Evaluation of SMC
Coverage, safety, efficacy, impact and drug resistance

Summary of progress and preliminary results
April 2017

Background

Despite progress in malaria control in many parts of the world, sub-Saharan Africa continues to have an enormous malaria burden and malaria is the leading cause of deaths in childhood. Seasonal malaria chemoprevention (SMC) was welcomed as a new tool because it offers the possibility of a very high degree of protection at moderate cost, in the absence of other practical options. Countries were quick to adopt SMC and, through the ACCESS-SMC project, high-quality, effective implementation has been scaled-up rapidly. But SMC is more complicated to deliver than many other interventions, and it is potentially vulnerable to the development of drug resistance. SMC programmes therefore have to be carefully monitored to ensure they are implemented effectively, and to provide evidence to donors of continued effectiveness.

Each SMC treatment provides a high degree of protection for about 4 weeks. In the sub- Sahel belt stretching from southern Senegal and northern Guinea in the west to Chad and northern Cameroon in the east, the main risk period lasts for about 4 months. Four SMC treatments, if well timed, are sufficient to provide a high degree of protection. It is important that children receive treatment each month, and adhere to the treatment regimen, both to give them the most complete protection, and to keep to a minimum the number of children with lapsed protection in whom SMC drugs are present at low levels which would favour the development of drug resistance. SMC programmes therefore aim to achieve high coverage at each monthly "cycle".

Monitoring delivery, efficacy, safety, impact, and drug resistance

To monitor the effectiveness of SMC delivery, the number of treatments administered in each monthly cycle has been documented, and coverage has been measured independently through household surveys at the end of each transmission season. These surveys as well as interviews with community health workers (CHWs) immediately after the monthly cycles were also used to assess adherence to the SMC regimen and quality of delivery. The purpose of these surveys was: a) to provide independent verification of SMC delivery; b) to determine the proportion of the eligible population that were reached and the proportion that were completely protected in the population overall, and in the most vulnerable sections of the population; and c) to determine the quality of delivery, which includes the appropriateness of the timing of

the SMC cycles, adherence to administration guideline by the CHWs, and children's adherence to the treatment regimen.

Safety monitoring being a concern at this scale, national pharmacovigilance (PV) capacity has been strengthened in all seven countries in order to ensure that any severe adverse drug reactions are properly investigated. PV has been based on targetted spontaneous reporting with a focus on the known severe adverse reactions to SMC drugs. In addition, active follow-up of a cohort of 10,000 children has been completed in Nigeria.

To determine the degree of protection from SMC (the efficacy of the treatments in preventing malaria), case-control studies have been used in Burkina Faso, Chad, Gambia, Mali and Nigeria.

The impact of the SMC programme in reducing the number of cases of confirmed malaria treated at health facilities has been assessed using reports of cases in the national health management information systems (HMIS), and by collecting more detailed data on all of the individual cases treated from selected health facilities that have served as sentinel sites for measuring the malaria burden more accurately than is possible from the national data. Sentinel data are required in addition to HMIS data because in most countries incomplete reporting makes the HMIS data difficult to interpret, and in all countries HMIS data are aggregated into three groups (under 5 years of age, 5 years and over, and pregnant women), and therefore cannot be used to determine whether there has been any increase in malaria incidence in the 5, 6 and 7 year-olds who recently stopped receiving SMC – an important concern with regard to safety.

Finally, it is important to be able to monitor the level of parasite resistance to SMC drugs across the sub-Sahel region. ACCESS-SMC has therefore measured the prevalence of molecular markers associated with resistance to SMC drugs in children, and in older age groups, to establish baseline frequencies of these markers in the children and in the general population before SMC was scaled up. The first baseline survey was carried out in late 2015 / early 2016, and it will be repeated at the end of 2017, to determine whether there has been an increase in the prevalence of markers of resistance in the general population after two years of SMC at scale in any of the countries. Sampling and laboratory methods have been standardised and the surveys were planned on a sufficient scale to be able to provide reliable indicators and reassure about sustained efficacy, as well as to able to detect, early-on, any important changes in sensitivity of parasite to SMC drugs if they occur.

This report presents short summaries of each evaluation component, and more detailed summaries are available as separate documents.

Coverage

In 2015, 87% of children in ACCESS-SMC areas received at least one SMC treatment, 73% were protected for at least 3 months, and 55% for four months. Similar coverage was achieved in 2016, while the population covered by ACCESS-SMC was doubled. The survey estimates for 2015 were validated against treatment registers in Mali. Register data for 640,000 children were entered, giving accurate estimates of the proportion of children who received 1, 2, 3 or 4 treatments, among those who were reached by the programme. Survey estimates agreed closely with these figures[1].

