Medicines to protect children from seasonal malaria: what are the options?

André-Marie Tchouatieu discusses the progress made to ensure appropriate medicines are available for SMC today and in the future

In some parts of Africa, more than 60% of malaria cases occur in just four months of the year, during the rainy season. Around 39 million African children under five years of age live in these regions of defined malaria seasonality, where an estimated 152 000 continue to die each year from malaria.[1]

Most of these young children live in the Sahel and sub-Sahel region, where the World Health Organization (WHO) recommends Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) for those aged between three and six years in areas of high seasonal malaria transmission, in which SP+AQ remain effective.[2]

SMC relies on the intermittent dosing of an antimalarial drug during the malaria season to protect children, by maintaining therapeutic drug concentrations in the blood throughout the period of greatest risk.

Senegal, one of the first countries to pilot SMC, scaled up SMC in 2014 leading to a 70% decrease in malaria morbidity between the critical rainy months of August and November in children under the age of 10. This translated to a 30% decrease over the year, leading to welcome reports of empty malaria wards. It is expected that as the in-country drug delivery systems improve, the decrease in malaria morbidity will continue to improve. While SMC is currently recommended for children aged between three months and six years, based on the very powerful results Senegal found in this age group, and an observed increase of malaria cases in older children, the country is pushing beyond these age limits and since 2013 has been administering SMC in children up to 10 years.

The Senegal experience makes it clear that SMC has huge potential to save lives. However, several challenges to its implementation exist in terms of logistics and supplies of medicine. It is vital to have sufficient quantities of well-tolerated, effective and child-friendly medicines available to administer today and in the future.

Medicines for Malaria Venture (MMV), a leading product development partnership in the field of antimalarial drug development and access, is a partner in the UNITAID-funded project ACCESS-SMC, which is co-led by Malaria Consortium and Catholic Relief Services (CRS).[3] Through the project, MMV is supporting the roll-out of SMC by National Malaria Control Programmes in seven countries in the Sahel region: Burkina Faso, Chad, Guinea, Mali, Niger, Nigeria, and The Gambia. In addition, MMV and partners have developed and are seeking to develop new SMC options:

i) Guilin Pharmaceutical, a Chinese company and one of MMV's industry partners, has developed a child-friendly formulation (dispersible, taste-masked) to replace the current SP+AQ presentation which must be ground up and mixed with sugar and water for young children, to mask the bitter taste.

ii) MMV is soliciting expert advisory guidance to explore future options to counter drug resistance, including:
   a. Repurposing existing medicines for the medium-term.
   b. Researching new medicines for the longer-term: MMV is refining the target product profile (TPP) of next-generation chemoprevention medicines, to clarify more precisely what is needed, as well as to inform future consultations with WHO and regulatory authorities about new emerging drug targets.

i. A new child-friendly SP+AQ formulation

The bitter taste of AQ makes it difficult to administer the correct dose of SP+AQ to children – they often gag or spit out the medicine. Furthermore, the tablets are hard to crush and mix with water to facilitate administration to children. These two factors not only jeopardize the efficacy of the intervention, but also increase the amount of time spent by health workers to administer the first dose. As such, the first logical step when thinking about new medicines for chemoprevention was to provide the malaria community with a child-friendly, taste-masked, easy-to-administer formulation of the current regimen.

Guilin Pharmaceutical, one of MMV's industry partners, has developed a dispersible, taste-masked formulation of SP+AQ that received a positive opinion from the WHO's Expert Review Panel and therefore was added on to the Global Fund list of malaria products in February 2016. As a result, more than 25 million doses have already been purchased for the 2016 SMC campaign, which began in June. To ensure availability of sufficient quantities of the drug from diverse

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> "I participated in the SMC campaigns and it has been quite good. The drug (SP+AQ) was not easy to administer because of its bitterness. Some children do refuse or spit it out. Overall it was successful and well appreciated by the mothers. The mothers were sensitized about the drug and it has reduced the burden of malaria in under 5's."
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> *Muhammed Joof, Community Health Nurse, The Gambia*

supply sources and to enable a total switch towards this formulation in the near future, MMV has also signed an agreement with an Indian-based company, S-Kant Healthcare, to develop and manufacture another child-friendly SP+AQ product.

