



# ACCESS SMC

Achieving catalytic expansion of seasonal malaria chemoprevention in the Sahel

## Progress Update

### SMC evaluative studies: Monitoring the prevalence of drug resistance molecular markers

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30.05.2017

This document is prepared by Malaria Consortium, based on preliminary survey data provided by London School for Hygiene and Tropical Medicine, April 2017 and project implementation reports.

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## Executive Summary

When implementing SMC, it is important that ensure that children receive treatment each month, and adhere to the treatment regimen, both to give them the most complete protection, and to minimise selection for drug resistance. In children with lapsed protection, SMC drugs are present at low levels favouring the development of drug resistance. Careful monitoring of SMC programmes is particularly important to ensure that SMC is delivered effectively, and that the drugs retain their efficacy. Case control studies can be used to measure clinical efficacy of SMC. Resistance to sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) is associated with specific gene mutations in the malaria parasite. Monitoring the prevalence of these markers, in malaria cases health facilities and in *P.falciparum* carriers in the general population, permits early warning of emerging problems with drug resistance. This progress update is on monitoring *P. falciparum* resistance markers.

The objective of the molecular monitoring through the ACCESS-SMC project was to establish a baseline for monitoring the prevalence of the markers across the subregion using standardised methods, and to determine if there have been any important changes in the prevalence of these markers after two years of SMC at scale. Care was taken to use standardized sampling and standardized laboratory methods, and to obtain a sufficiently large sample size to permit accurate assessment of the prevalence of the markers.. The baseline surveys were done at the end of the 2015 transmission season in all seven countries. (In 6 countries, sampling was done in areas which had not started SMC but would implement the following year. In The Gambia, sampling was in an area where SMC had been implemented for two years). In each country, one locality was chosen, , blood samples were collected from approximately 2000 children under 5 years of age and 2000 individuals 10-30 years of age per country, taken onto filter paper and shipped to London to the LSHTM laboratories for analysis. The older age group was included because they would not be treated with SMC drugs, assessment of trends in the prevalence of markers of resistance in this group therefore allows us to determine whether SMC is leading to changes in the circulating parasite population.

A standardised sampling and laboratory protocol was followed. Probability sampling was used to select a representative sample of the population in each locality. All children aged 3-59 months, and all persons 10-30 years, were invited to participate, and those who consented were interviewed using a standardized questionnaire and asked to provide a finger prick blood sample which was taken onto filter paper (Watmann No. 3). To date, DNA from 26,813 (89%) of the total 30,268 samples collected has been extracted and tested for the presence of *P. falciparum*, and subsequently *P. falciparum*-positive samples were subjected to genetic sequencing for *Pfmdr1*, *Pfdhfr* and *Pfdhps* genes. The analysis and sequencing for the remaining 11% samples, and the analysis of samples from case-control studies, is currently being completed.

The baseline surveys, before scale-up of SMC, showed very low frequencies of mutations associated with SP and AQ resistant genotypes. The markers indicative of resistance to SMC drugs are shown in the following table:

<b>Amodiaquine</b>	<i>Pfcrt</i> CVIET + <i>Pfmdr1</i> 86Y + <i>Pfmdr1</i> 184Y + <i>Pfmdr1</i> 1246Y
<b>Sulfadoxine</b>	<i>Pfdhps</i> 431V + 436A + 437A + 540G + 581G
<b>Pyrimethamine</b>	<i>Pfdhfr</i> 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 *Pf dhfr* 51I, 59R and 108R is associated with resistance to pyrimethamine monotherapy. Although pyrimethamine resistance developed quickly in Africa, the combination with sulfadoxine was highly effective as pyrimethamine and sulfadoxine together work synergistically. Resistance to sulfadoxine increases in relation to the number of *Pf dhps* mutations. The presence of *Pf dhps* 437A and 540G, together with the triple *Pf dhfr* mutation, is associated with early treatment failure when SP is used to treat clinical cases of malaria. When *Pf dhps* 581G is also present there is a higher level of resistance. The mutations tend to arise progressively, starting with *Pf dhfr* 51I, 59R and 108R, followed by *Pf dhps* 437A, and *Pf dhps* 540G.

Individuals can be infected with multiple parasite clones. The number of clones (multiplicity of infection) is greater in areas with more intense malaria transmission and can vary seasonally. The recorded prevalence of a mutation in a survey depends on the sensitivity of the methods used, because more sensitive methods are more likely to detect mutations in the less abundant parasite clones. Hence the importance of a standardized approach to sampling and laboratory methods. In particular samples, if there is a mixed infection, it may not be possible to determine whether mutations occur in the same parasite, however in the case of SP in Africa, the presence of the *Pf dhps* 540G mutation is indicative of the quintuple mutation as it tends to occur only in the presence of the other mutations.

