Seasonal malaria chemoprevention: how to sustain the impact in Africa's sub-Sahel region?

Over recent years, countries in the sub-Sahel of Africa have witnessed the life-saving impact of SMC. Medicines for Malaria Venture (MMV) discusses the challenges that remain to widespread implementation of this strategy

In some regions of the sub-Sahel of Africa, Seasonal Malaria Chemoprevention (SMC) has reduced malaria cases in children under 5 years by up to 65% during the transmission season.[1] As a result of this impressive impact and with support from several organisations, implementation of SMC by the National Malaria Control Programmes in 11[2] of 15 eligible countries plus Togo (which was not initially identified as an eligible country but has implemented) has expanded year-on-year since 2014. The next step is to explore how to reach almost all the estimated 25 million children eligible for the intervention in all 15 eligible countries in the sub-Sahel region.[3]

SMC, recommended by the World Health Organization (WHO) since 2012, involves the intermittent, monthly, dosing of the antimalarial drug combination of sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) during the rainy season. The dosing regimen enables therapeutic drug concentrations to be maintained in the blood, thus providing protection from malaria throughout the period of greatest risk. SMC is recommended for children below 5 years of age.

The regions considered eligible for the intervention are those in Africa where these drugs still remain efficacious and where more than 60% of malaria cases occur in just 4 months of the year, during the rainy season. At present, these criteria restrict the intervention to specific regions in some 15 countries in the sub-Sahel, namely Benin, Burkina Faso, Cameroon, Chad, The Gambia, Ghana, Guinea, Guinea Bissau, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Sudan as well as Togo. So far, Benin, Mauritania, Sierra Leone and Sudan have not yet implemented SMC.[4]

Moving towards wide-scale implementation: what's the progress?

SMC is gaining traction as countries experience the benefit first-hand. Since 2014, implementation in the aforementioned 12 countries has been gradual for logistical reasons as well as owing to insufficient funding.

The 12 countries have integrated SMC into the package of interventions provided by community health workers and volunteers, and community leaders have been heavily involved in supporting local information campaigns. This resulted in SMC coverage beyond 85% of target children in all countries. In some areas of Guinea, coverage reached up to 100% in 2015 during the fourth round of distribution.[6] Also, from one year to the next, mothers and caregivers are noticing a reduction in malaria morbidity in their children.

'All my children have had malaria so I am very happy to have SMC now. Since my son started taking this medication, he has not been sick. This is the first year he has not had malaria.'

Salamatu, mother, Sokoto, Nigeria[7]

From 2015 to 2017, the ACCESS-SMC project funded by UNITAID and led by Malaria Consortium and Catholic Relief Services has been critical in scaling-up SMC implementation in seven countries: Burkina Faso, Chad, Guinea, Niger, Nigeria, Mali and The Gambia. The project reported a 24–65% decrease in malaria case incidence during the transmission season in SMC areas in children under 5 years of age. With the reduction in malaria cases in the 0-5 year age group, the burden of malaria is being pushed up the age ladder for unprotected children, as those in the 5-10 year age group are still falling sick at the same rate as before. This relative increase in malaria cases in the 5-10 year age group led Senegal to extend the intervention to this older age group in 2014, and Mali to start piloting SMC in older children in two districts as of 2016.

In line with the expansion in implementation of SMC, a concomitant increase in production and distribution of SPAQ has occurred: from a distribution of 9 million treatments in 2015 to more than 60 million treatments in 2016. The formulation, too, has evolved. At the beginning of the campaign only a hard tablet was available, obliging health workers and mothers to crush the tablets and mix them with sugar before administration to children. In 2016, dispersible, child-friendly formulations of both SP and AQ were made available by Guilin Pharma, a member of Fosun Pharma. This has helped improve convenience of the treatment and, thus, compliance. By 2017, just 3% of total country orders were for hard tablets,[8] confirming an almost complete switch to the child-friendly formulation.