ii. Future options to counter drug resistance

The most significant challenge that could undermine SMC's effectiveness in the future is the threat of drug resistance to SP+AQ. While malaria parasites have become resistant to malaria treatment with SP+AQ in many parts of Africa, today the medicines remain effective in areas of the Sahel and sub-Sahel for chemoprevention.[4] The concern is, however, that the large-scale implementation of SP+AQ for SMC may ultimately accelerate resistance to this combination in the Sahel, thereby undermining its life-saving impact. In addition, there are other areas of eastern and southern Africa where SMC would be beneficial, but cannot be implemented today due to the high prevalence of resistance markers to both SP+AQ. An alternative to SP+AQ has the potential to significantly expand the footprint of SMC across Africa and to ensure a longer life for this important intervention. In January 2016, within the framework of the ACCESS-SMC project, MMV convened an expert consultation to discuss alternatives to SP+AQ. Discussions focused on two key areas: repurposing of existing medicines and developing new medicines for the future.

Repurposing existing medicines

The process from discovery to delivery of a new antimalarial combination normally takes 13–15 years. Given the history of antimalarial drug resistance and the current pressure on SP+AQ, the combination may be rendered ineffective before new medicines are developed. Repurposing currently available antimalarial medicines provides an interim solution. Work is currently underway to determine all viable options. For example, the artemisinin combination therapy (ACT) dihydroartemisinin-piperaquine (DHA-PQP) has shown good preventive efficacy when studied as a potential SMC therapy.[5] However, its widespread use for SMC could increase the risk of resistance to DHA-PQP; and given that DHA has a much shorter half-life than PQP, it is not an ideal partner drug in an SMC combination. Moreover, WHO recommends that in a given setting, different combinations should be used for chemoprevention versus for treatment.

One possible way forward could be to evaluate other partner drugs for PQP, such as azithromycin (AZ). AZ is an effective chemoprotective agent in malaria, and reduces the incidence of respiratory tract infections, and diarrhoea among other public health concerns in children. However, the risk of bacterial resistance development with more widespread use of AZ needs to be better defined.

Chloroquine is a very well-known drug that has been used previously for prophylaxis in Africa and could also become part of an SMC combination. While it succumbed

A mother administering SP+AQ to her baby in the Republic of Niger. Photo courtesy of Alena Koscalove/MSF

to drug resistance in the 1970s and 1980s, today it is regaining efficacy in regions in Africa where it was withdrawn in the 90s.[6–8] More information is needed regarding the potential for the re-emergence of CQ resistance.

Developing new medicines

MMV has drafted a TPP for SMC and is working to discover and develop new compounds to meet it. The TPP states that in addition to being efficacious and well-tolerated, new medicines for SMC should have a long shelf-life, provide long-duration protection, offer simple administration, and be formulated as child-friendly fixed-dose combinations suitable for community distribution channels. An injectable intramuscular formulation could also be considered, if the dose for the season could be administered with one single injection. This would remove the logistical hurdle of going door to door to deliver the drugs within a four to five-day window each month for four months.

Another hurdle that must be overcome is the regulatory process. Whether new medicines are developed or existing medicines repurposed for SMC, regulatory approval for their use for SMC is imperative. As the regulatory route for registering a drug developed expressly for SMC is unprecedented, MMV is consulting in advance with various regulatory experts and agencies to determine a suitable strategy.

It is a great achievement that in 2015 more than 3.2 million children in the Sahel received chemoprevention through the ACCESS-SMC project. In 2016, ACCESS-SMC aims to provide chemoprevention to an estimated 7.5 million vulnerable children, making this one of the fastest growing new interventions to reduce malaria death and morbidity. To ensure an even greater sustained impact from SMC, MMV and partners will maintain a Research and Development focus on the next-generation of chemoprevention medicines to complement or replace SP+AQ.

To keep up to date with our progress, sign-up for the ACCESS-SMC (www.access-smc.org) and MMV newsletters (www.mmv.org).

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