In the baseline surveys conducted after the 2015 transmission season, no samples contained both SP and AQ resistant genotypes.

- The presence of the *Pf crt* CVIET mutation varied among countries, and was more common in countries that had used artesunate-amodiaquine primarily for first line treatment for malaria in the past, and less common in countries that had primarily used artemether-lumefantrine.
- Only four samples were positive for both the *Pf mdr1* 86Y and *Pf mdr1* 184Y mutations associated with AQ resistance, and these were all from Niger. One of these samples also contained the *Pf crt* CVIET mutation, but this was mixed with the *Pf crt* wild type, and therefore it was not possible to be sure whether the same parasites carried all three mutations.
- Eight samples (7 from Guinea and one from Niger), carried the quintuple mutation (*Pf dhfr* triple mutation (51I + 59R + 108R) and *Pf dhps* mutations 431 and 437A and 540G), associated with resistance to SP. None of these samples carried *Pf mdr1* 86Y+*Pf mdr1* 184Y associated with resistance to amodiaquine.
- High prevalence of the *Pf dhfr* triple mutation with the *Pf dhps*437A was observed in Burkina Faso, but the *Pf dhps* 540G mutation was not detected.

It is not known how protective efficacy of SMC will decrease as the prevalence of these mutations increases. Case control studies, alongside surveys of molecular markers, allow efficacy to be measured and related to the prevalence of the markers. Continued demonstration that the key mutations remain at low frequencies will be good evidence that SMC remains effective. 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. Analysis of samples from the cases in children who received SMC, will allow the link between presence of markers and the level of protection to be better determined.

Steps can be taken to minimise selection for drug resistance. Factors that may influence the development of resistance, and should be monitored, include:

- i. Poor adherence to SMC doses, and under-dosing.
- ii. Breakthrough malaria cases should be promptly treated with a drug regimen that does not include SP or AQ.
- iii. Parasites carrying the CVIET haplotype of *Pf crt* and the 86Y allele of *pf mdr1*, associated with AQ resistance, are more sensitive to artemether-lumefantrine (AL, coartem), so prompt

treatment of breakthrough infection with AL may impede selection for AQ resistance by SMC drugs.

- iv. SMC if widely deployed can reduce malaria morbidity substantially, reducing the need for first line treatment, and therefore limiting the scope for selection for resistance to first line drugs. But this advantage will be fully realised only if all suspected malaria cases are tested with an RDT. It is therefore particularly important to take steps to ensure use of RDTs for malaria confirmation in SMC areas.

Monitoring of SMC programmes should include documenting adherence to these good practice guidelines in the districts where SMC is implemented.

The low frequency of markers of resistance to SMC drugs observed in the baseline surveys is consistent with the high clinical efficacy of SP+AQ SMC treatments estimated using case control studies and with the impact of SMC on the number of confirmed malaria cases reported in national HMIS data. However, it is critical to repeat the resistance marker surveys after two years of SMC at scale, and at intervals thereafter, to determine whether *P. falciparum* parasite genotypes resistant to SMC drugs have become more common.

## 1. Introduction

### 1.1 Background

During the first SMC campaign season in 2015, the project administered over 12 million treatments of SMC to over 3 million children. In 2016, this number more than doubled to over 25 million treatments being administered to over 6.4 million children. 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. This is particularly relevant as SMC programmes reach greater scale.

It is essential that SMC programmes are carefully monitored to ensure that SMC is delivered successfully by national Malaria Control Programmes, reaching a high proportion of eligible children in each monthly cycle. Resistance to SP and AQ is associated with specific gene mutations in the malaria parasite, which can be monitored to give early warning of developing resistance brought about by selective pressure due to scaling up of SMC. This progress update is on monitoring *P. falciparum* resistance markers in 2015 and 2016.

**Table 1: Genetic markers that indicate presence of a risk of resistance to drugs used for SMC treatments**

Molecule	Genetic markers indicative of resistance to SMC drugs
Amodiaquine	Pfcr1 CVIET + Pfmdr1 86Y + Pfmdr1 184Y + Pfmdr1 1246Y
Sulfadoxine	Pfdhps 431V + 436A + 437A + 540G + 581G
Pyrimethamine	Pfdhfr 51I + 59R + 108R + 164L

The joint presence of *Pfcr1* CVIET with *Pfmdr1* 86Y and *Pfmdr1* 184Y is associated with resistance to AQ, while the joint presence of *Pfdhfr* 51I, 59R and 108R, and *Pfdhps* 437A and 540G, confers resistance to SP. The presence, in addition, of *Pfdhfr*164L and *Pfdhps*581G confers a higher level of resistance to SP.

