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Policy Brief

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SEASONAL MALARIA CHEMOPREVENTION: WHERE ARE WE TEN YEARS ON?

Ten years ago, the World Health Organization (WHO) first recommended the use of antimalarial drugs to prevent severe malaria in children under five in areas with high infection loads and high seasonal transmission of malaria. To mark this ten-year point, L'Initiative has produced a guidance note to outline the fundamental contribution of seasonal malaria chemoprevention (SMC) to reducing malaria burden in infants and young children, as well as the operational and strategic challenges to be addressed to optimize the impact of SMC in the future.

1| An effective prevention tool…

Malaria remains a serious health problem in many parts of the world. Although the disease is preventable and treatable, it affected 240 million people in 2020, of which 627,000 died. Africa accounts for about 95% of cases and 96% of deaths worldwide; 80% of all deaths in the region are among children under five.

Throughout the Sahel sub-region, the highest malaria-related mortality and morbidity rates are generally during short rainy season. Seasonal malaria chemoprevention (SMC), the intermittent administration of an oral treatment every three to four months during the peak malaria transmission season, regardless of whether or not the person is infected, has been shown to be effective in preventing the disease and reducing the number of malaria deaths in children.

A 2012 Cochrane systematic review[i], based on seven trials involving a total of 12,589 children, found that SMC prevented up to 75% of malaria and severe malaria episodes. It was on the basis of these conclusive results, that in same year WHO recommended SMC for the first time:

"SMC is recommended in areas of highly seasonal malaria transmission throughout the Sahel sub-region. A complete treatment course of sulfadoxine–pyrimethamine (SP) plus amodiaquine (AQ) should be given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, up to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy)." [1]

1. WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa Geneva, 2012.

2| …with potential to be even more effective

Now, ten years on, WHO has updated and shortened these recommendations. It is now recommended that *"in areas of seasonal malaria transmission, children belonging to age groups at high risk of severe malaria should be given antimalarial medicines during peak malaria transmission seasons to reduce disease burden*[2]*"*. The reason for this simplification is that the WHO wanted to give countries greater flexibility to adapt their interventions to local epidemiological contexts, in line with findings from a WHO technical consultation in October 2019[3]. The prescriptive nature of existing recommendations may limit the scope for adaptability. The new guidelines make it possible to factor in expanding the geographic target areas, the age of children to be targeted, the duration of treatment, but also to take into account the emergence of resistance to antimalarials used as part of the seasonal prevention regimen.

In other words, it seems clear that SMC has not fulfilled its full potential in terms of reducing the burden of malaria. In order to do so, SMC needs to be reconfigured or potentially scaled up to meet diverse challenges faced by countries most heavily affected by malaria. With this in mind, the section below suggests that potential developments are reviewed alongside having a full understanding of the main issues in a given context.

3| Geographic coverage

To date, fourteen primarily Sahel countries (Benin, Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea Bissau, Mali, Mauritania, Niger, Nigeria, Senegal and Togo) have rolled out SMC, in accordance with international guidelines. The decision to focus SMC in Sahel countries was fundamentally based on two factors: the highly seasonal transmission of malaria in this area, and the lack of resistance to the main molecules used in SMC (SP-sulfadoxine-pyrimethamine and AQ-amodiaquine) - contrary to what was observed in Southern African countries. The experience of countries such as Uganda, which observed that SMC reduced cases by about 85% in children aged 3 months to 5 years, also helped to strengthen evidence and encourage WHO to update their recommendations.

The recommendations now recognize that **countries in other parts of Africa with large seasonal variations in malaria burden could also benefit from SMC**, even if the incidence does not fall to zero between two seasons, and that the availability of new medicines could make it a viable intervention in these regions. A better understanding of the efficacy of chemoprevention with SPAQ, including the role of drug dosing and parasite resistance, will help predict the future efficacy of SMC, and inform the expansion of the intervention in East and Southern Africa[ii].

4| Target age

Routine household surveys revealed administering SMC to children over 59 months of age in several countries appeared to be common, with positive results in terms of morbidity and mortality. For example, in Senegal, Ndiaye et al.[iii] reported a substantial advantage of administering SMC to children aged 5-9 to reduce the prevalence of parasitemia and anemia. In Mali, other research conducted by Diawara et al[iv] showed a significant 40% reduction in the prevalence of parasitemia in children aged 5-9 receiving SMC, but with no impact on anemia. The authors note, however, that these school-age children are more susceptible to parasitic infections, which are known to be risk factors for anemia. **However, these examples prove the effectiveness of SMC beyond the age of five** and to generally reduce the burden of pediatric malaria, which is now possible based on the new recommendations.