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[1] From administration registers in Mali, the percentage of children who received at least 3 treatments, and the percentage who received 4 treatments, were 69% and 50% respectively, in 2015. The estimates from the survey were almost exactly the same, 70% and 51%. The coverage at cycle 1,2,3 and 4 was 88%, 79%, 72% and 64% from register data, the corresponding estimates from the survey, among those children who received SMC at least once, were 81%, 77%, 62% and 58%. Coverage was slightly lower at successive at cycles, but the survey somewhat under-estimated the true coverage at cycles 3 and 4 (among those who were treated at least once).

Estimating the coverage at each monthly cycle is more prone to error than estimating the number of cycles a child received, as the former relies on more accurate recording on the SMC card, and on more accurate recall by the caregiver. The surveys showed that in several countries a high percentage of older children aged 6 to 7 years are receiving SMC. Treatment above the upper age limit was less common in The Gambia, Mali and Niger. In Mali and Niger, this may be linked to the extensive use of fixed-point delivery approaches led by trained health workers, as opposed to CHW-led door-to-door approaches in other countries. In The Gambia, administration was linked to the scanning of the child's SMC card using hand held devices, for which better trained and qualified staff had been selected (possible also because of the limited scale of the intervention in the country). Overall, coverage was better in countries that primarily employed door-to-door delivery.

Coverage of SMC in 2015

Country	Target	No. surveyed	No. eligible	% with SMC card retained	% treated at least once	% received at least 3 cycles	% received 4 cycles	% of 6-7yr olds treated	% slept under ITN last night
Burkina Faso	707,317	1,070	786	74%	96%	91%	86%	82%	89%
Chad	268,956	846	707	68%	96%	63%	24%	85%	81%
Gambia	88,748	1,174	690	90%	94%	85%	56%	30%	72%
Guinea	253,252	1,790	1,258	61%	94%	76%	57%	82%	83%
Mali	875,330	1,037	740	73%	87%	62%	45%	17%	94%
Niger	596,355	5,480	4,127	56%	84%	64%	48%	34%	91%
Nigeria	860,497	1,380	1,112	63%	77%	77%	54%	61%	83%
Overall	**3,650,455**	**12,777**	**9,420**	**67%**	**87%**	**73%**	**55%**	**53%**	**87%**

Coverage of SMC in 2016

Country	Target	No. surveyed	No. eligible	% with SMC card retained	% treated at least once	% received at least 3 SMC cycles	% received 4 SMC cycles	% of 6-7yr olds treated	% slept under ITN last night
Burkina Faso	2,056,169	1,136	874	67%	96%	91%	86%	82%	97%
Chad	514,042	1,328	1,010	48%	92%	40%	12%	61%	96%
Gambia	90,925	1,706	1,138	50%	81%	64%	43%	11%	61%
Guinea	438,123	2,612	1,743	40%	96%	83%	73%	79%	84%
Mali	1,492,137	1,023	799	33%	90%	77%	57%	53%	97%
Niger	1,050,932	5,340	5,135	47%	91%	72%	49%	43%	94%
Nigeria	1,909,163	2,221	1,662	48%	85%	46%	21%	59%	38%
Overall	**7,551,491**	**15,366**	**12,361**	**50%**	**91%**	**70%**	**53%**	**62%**	**79%**
Nigeria*		*1,265*	*932*	*41%*	*90%*	*50%*	*30%*		*34%*
Chad*		*1,111*	*797*	*44%*	*90%*	*39%*	*15%*		*97%*

*LGAs or districts which delivered 4 cycles. In 2016, in Nigeria, cycle 1 was not implemented in some areas due to temporary shortage of drugs caused by delays in registration of dispersible tablets by the local drugs authority. In Chad, cycle 4 was not implemented in some areas due to shortage of drugs caused by underestimation by health authorities of urban populations in the capital N'djamena. Coverage for the areas which did deliver 4 cycles is shown.