### 1.2 Objectives

The objective of the monitoring of molecular markers of resistance to SMC drugs was to establish a baseline for the prevalence of markers associated with resistance to SP and AQ, using standardized sampling and laboratory methods, and to determine if there any important changes in prevalence after two years of SMC at scale. This summary report presents an update on monitoring markers of drug resistance in relation to the evaluating the delivery of SMC. This report is prepared by Malaria Consortium, based on reports and preliminary results provided by London School for Hygiene and Tropical Medicine, April 2017 and project implementation reports.

## 2. Methodology resistance markers surveys

### 2.1 Overview and study sites

A series of studies to evaluate SMC programmes were implemented as a partnership between research institutions supporting the National Malaria Control Programmes in each of the seven countries, Malaria Consortium and CRS in each country, the Universite Cheikh Anta Diop, WHO/TDR and LSHTM. LSHTM developed the protocol and was responsible for scientific coordination, while UCAD and WHO/TDR contributed to project coordination and communication. The protocol for monitoring drug resistance was developed following a consultation with national malaria control programmes, research institutions in each country, the WWARN (WorldWide Antimalarial Resistance Network), LSHTM, UCAD and TDR, at a meeting in Dakar in September 2014. The monitoring plan was presented to the MERG (the Monitoring and Evaluation Reference Group of Roll Back Malaria,

25th meeting, Istanbul, Oct 2015) and reviewed by the WHO Technical Expert Group on Drug Efficacy and Response in December 2015. The ACCESS-SMC project Technical Committee met periodically to monitor progress and advise on the technical aspects of the study (a list of names of the study team is annexed to this report). Surveys were conducted by research groups in each country, laboratory analysis was done in London in collaboration with the country research teams who sent a laboratory scientist to London to work on their samples.

The study sites chosen were districts were the ACCESS-SMC project implementation districts or local government authorities in Burkina Faso, Chad, The Gambia- Upper river region and central river region, Guinea, Mali, Niger and Nigeria, which were under the management of CRS or Malaria Consortium.

## **2.2 The baseline survey**

This report presents and update on analysis of baseline survey data. A second survey is planned to be conducted in each country at the end of the 2017 transmission season. The baseline surveys were done at the end of the 2015 transmission season. The processing of blood samples from 2000 children under 5 years of age and 2000 individuals 10-30 years of age is still ongoing. Blood specimens were taken onto filter paper and shipped to London to the LSHTM laboratories for analysis.

## **2.3 Sample size determination**

The sample size was 2200 children eligible for SMC (3-59 months), and 2200 older children and adults aged 10 to 30 years, at baseline and follow-up surveys in order to have at least 90% power to detect an odds ratio of 1.4 compared to baseline in pooled analysis and an odds ratio of 2.5 in each country. This sample size was also sufficient to be able to rule out the possibility of an important increase if none was observed (see Annex for further details). The older age group was included to enable the monitoring of trends of molecular markers in individuals who because they had not received SMC, reflect changes in the circulating parasite population.

## **2.4 Sampling and laboratory methods**

Baseline surveys were conducted at the end of the 2015 transmission season. In each country, a district was selected that had not started SMC but would implement at scale from 2016 (except in The Gambia where SMC had already started in all regions targeted for SMC). Where possible districts were chosen which included sites used by the national malaria control programme for monitoring efficacy of first line drugs, for comparability and to concentrate capacity. The population of the district was sampled by selecting villages with probability proportional to size, and then using compact segment sampling in each village to select survey participants. This method was chosen in order to minimise selection bias and to provide a survey sample that could be repeatedly sampled in future years. All children eligible for SMC, and all persons 10-30 years, were invited to participate in the survey. Those who consented asked to provide a finger-prick blood sample to make at least two blood spots on filter paper (Watmann No. 3), and a questionnaire was completed to record demographic details, care seeking for malaria, recent antimalarial treatment, and use of malaria protective measures. Please see annex for information sheets and consent forms. Filter papers identified with a barcode were shipped to London for DNA extraction, PCR for detection of *P. falciparum* and subsequently analysis of positive samples by sequencing for *Pfmdr1*, *dhfr* and *Pfdhps* genes, following a standardised protocol.

## **2.6 Ethical considerations and quality assurance**

Ethics committees in each participating country, and the LSHTM ethics committee, reviewed and approved the protocol. Consent was sought from all participants after explaining the aims and procedures of the study in the local language (signed consent for adults; for children, consent signed

by parent or guardian, and for older children assent was also sought). Survey planning and conduct was monitored by staff from UCAD and LSHTM.