5| Duration of treatment

Recommendations on the duration of treatment have also evolved to allow countries to tailor chemoprevention strategies to their specific needs. The 2012 guidelines limited SMC to countries with a "highly seasonal" malaria cycle, meaning where at least 60% of malaria cases occur for four consecutive months. The new recommendations no longer set a limit on the number of months to provide SMC, this is in particular

2. WHO Guidelines for malaria, 2022, June 3rd.

3. WHO technical consultation to review the role of drugs in malaria prevention for people living in endemic settings, 16-17 October 2019.

» to take account of the annual variation in the exact timing of the start of the transmission season. Currently, there are about 20 million children living in areas where a fifth month of SMC would cover more than 10% of the annual burden. In addition, the updated guidelines state that **SMC must be administered during the malaria transmission season, without defining the specific number of monthly cycles**.

6| Molecules and resistance

In addition to relaxing the recommendations, there are other challenges that SMC faces related to resistance issues, whereby scientific research is needed to provide a satisfactory response Seasonal malaria chemoprevention consists of administering drugs that combine prevention (one dose of sulfadoxine-pyrimethamine) and treatment (three doses of amodiaquine) in relation to infections by *Plasmodium* parasites. In addition to the need to identify or develop a more simple treatment, which would not require, for example, administration over three days or every month, there is a lack of empirical evidence around the thresholds of resistance beyond which SMC loses effectiveness - both as a preventative or as a treatment.

The appearance and spread of drug resistance is likely an inevitable consequence of their widespread use. The incidence of SP-resistant parasites remains high[4], including in areas where this drug has not been widely used for several years. Conversely, chloroquine susceptibility is returning after being replaced as a first-line treatment in some countries (i.e. Malawi, Zambia).

In any case, **routine monitoring of molecular markers associated with resistance is to be encouraged, as are drug development and repositioning studies** that explore the potential uses of existing molecules for different diseases, in this case malaria, than those they were initially designed to treat.

4. See wwarn.org and WHO's Malaria Threat Map.

5. "Achieving Catalytic Expansion of Seasonal Malaria Chemoprevention in the Sahel": this project supported NMCPs in 7 countries to expand access to SMC in the Sahel.

6. "Seasonal chemoprevention as an effective malaria preventive strategy for children in the Sahel". London, UK: Malaria Consortium; 2019. Available from: https://www.malariaconsortium.org

7| Distribution

Despite evidence of its effectiveness, and following the 2012 recommendations, SMC was administered on a small scale, or as part of pilot projects. To facilitate scale up, in 2014 UNITAID launched the ACCESS-SMC project,[5] which helped improve demand forecasting, and ensured that the procurement of quality-assured, dispersible medicines was centralized. The project contributed to the increase from 9.9 million treatments provided to target countries in 2014 to more than 70 million in 2017[6].

Nonetheless SMC faces implementation challenges that require operational innovations to ensure optimal coverage of this prevention tool for all children in need.

Integrating SMC with existing distribution platforms is encouraged, but additional and complementary approaches should be considered. Is it possible to make greater use of SMC delivered in health facilities or through local community actors? Could SMC be linked to other health consultations (*i.e.* vaccinations, nutrition, school health)? With regard to community distribution, is a static administration point more efficient than door-to-door administration? Whether or not to use the Directly-observed therapy (DOTs) approach? Experience shows that different responses will be selected by countries in order to respond to different realities (Barry et al 2018 in Mali[v], Strachan et al 2016 in Nigeria[vi]).

8| SMC and the RTS,S vaccine

Finally, for a year now, the malaria response has had a vaccine in its arsenal (RTS,S), which is recommended by WHO for children at risk of contracting the disease. Despite a relatively low rate of protection and a high number of injections required, the vaccine has been assessed as being no less effective than SMC for preventing malaria. **The combination of these two interventions significantly reduces the incidence of malaria, severe malaria and deaths compared to either intervention individually**[vii].

Conclusion

In the aftermath of the COVID-19 pandemic, the potential of SMC remains very strong but not sufficiently explored: it is an effective, cost-efficient response and should be scaled up urgently in a coordinated way in places where it has not been yet. In this way, it appears necessary to strengthen community mobilization among the populations concerned, within families, in all relevant countries: there is no doubt that SMC use would increase if demand also came from the community. Recommendations from WHO or from governments, although essential, are certainly not sufficient to change practices at the local individual level.

Despite how effective and promising SMC is, in order to increase its impact tenfold, it must not be considered in isolation, but rather alongside the range of malaria control tools, such as long-lasting insecticidal net (LLINs), indoor residual spraying, treatments, and finally the RTS,S vaccine. Only a combined and consistent prevention strategy can sustainably reduce malaria worldwide.

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