In 2014, when SMC was launched, the active pharmaceutical ingredients (APIs) for sulfadoxine and pyri-

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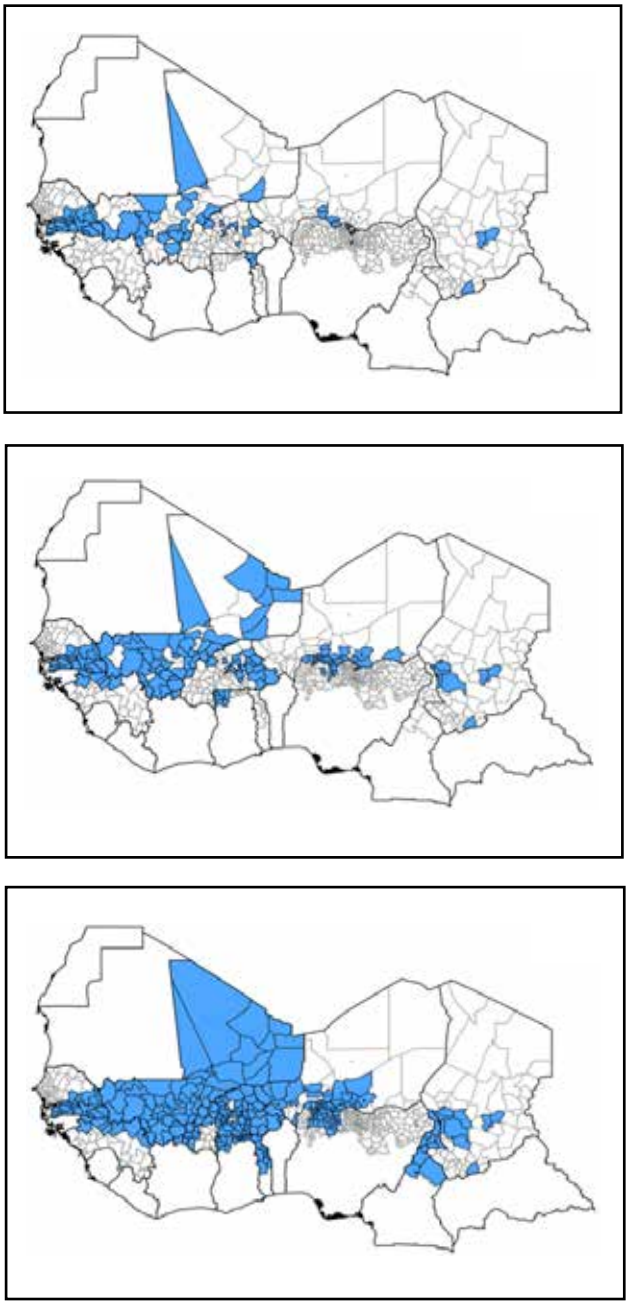

Expansion of SMC implementation (marked in blue) across the Sahel region from 2014 (top) to 2016 (bottom)[5]

methamine were not available on the WHO prequalification list. At the time, SP was only recommended for intermittent preventive treatment in pregnancy, which was not widely adopted (the coverage rate for IPTp in 2014 was estimated at 22–24%).[9] The implementation of SMC has, however, increased demand for SP, reviving the market and leading to the WHO prequalification of two sources of sulfadoxine API and one of pyrimethamine API in 2017.

Remaining challenges to widespread implementation and possible solutions

Respecting eligibility criteria: With the uptake and success of SMC, the biggest challenge countries face is ensuring sufficient funds to sustain the intervention where it has already been implemented. With success, comes the risk of over-implementation; that is, expanding SMC implementation to areas and age groups beyond WHO recommendations. Expanding to new areas/districts should ideally only be considered once the requirements for existing implementing areas have been met.

Sustained support: The ACCESS-SMC project ran from 2015 to 2017, providing both technical and financial support to SMC programs in seven countries. Anticipating the end of the project and the financial gap it would leave, countries eligible for both SMC and Global Fund grants have added requests to support the intervention to their Global Fund proposals and concept notes. New funders have also entered the malaria arena, like the Islamic Development Bank in Cameroon, and countries like Mali and Ghana have secured their own government funding to fill anticipated shortfalls from external donors. The US President's Malaria Initiative (PMI) has been supporting malaria programmes for several years in Senegal and Mali, including SMC, and has recently integrated new countries such as Burkina Faso, Cameroon and Niger. Most of these solutions are however short-term and will need to be sustained and expanded to ensure SMC can continue to be implemented.

Cost and resources: In 2016, the average cost of providing four cycles of SMC was US $3.55 per child, lower than the 2015 estimate of US $4.27.[10] However, SMC is increasing the burden on the health workers who are already in high demand. This could in-part be addressed by exploiting synergies within the local health system e.g. by coupling SMC with other public health interventions, such as nutrition supplementation distribution or vaccine administration campaigns. Such an approach would decrease the work load on the health workers and potentially further optimise the cost of the intervention.