### 3. Progress update: resistance marker surveys

#### 3.1 Baseline survey findings

A total of 30,292 samples were collected, DNA extraction and analysis is nearing completion, to date DNA has been extracted from 27,698 samples, 25,641 have been tested, 3,498 (14%) were positive and of these 2,441 have been sequenced. The analysis and sequencing for the remaining samples, and the analysis of samples from case control studies, is currently being completed.

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 preliminary results show that, before scale-up of SMC, amodiaquine resistant mutations were only found in 4 samples, and SP resistant mutations in 8 samples. No samples contained both SP and AQ resistant genotypes.

#### 3.2 Amodiaquine resistance

The details on amodiaquine resistance markers identified are as follows:

- The presence of the *Pfcr*t CVIET mutation varied among countries, and was more common in countries that had used artesunate-amodiaquine primarily for first line treatment for malaria and less common in countries that had primarily used artemether-lumefantrine.
- Only four samples (all of them from Niger) carried the *Pfmdr*1 86Y and *Pfmdr*1 184Y mutations associated with AQ resistance. One of these samples also contained the *Pfcr*t CVIET mutation, but this was mixed with the *Pfcr*t wild type, it was therefore not possible to determine if *Pfcr*t CVIET occurred in the same clone that had the *Pfmdr*1 86Y and *Pfmdr*1 184Y double mutation.

#### 3.3 Sulfadoxine-pyrimethamine resistance:

- Eight samples (7 from Guinea and one from Niger) carried the quintuple mutation associated with SP resistance (*Pfdhfr* triple mutation (51I + 59R + 108R) and *Pfdhps* mutations 431 and 437A and 540G).
- None of these samples carried *Pfmdr*1 86Y+*Pfmdr*1 184Y that is linked to 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.

#### 3.4 Implication of findings

Parasite genotypes associated with resistance to SMC drugs occur at very low frequencies. 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. It is important that surveys are repeated at intervals of 2-3 years to provide early warning of developing resistance. We will also analyse samples from malaria cases in children, as breakthrough cases 2-3 weeks after SMC are likely to be more resistant, and analysis of those samples will indicate the particular markers which are associated with breakthrough infection.

Factors that may influence the development of resistance, and should be monitored, include:

- i. Poor adherence to SMC doses, and under-dosing: children should receive SMC each month and should adhere to the regimen each month, and under-dosing should be avoided. The main risks here include:
  - inadvertently including children older than 59 months;
  - giving infant doses to older children;

- children receiving incomplete doses due to spitting out medication.
- ii. Breakthrough malaria cases should be promptly treated with a drug regimen that does not include SP or AQ.
- iii. Parasites carrying the CVIET haplotype of *pfcr1* and the 86Y allele of *pfmdr1*, associated with AQ resistance, are more sensitive to artemether-lumefantrine (AL, coartem), therefore prompt treatment of breakthrough infection with AL may be expected to impede selection for AQ resistance by SMC drugs.
- iv. SMC, by reducing malaria morbidity, substantially reduces the need for first line treatment, limiting the scope for selection for resistance to first line drugs. This potential advantage will be fully realised only if all suspected malaria cases are tested with an RDT. It is therefore especially important in SMC areas that health staff use RDTs to test children with suspected malaria. This can be an issue as RDTs are underfunded in many countries and costs of RDTs are not covered by SMC donors.

Monitoring should be done to document adherence to these good practice guidelines in the districts where SMC is implemented.

#### **4. Conclusion**

The low frequency of markers of resistance to SMC drugs observed in the baseline surveys is consistent with the high clinical efficacy of SP+AQ SMC treatments estimated using case control studies and with the impact of SMC on the number of confirmed malaria cases reported in national HMIS data. However, it is critical to repeat the resistance marker surveys after two years of SMC at scale, and at intervals thereafter, to determine whether *P. falciparum* parasite genotypes resistant to SMC drugs have become more common.

There will be further progress updates, when the analysis of the collected DNA samples is complete, and when the resistance marker surveys for 2017 are launched. Monitoring should be reinforced in order to document adherence to guidelines and good practice wherever SMC is implemented in order to minimise selection for resistance.

