported treatment of severe malaria with Inj AS and RAS among the top 30 most impactful interventions in terms of cost per disability-adjusted life year averted.

Protecting children during the malaria season

Malaria is a major cause of childhood death across the Sahel region of Africa. Most of the malaria mortality and morbidity occurs during the rainy season. Administering seasonal malaria chemoprevention (SMC)[18] during this period has been shown to significantly prevent malaria-related illness and death in children. SMC has been shown to prevent ~75% of all malaria and severe malaria episodes, reduce child mortality to 1 in a 1000, and reduce incidence of moderately severe anaemia.[19]

In March 2012, WHO recommended SMC using a combination of sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) once a month for 4 months during the malaria transmission season for children aged between 3 and 59 months. MMV has been supporting this recommendation and working to enhance the reach of this treatment to populations that need it.

To do so, MMV has been working with S Kant Healthcare Ltd. in India to develop and obtain WHO prequalification of a SPAQ formulation for children, thus helping to ensure a sustainable supply of the drug. Then, MMV and partners have produced SMC training materials and are facilitating their implementation in collaboration with the SMC Working Group within the West and Central Africa Roll Back Malaria Network (WARN/CARN). Also, from 2014 to 2016, as part of the UNITAID-funded ACCESS-SMC Consortium, MMV supported the scale-up of SMC in seven countries in the Sahel region. Overall in 2017, 15 million children across 12 countries in Africa's Sahel sub-region received at least one dose of SMC. Yet, almost half of these children did not receive all four recommended doses and 13.6 million children in the Sahel remained unprotected.[1] More work remains to be done to improve coverage of SMC in the eligible regions.

Conclusions

Better medicines for children, prequalified by WHO, exist and their use needs to be maximized alongside appropriate diagnostics, to ensure children receive the best care possible. Dedicated groups, including drug developers, policy makers, healthcare professionals and procurement agencies, must continue to collaborate to maintain and accelerate the gains made in treating children with malaria.

Prioritizing the needs of children in the development of new medicines for malaria is a moral imperative and essential if we are to substantially reduce childhood mortality. Together with its partners, MMV remains committed to accelerating the development and delivery of available and next-generation interventions to treat and protect children across the world from malaria.

17. Horton S *et al.* Ranking 93 health interventions for low- and middle-income countries by cost-effectiveness, *PLOS*, August 2017.
18. SMC is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness by maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial transmission.
19. WHO Policy Recommendation: Seasonal malaria chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa: http://www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/

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