Safety monitoring: SMC is a relatively new drug intervention; as such its scale-up should be accompanied by robust safety monitoring. The ACCESS-SMC project included a safety monitoring component to detect and report adverse reactions related to SMC drugs with an emphasis on serious reactions. The aim was to define the safety profile of SMC medicines and strengthen or support pharmacovigilance systems in countries. The approach was to take pharmacovigilance activities for SMC as the 'building and training ground' for overall pharmacovigilance systems with the goal of ultimately strengthening the country's ability to introduce other new products and strategies. These efforts have achieved good results: in one example, Chad became a part of the WHO Programme for International Drug Monitoring.[11] These efforts to build and/or strengthen pharmacovigilance systems will, however, need to be sustained.

Resistance monitoring: Routine monitoring for signs of decreasing efficacy is an important long-term consideration to accompany widespread use of SPAQ in the Sahel region. SP resistance is caused by mutation on two genes, the dihydrofolate reductase (Pfdhfr) and the dihydropteroate synthetase (Pfdhps). Mutations in the *Plasmodium falciparum* genes pfcrt and pfmdr1 are selected by amodiaquine treatment in Africa.[12] Continued use of SMC on a massive scale year-over-year will put increasing drug pressure on SPAQ throughout the Sahel region and accelerate the emergence of greater drug resistance to this chemoprevention.

The risk of rebound after cessation of SMC: Children between the ages of 3 months and 60 months who routinely receive SMC may benefit from years of protection against malaria. However, their reduced exposure to malaria may have a downside: the failure to develop strong immunological responses to malaria infection which may make them vulnerable again once they are no longer eligible for SMC.[13] This is one of the reasons some countries, for example Senegal, are choosing to implement SMC in older age groups.

Supply chain management: Several cases of late or partial delivery of SMC drugs are still being noted. Early planning by countries and local implementers as well as timely ordering of the commodities will help to improve the supply chain, which is also reliant on early commitment from funding partners. Today, there is only one WHO prequalified manufacturer of SPAQ (both tablet and child-friendly formulations). A diversified manufacturer base could help diminish the risk of disruptions in global SMC supply lines – a negative phenomenon which did in fact occur in 2015 after API sources for SPAQ were disrupted. To help address this, MMV is working with S Kant to achieve WHO prequalification of a second child-friendly formulation of SPAQ.

Migrant populations: Another challenge is the migratory nature of some populations in SMC eligible areas, which can negatively impact coverage rates. To address this challenge, the West African Health Organization (WAHO) is leading a cross-border collaboration to ensure parallel implementation of SMC across all regions.

MMV's role and future plans

MMV's involvement in SMC began in 2013 with the development of a tool kit to support SMC implementation. As a member of the UNITAID-funded ACCESS-SMC project led by Malaria Consortium since 2014, MMV has subsequently designed an online forecasting platform, which provides partners with country information on the number of children targeted by district and therefore the number of treatments needed for the subsequent 3 years. This information will help stakeholders to plan and deliver SMC on a timely basis. The tool also supports critical production planning activities for manufacturers by providing aggregated demand across all SMC countries. Recently, the tool has been expanded to enable access by other SMC stakeholders, enhancing transparency and facilitating collaboration across the broader community of SMC-eligible countries.

As an R&D-driven product development partnership, MMV also recognizes that it has a role to play in developing replacement medicines should drug resistance undermine current standards of care. Given the longer-term risks of resistance to SPAQ described above, MMV is considering which existing drugs might be used in a new combination as an alternative to SPAQ. Both components of a new combination should have a long half-life, an excellent safety profile, and ideally no history of drug resistance in sub-Saharan Africa. Although such an alternative should have a slow onset of action and would not be reliant on an artemisinin derivative, it would need to demonstrate 90% parasite clearance at day 7. Based on this profile, MMV aims to identify a potential alternative combination for SMC by the end of 2018. The combination would then need to undergo efficacy studies in SMC settings.

Conclusion

SMC is a highly-cost-effective, widely-adopted tool that is providing significant protection for young children in select regions of Africa. However, it remains a relatively new and time-bound intervention, requiring strong planning, monitoring and evaluation. The implementation campaign can be very time consuming for health care personnel at community level, substantially increasing their work load. The malaria community is coming together to address these and other challenges to SMC's widespread implementation. Furthermore, with the success of SMC in children, opportunities to consider its wider use across whole communities could make SMC relevant for the malaria elimination agenda. For now, the key focus for the SMC community, particularly following the completion of the ACCESS-SMC project in 2017, is to sustain funding and programmatic support so that SMC might reach every one of the 25 million children eligible for this life-saving intervention in Africa's sub-Sahel region.

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