## 5. Appendix

### 5.1 Investigators Details (resistance monitoring)

**Table 2: Principal Investigators**

Country	Institution	Name	Contact details
UK	LSHTM	Paul Milligan	<a href="mailto:paul.milligan@lshtm.ac.uk">paul.milligan@lshtm.ac.uk</a>
UK	LSHTM	Colin Sutherland	<a href="mailto:colin.sutherland@lshtm.ac.uk">colin.sutherland@lshtm.ac.uk</a>
UK	LSHTM	Khalid Bashir	<a href="mailto:Khalid.Beshir@lshtm.ac.uk">Khalid.Beshir@lshtm.ac.uk</a>
Burkina Faso	IRSS	Jean-Bosco Ouedraogo	<a href="mailto:jbouedraogo@gmail.com">jbouedraogo@gmail.com</a>
Chad	CSSI	Daugla Doumagoum	<a href="mailto:daugla.doumagoum@cssi-td.org">daugla.doumagoum@cssi-td.org</a>
Gambia	MRC	Serign Ceesay	<a href="mailto:sjceesay@mrc.gm">sjceesay@mrc.gm</a>
Guinea	GANU	Kovana Loua	<a href="mailto:louakovanamarcel@gmail.com">louakovanamarcel@gmail.com</a>
Mali	MRTC	Alassane Dicko	<a href="mailto:adicko@icermali.org">adicko@icermali.org</a>
Niger	CERMES	Ibrahim Laminou	<a href="mailto:lamine@cermes.org">lamine@cermes.org</a>
Nigeria	JEDIMA	Sonny Ogboi	<a href="mailto:ogboijb@yahoo.com">ogboijb@yahoo.com</a>

**Table 3: Co-investigators**

Role	Institution	Name	Contact details
Statistics	LSHTM	Matt Cairns	<a href="mailto:matthew.cairns@lshtm.ac.uk">matthew.cairns@lshtm.ac.uk</a>
Data coordination	LSHTM	Paul Snell	<a href="mailto:paul.snell@lshtm.ac.uk">paul.snell@lshtm.ac.uk</a>
Senegal	UCAD	Jean Louis NDiaye	<a href="mailto:jindiaye@yahoo.com">jindiaye@yahoo.com</a>
Senegal	UCAD	Abdoulaye Diallo	<a href="mailto:diallaye@yaho.fr">diallaye@yaho.fr</a>
Africa Region	MC	Ebenezer Baba	<a href="mailto:e.baba@malariaconsortium.org">e.baba@malariaconsortium.org</a>
Public Health Specialist	MC	Harriet Kivumbi	<a href="mailto:h.kivumbi@malariaconsortium.org">h.kivumbi@malariaconsortium.org</a>
Regional Project Director	MC	Diego Moroso	<a href="mailto:d.moroso@malariaconsortium.org">d.moroso@malariaconsortium.org</a>

**Table 4: National Malaria Control Programme Focal persons**

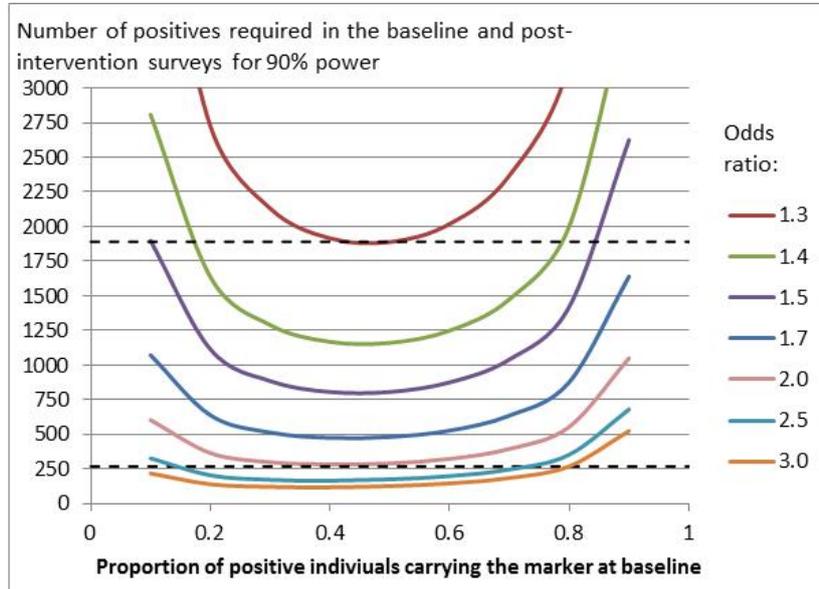
Country	Institution	Name	Contact details
Burkina Faso	PNLP	Savadogo Yacouba	<a href="mailto:syacouba2002@yahoo.fr">syacouba2002@yahoo.fr</a>
Chad	PNLP	Clément KeraH Hinzoumbe	<a href="mailto:kerah_clement@yahoo.fr">kerah_clement@yahoo.fr</a>
The Gambia	NMCP	Balla Kandeh	<a href="mailto:ballakandeh@yahoo.co.uk">ballakandeh@yahoo.co.uk</a>
Guinea	PNLP	Moussa Keita Timothe Guilavogui	<a href="mailto:msskeita@yahoo.fr">msskeita@yahoo.fr</a> <a href="mailto:gui_timothee@yahoo.fr">gui_timothee@yahoo.fr</a>
Mali	PNLP	Diakalia Kone	<a href="mailto:dkone1311@yahoo.fr">dkone1311@yahoo.fr</a>
Niger	PNLP	Hadiza Jakou Djermakoye	<a href="mailto:hadizou_jakou@yahoo.fr">hadizou_jakou@yahoo.fr</a>
Nigeria	NMEP	Nnenna Ezeigwe	<a href="mailto:drninaezeigwe@gmail.com">drninaezeigwe@gmail.com</a>