Efficacy of SMC treatments (case-control studies)

It is important to monitor the clinical protection provided by SMC treatments, and case-control studies can be used to determine the protective efficacy of vaccines and other preventive interventions used in public

health programmes, such as SMC. While it is not ethically acceptable to compare malaria incidence in treated and untreated children in a cohort study, it is however possible to determine efficacy by noting that children who develop malaria are less likely to have received SMC than children who remain free of malaria. By comparing the proportion of malaria cases who had received SMC in the previous 4 weeks with the proportion of children in the general population (the controls) who had not received SMC in the previous 4 weeks, the protective efficacy can be calculated. The project recruited cases and controls in The Gambia, Burkina Faso, Chad, Mali and Nigeria. Protective efficacy was at least 80% (80% in Gambia, 95% in Mali; preliminary results for other countries indicate similar efficacy, final analyses for other countries are currently being undertaken). These results confirm that efficacy is as high in SMC programmes as was seen in clinical trials. The results also showed that efficacy falls off rapidly beyond 5-6 weeks after treatment, as expected. This is an important result as it provides some validation of the methodology.

The efficacy of 80% to 90% over 4 weeks permits a prediction of the impact of the ACCESS-SMC programme to be made. About 14.5million treatments were administered in 2015 and 30million in 2016. We previously estimated that in SMC areas, before SMC was introduced, the average malaria incidence ranged from about 0.4 to 1 episode per child during the 4-months of the peak transmission season (i.e. about 0.1 to 0.25 cases per child per month). The total number of cases prevented over the 2 years 2015-2016 is therefore predicted to be between 3.6M and 10M malaria episodes, and assuming a case fatality of 0.45%, between 16,000 and 45,000 malaria deaths are predicted to have been prevented. LSHTM are in the process of deriving more detailed predictions, using spatial estimates of incidence from the Malaria Atlas Project and from the Imperial College malaria model, scaled to observed incidence using field data from SMC countries, to estimate the number of cases, severe cases and malaria deaths averted by SMC in each country.

Drug resistance

Resistance to SP and AQ is associated with specific gene mutations in the malaria parasite, it is therefore important to measure the prevalence of these mutations and to monitor any changes brought about by selective pressure due to scaling up of SMC. Baseline surveys were done in each of the 7 countries at the end of the 2015 transmission season, by collecting blood samples in 2000 children under 5 years of age and 2000 individuals 10-30 years of age; blood samples were taken onto filter paper and shipped to London for analysis, and processing of these samples is almost complete. LSHTM have so far extracted DNA from 26,813 (89%) of the total 30,268 samples, tested the extracted samples for presence of *P.falciparum,* and subsequently sequenced *pfmdr1*, *dhfr* and *pfdhps* genes of the positive samples. The analysis and sequencing for the remaining samples, and analysis of samples from case control studies, is now being completed. The baseline surveys, before the scale-up of SMC, showed very low frequencies of mutations associated with SP and AQ resistant genotypes in the region. This is the first time the frequencies of these markers have been measured on a sufficiently large scale, using standardised methods, to provide reliable estimates of prevalence.

The markers indicative of resistance to SMC drugs are as follows:

Amodiaquine	*Pfcrt* CVIET + *Pfmdr1* 86Y + *Pfmdr1* 184Y + *Pfmdr1* 1246Y
Sulfadoxine	*Pfdhps* 431V + 436A + 437A + 540G + 581G
Pyrimethamine	*Pfdhfr* 51I + 59R + 108R + 164L

The joint presence of *Pfcrt* CVIET with *Pfmdr1* 86Y and *Pfmdr1* 184Y is associated with resistance to AQ. The joint presence of *Pfdhfr* 51I, 59R and 108R and P*fdhps* 437A and 540G, confers resistance to SP.

Amodiaquine resistance: Only four samples, all from Niger, carried the *pfmdr1* 86Y and *pfmdr1* 184Y mutations. One of these samples also contained the *pfcrt* CVIET mutation, but this was mixed with the p*fcrt* wild type. The presence of the *pfcrt* CVIET mutation varied among countries, and was more common in

countries that had used artesunate-amodiaquine as first line treatment for malaria, and less common in countries that had primarily used artemether-lumefantrine.

Sulfadoxine-pyrimethamine resistance: Eight samples, 7 from Guinea and one from Niger, carried the *pfdhfr* triple mutation (51I + 59R + 108R) and *pfdhps* mutations 431 and 437A and 540G, associated with resistance to SP. None of these samples carried *pfmdr1* 86Y+*pfmdr1* 184Y associated with resistance to amodiaquine. High prevalence of the *pfdhfr* triple mutation with the *pfdhps*437A was observed in Burkina Faso, but the *pfdhps* 540G mutation was not detected.