**Access-SMC Technical Committee:** Diego Moroso, Ebenezer Baba, James Tibenderana, Harriet Kivumbi, Arantxa Roca, Eric Hubbard, Lanto Razafindralambo, Suzanne van Hulle, Gladys Tetteh, David Collins, Paul Milligan (chair).

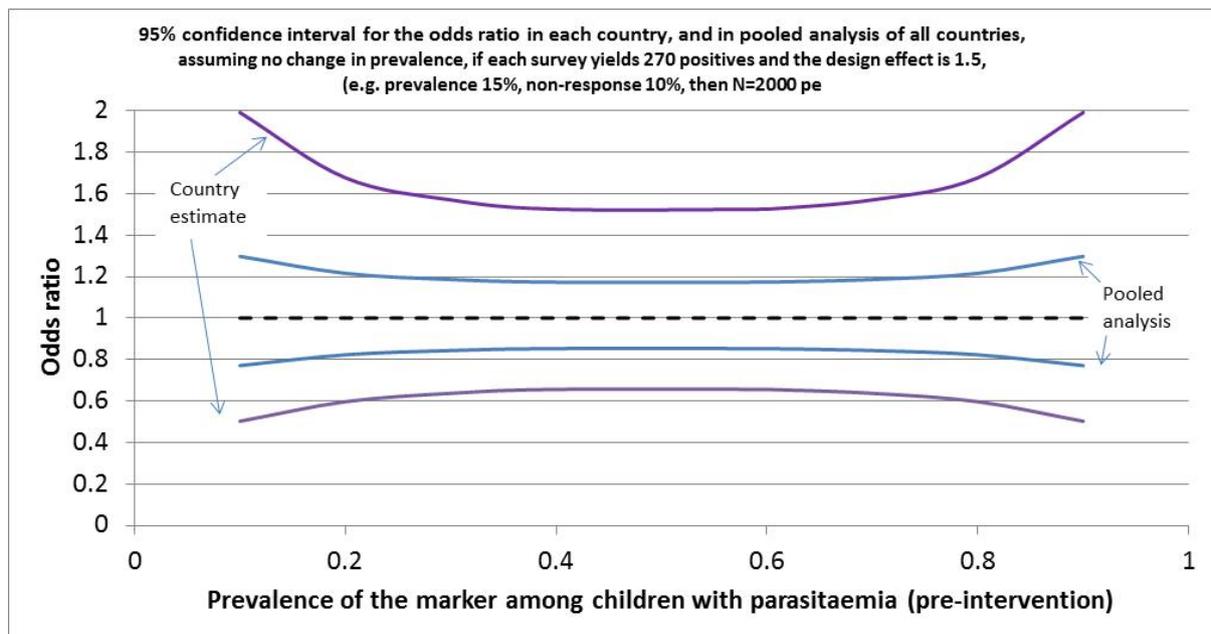
### 5.3 Sample size calculations (as per protocol)

The aim was to be able to estimate changes in prevalence of markers of resistance, with enough precision to provide reassurance here has been no important increase, if none occurs, while having adequate power to detect important changes if they occur. A design effect of 2 has been assumed for these calculations. The figure below shows the sample size (no. of parasite positive individuals) required for 90% power (using a 5% significance level) to detect a change in prevalence of the marker among parasite positive individuals, if the true change post-intervention is as indicated, assuming a design effect of 2. The dashed lines, corresponding to 270 positive individuals in each

country (lower line), i.e.  $7 \times 270 = 1890$  in a pooled analysis of 7 countries (upper line), show that with this number we would have 90% power to detect an odds ratio of at 1.4 or more in a pooled analysis and of 2.5 or more in each country. 270 was chosen here as this corresponds to the minimum number it may be feasible to obtain in a survey of manageable size (corresponding to the number that would be obtained in a survey of 2200, if the prevalence is towards the lower end of the expected range, 15%, and loss to follow-up is 10%).



It is also important that confidence intervals are sufficiently narrow to be able to rule out an important change if none is observed. The figure below shows the 95% confidence interval that would be obtained on the odds ratio for the change in frequency of markers after two years, among parasite positive individuals, if surveys in each country yield 270 positives, and there has been no change in the prevalence of markers:



## **5.4 SMC resistance molecular markers monitoring survey: participant information sheets and consent forms**

### **SMC monitoring survey: Information sheet (children) Dated 24 May 2015, V1.**

*Name of research institution*

Your child is being invited to take part in a research study. To help you decide if your child can participate, we will explain why we are doing the study, and what it will involve. If there is anything that you do not understand, ask for it to be explained until you are satisfied. Take time to decide whether or not you wish to take part.

#### **1. Why is this study being done?**

Seasonal Malaria Chemoprevention (SMC), where children are given drug treatment each month to prevent malaria, is being introduced for children in this area. The drugs are very effective against the parasites that cause malaria, but in other parts of Africa some malaria parasites are resistant to these drugs. The National Malaria Control Programme and <research institution> are doing this survey to make sure that none of these resistant malaria parasites have come to this area. We will also test the blood of each child in the survey to check that the drugs used for SMC can work well. The information from this survey will help the malaria control programme ensure SMC remains effective.

#### **2. Why has my child been chosen?**

We are including children who received SMC or may receive SMC in the future. We need about 2000 children in the survey and have selected certain villages to participate.

#### **3. Does my child have to take part? What happens if I change my mind?**

You do not have to let your child take part. If you decide they can take part, you are still free to stop their involvement whenever you wish without having to justify it, this won't affect their normal health care. If you decide to join the study, you will need to sign or thumbprint a consent form saying you agree to be in the study. You will receive a copy of this.

#### **4. What does this study involve?**

If you agree for your child to participate:

- we will ask to take a sample of blood from the finger,
- we will ask some questions about your child's age, date of birth, any recent illness and travel, the family's ethnicity, and we will ask to see where they slept last night to inspect the bednet if there is one.

#### **5. Expenses and payments**

There will be no payment for participation.

#### **6. What are the risks or disadvantages of participation?**

The finger prick can cause discomfort but is safe and will be done by staff who are trained to do it safely with a minimum of discomfort.

#### **7. What are the benefits of participation?**

If your child is unwell, we will test for malaria and if the test is positive we will treat them for malaria as the nurse would do in the clinic or refer them to the clinic where they will be treated for malaria free of charge.

## **8. What will happen to the samples taken in this study?**

We will put two spots of blood onto absorbent paper to be analysed to test any parasites present in the blood to see if they are the type that are resistant to SMC drugs. We will also keep the blood sample to test if the SMC medicines can work well.

Some people have characteristics in their blood that make the medicines work less well. These characteristics (called genes) are inherited from one's parents (in the same way that children resemble their parents because of other inherited characteristics). We will use these samples to find out how many people have these characteristics.

These tests may be done at a later time by our collaborators outside this country so we will send them part of your child's blood sample. Your child's name will not be linked to the sample so no-one will know the name of the person that gave the sample. We would also want to keep some of the leftover sample for further tests in the future when we understand more about the parasites.

## **9. How will your personal records remain confidential and who will have access to them?**

The personal information we collect about your child will be kept private, the only people who will be allowed to see the information will be the study investigators.

## **10. Who is organising and funding the research?**

The study is being organised by <research institution> in collaboration with the National Malaria Control Programme, the London School of Hygiene & Tropical Medicine, Malaria Consortium and the Catholic Relief Services. The work is funded by UNITAID as part of the project ACCESS-SMC.

## **11. Who has approved the study?**

The study has been approved by the ethics committee in <country>.

Do you have any questions now? If you have any questions later about the study you may contact <Name and contact details of the principal investigator>.

**SMC monitoring survey: Information sheet (adults) Dated 24 May 2015, V1.**

Name of research institution

You are being invited to take part in a research study. To help you decide to participate, we will explain why we are doing the study, and what it will involve. If there is anything that you do not understand, ask for it to be explained until you are satisfied. Take time to decide whether or not you wish to take part.

**1. Why is this study being done?**

Seasonal Malaria Chemoprevention (SMC), where children are given drug treatment each month to prevent malaria, is being introduced for children in this area. The drugs are very effective against the parasites that cause malaria, but in other parts of Africa some malaria parasites are resistant to these drugs. The National Malaria Control Programme and <research institution> are doing this survey to make sure that none of these resistant malaria parasites have come to this area. The information from this survey will help the malaria control programme ensure SMC remains effective.

**2. Why have I been chosen?**

We are including adults living in areas where SMC will be used. Although SMC is for children, adults harbour the parasites and can transmit them to mosquitoes. We need about 1500 adults in the survey and have selected certain villages to participate.