No samples contained both SP and AQ resistant genotypes. These results are consistent with the high clinical efficacy of SMC treatments observed in case-control studies, and the substantial impact of SMC programmes that we have seen in HMIS data.

It is critical to repeat the sampling after two years of SMC at scale, and at intervals thereafter, to determine whether parasite genotypes resistance to SMC drugs has become more common. Repeat surveys in the same locations using the same sampling methods will be performed at the end of the 2017 transmission season, to assess effects after 2 years of SMC at scale. We will also analyse samples from malaria cases in children. Breakthrough cases 2-3 weeks after SMC, are likely to be resistant and analysis of those samples will indicate the particular markers which are associated with breakthrough infection.

Demonstration that the key mutations remain at low frequencies will be crucial for sustaining donor support for SMC.

Impact of ACCESS-SMC

Preliminary estimates of the impact of SMC have been obtained from analysis of sentinel surveillance data and HMIS data. Impact estimates rely primary on sentinel surveillance data, as HMIS data are limited in terms of quality and completeness, in some countries preventing meaningful estimates of impact to be made[2].

Mali sentinel surveillance showed a reduction of 50% in the number of malaria cases associated with SMC in the transmission season of 2015 (see figure). Final data collection for sentinel surveillance to December 2016 is currently being completed in each country. Provisional estimates of impact from HMIS data show reductions during the 2015 transmission season of over 60% in Gambia, 49% in Mali, 24% in Chad, and 45% in Burkina Faso. Data on deaths in district hospitals in SMC areas in Burkina Faso for the period 2013-2015 show a reduction of about 14% in the number of deaths in children under 5 years of age since when SMC was introduced in 2015, compared to expected trends.

Safety

The aim of the pharmacovigilance component of ACCESS-SMC was to support countries to strengthen spontaneous reporting, with an emphasis on the known severe side effects of SMC drugs (severe skin reactions, liver problems, neurological side effects, severe vomiting, and blood disorders). Before the project started, PV systems in SMC countries were very weak. Through the activities of ACCESS-SMC, all countries

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[2] In Niger, national HMIS data were not available for malaria, and the PNLP are currently obtaining records from each district. In Nigeria, data for 2013 (an important year for establishing pre-intervention burden) are largely missing; and in Guinea data are incomplete. In all countries, aggregated data are available only for three age groups: under 5, over 5 years, and pregnant women (except in Burkina Faso, where data are given separately for children 5-14 years of age and persons 15 and older). This makes it impossible to assess whether malaria risk is increased in children aged 6 and 7 who have stopped receiving SMC. Sentinel surveillance data give more detailed information and will permit more reliable estimates of impact in each country.

are now reporting events, mostly through VigiBase, the international drug safety database, and all SMC countries are now members or associate members of the WHO safety monitoring network. Reassuringly, there have been no cases of severe skin reactions in children under 5 years of age in ACCESS-SMC countries (three cases have been reported, all in older children, in Senegal). There have been two cases of extra-pyramidal syndrome (in Niger and Gambia), two cases of jaundice (The Gambia), three cases of oedema (Burkina Faso, Chad and Mali). As of April 2017, a total of 1,333 reports related to SMC for children under 5 years of age were uploaded into VigiBase for the years 2015-2016. Vomitting, diarrhoea and abdominal pain were the most common symptoms. The Nigeria cohort confirmed that adverse reactions are rare, with only five PV reports in over 10,000 children, though underreporting of mild events by families may be an issue.

Workshops were organised in 2014, 2015 and 2016 bringing together national PV coordinators, PV focal persons from the national malaria control programmes and project members to familiarise staff with the known side effects of SMC drugs and to assist countries to develop plans for PV for SMC. PV was included in cascade training in each country at the start of each SMC campaign. Reporting forms were printed and distributed to health facilities, and an information sheet describing the known adverse reactions to SMC drugs and who to notify in case of detection was widely distributed.

In each country, research groups involved in evaluation of ACCESS-SMC provided technical support to the PV centre. The project has also been able to catalyse support for PV for SMC from WHO-TDR, who supported training workshops in 2014 and 2016, and from WHO Safety and Vigilance, who developed training materials for PV for SMC and organised a workshop on PV for SMC in Burkina Faso in 2016 for PV coordinators. An international SMC safety committee has been established under the auspices of WHO Safety and Vigilance, with the role of reviewing safety of SMC annually, and reporting events to the WHO Advisory Committee on Safety of Medicines and Medicinal Products.