**3. Do I have to take part? What happens if I change my mind?**

You do not have to take part. If you decide to take part, you are still free to stop whenever you wish without having to justify it, this won't affect your normal health care. If you decide to join the study, you will need to sign or thumbprint a consent form saying you agree to be in the study. You will receive a copy of this.

**4. What does this study involve?**

If you agree to participate:

- we will ask to take a sample of blood from the finger,
- we will ask some questions about your age, date of birth, any recent illness and travel.

**5. Expenses and payments**

There will be no payment for participation.

**6. What are the risks or disadvantages of participation?**

The finger prick can cause discomfort but is safe and will be done by staff who are trained to do it safely with a minimum of discomfort.

**7. What are the benefits of participation?**

If you are unwell, we will test for malaria and if the test is positive we will treat you for malaria as the nurse would do in the clinic or refer you to the clinic where you will be treated for malaria free of charge.

**8. What will happen to the samples taken in this study?**

We will put two spots of blood onto absorbent paper to be analysed to test any parasites present in the blood to see if they are the type that are resistant to SMC drugs.

### **9. How will your personal records remain confidential and who will have access to them?**

The personal information we collect about you will be kept private, the only people who will be allowed to see the information will be the study investigators.

### **10. Who is organising and funding the research?**

The study is being organised by <research institution> in collaboration with the National Malaria Control Programme, the London School of Hygiene & Tropical Medicine, the Malaria Consortium and the Catholic Relief Services. The work is funded by UNITAID as part of the SMC programme.

### **11. Who has approved the study?**

The study has been approved by the ethics committee in <country>.

Do you have any questions now? If you have any questions later about the study you may contact <Name and contact details of the principal investigator>.

**Study title: SMC monitoring survey**

**Name of Principal Investigator:**

## Consent Form (children)

Child's name: \_\_\_\_\_ Participant No. |\_\_|\_\_|\_\_|\_\_|

*Tick as appropriate :*

I have had the information (dated 25/5/15) explained to me by the study team:

I understand that participation is voluntary:

I have been able to ask questions about this study:

I agree for data about my child to be used by the investigators:

I agree for my child to take part in this study:

I agree to further research on my child's samples as described in the information sheet:  
 **Yes**  **No**

_____ Name of Parent/guardian <i>(printed)</i>	_____ Signature/Thumbprint	_____ Date
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_____ Name of Person taking consent	_____ Signature	_____ Date
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The participant is unable to read the information sheet. As a witness, I confirm that all the information about the study was given and the participant consented to taking part:

_____ Name of Impartial Witness <i>(if required)</i>	_____ Signature	_____ Date
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**Study title: SMC monitoring survey**

**Name of Principal Investigator:**

**Assent Form (children)**

Participant No. |\_\_|\_\_|\_\_|\_\_|

The information about the survey has explained to me. I understand I do not have to take part.

I agree to take part in this study:  **Yes**  **No**

\_\_\_\_\_  
Name of child  
*(printed)*

\_\_\_\_\_  
Signature/Thumbprint

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Person taking assent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**Study title: SMC monitoring survey****Name of Principal Investigator:****Consent Form (adults)**

Participant No. |\_\_|\_\_|\_\_|\_\_|

*Tick as appropriate :*I have had the information (dated 25/5/15) explained to me by the study team: I understand that participation is voluntary: I have been able to ask questions about this study: I agree for data about me to be used by the investigators: I agree to take part in this study: 

Name of Participant <i>(printed)</i>	Signature/Thumbprint	Date
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Name of Person taking consent	Signature	Date
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The participant is unable to read the information sheet. As a witness, I confirm that all the information about the study was given and the participant consented to taking part:

Name of Impartial Witness <i>(if required)</i>	Signature	Date
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***Referenced documents and reports***

- Evaluation of SMC coverage, efficacy, safety, drug resistance, and impact: Summary of progress and preliminary results, Paul Milligan, paul.milligan@lshtm.ac.uk, LSHTM, April 2017.
- Presentation at the joint SMC consultation meeting, Ouagadougou, February 2017, presentation entitled: Strengthening systems for safety monitoring for SMC in the Sahel, by Prof Jean Louis Ndiaye on behalf of WARN/CARN SMC working group
- Field Guide for Training & Service Delivery of Seasonal Malaria Chemoprevention in Nigeria, Malaria Consortium, 2016
- Progress report SMC- submitted to UNITAID, September 2016
- ACCESS-SMC M&E Strategy, Annex III; Protocol for Monitoring efficacy of SMC treatments; Evaluation safety of the drugs; SMC coverage and the public health impact of SMC scale-up, ACCESS-SMC project, 2015