ACCESS SMC

Achieving catalytic expansion of seasonal malaria chemoprevention in the Sahel

Progress Update

Pharmacovigilance: Monitoring SMC drug safety

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Lay Summary

Introduction

Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine + amodiaquine (SP+AQ) was shown in clinical trials to have the potential to reduce malaria morbidity, and severe malaria, by at least 75 percent in areas with high seasonal transmission, in the Sahel region of sub-Saharan Africa, even in areas where most children are using long-lasting insecticide treated nets (LLINs)[1]. The UNITAID-funded ACCESS-SMC project (2014-2017), managed by Malaria Consortium has been a leader in catalysing the scale-up of SMC delivery to children 3-59 months of age. ACCESS-SMC is implemented in Chad, Burkina Faso, Nigeria, Niger, Mali, Guinea and The Gambia.

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, with over 25M treatments administered to over 6.3 million children. SMC drugs are known to be well tolerated and the risk of severe adverse reactions is low, but as with all public health programmes involving medicines, it is important to maintain effective safety monitoring (pharmacovigilance, PV) to ensure the drugs remain safe and to mitigate any risks. PV systems in Africa are known to be weak, one of the objectives of ACCESS-SMC therefore was to contribute to strengthening national PV systems to be able to monitor safety of SMC effectively.

This summary report presents an update on safety monitoring activities under ACCESS-SMC.

Methods:

The approach to PV for SMC was to strengthen the national PV system, to ensure that adverse reactions to SMC drugs were detected, effectively managed, and reported. The emphasis was on the known severe adverse reactions to SMC drugs, through targetted spontaneous reporting, supplemented by active follow up by the community health workers visiting households each month to deliver SMC who were trained to refer and report any severe cases. To document the occurrence of mild and moderate symptoms, a sample of caregivers were asked about adverse reactions to SMC during household surveys at the end of each cycle and at the end of each year. Innovative approaches that were used included sending SMS reminders about PV reporting to all health facility staff before each SMC cycle.

Progress update

At project baseline the PV systems in the seven countries were assessed as being very weak. Most target countries had completed very few PV reports of any kind in the past, and Chad was not a member of the WHO safety monitoring system. Through the activities of ACCESS-SMC, PV has been strengthened, all countries are now reporting events, there has been an increase in reporting in general not just for SMC-related events, and now all SMC countries are members or associate members of WHO safety monitoring network.

The project has also been able to catalyse support for PV for SMC from other agencies. WHO-TDR, contributed to the organisation of training workshops in 2014, 2015 and 2016, and WHO Safety and Vigilance supported training and developed training materials for PV for SMC. An international SMC safety committee has been established, with the role of reviewing safety of SMC annually, and reporting to ACSoMP, the committee which advises WHO on the safety of medicines.

The seven ACCESS-SMC project countries have reported only a small number of cases of severe adverse events (SAEs) linked to SMC drugs to date. No drug-related deaths have been reported. As of April 2017, there are a total of 1,333 reports in VigiBase related to SMC in children under 5 years of

[1] http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf?ua=1

age and treated in the years 2015-2016. Minor reactions such as vomiting, diarrhoea and abdominal pain were the most common symptoms.

However, some problems were detected when analysing PV data, especially related to the limited quality of the national PV reporting systems and data. There is a need to improve the completeness of PV reports so that all critical data for analysis are collected. National technical committees need strengthening to be able to review reports and assess causality.

Conclusion and recommendations

ACCESS-SMC has contributed to strengthening national capacity for monitoring the safety of medicines and improving PV reporting. SMC drugs delivered at scale through ACCESS-SMC have been found safe and well tolerated. The strengthening of PV systems through SMC , primarily ACCESS-SMC, is seen as a successful model with lessons to be learned for other programmes. Successful strengthening of PV systems in Africa requires a collaborative approach. ACCESS-SMC benefited from partnerships between national PV centres, malaria control programmes, research institutions, WHO, TDR, the WHO collaborating centres in Morocco and Ghana, and ACCESS-SMC partners. Since 2014, substantial progress has been made in SMC countries, but more still needs to be done. The following recommendations should be put into action:

I) Additional resources are needed for countries to adequately monitor safety during mass drug administration campaign (MDAs) such as SMC.
II) All public health programmes should include funds for PV and PV centers in their budgets.
III) Innovative approaches and new technologies to facilitate prompt and accurate reporting should be pursued.
IV) National PV reporting forms need to be revised in order to collect all critical data for analysis.
V) Appropriate quality control methods should be developed at country level to limit data duplication
VI) Appropriate training of national PV technical committees should be considered to improve capacity for causality assessment

More information in the detailed report

1. Introduction

Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine + amodiaquine (SP+AQ) medicines was shown in clinical trials to have the potential to reduce malaria morbidity in children 3-59 months of age by 75 percent in areas with high seasonal transmission, in the Sahel region of sub-Saharan Africa, even in areas where there is high coverage of using long lasting insecticide treated nets (LLINs)[2]. The UNITAID funded ACCESS-SMC[3] project (2014-2017), managed by Malaria Consortium, has been a key project in catalysing the scale-up of SMC interventions. ACCESS-SMC is implemented in Chad, Burkina Faso, Nigeria, Niger, Mali, Guinea and The Gambia. During the first SMC campaign season in 2015, the project administered over 12 million treatments of SMC to over 3.2 million children. In 2016, this number more than doubled to over 25 million treatments administered to over 6.4 million children during the second year of implementation.

Severe adverse reactions to SMC drugs are uncommon, but as with all public health programmes it is important that adequate safety monitoring is in place to ensure drugs remain safe and to mitigate any risks. It is not known why some children are at greater risk of adverse drug reactions, but genetic factors may be important. Variants in the CYP2C8 gene are associated with a reduced rate of metabolism of amodiaquine to its active antimalarial metabolite, N-desethylamodiaquine[4]; therefore, people with these gene variants that eliminate amodiaquine more slowly than normal, especially homozygotes, may be at increased risk of adverse events related to amodiaquine. A study of patients treated with amodiaquine-artesunate[5] found that heterozygotes and homozygotes for the CYP2C8*2 genotype were more likely to report abdominal pain compared to those with the wild-type, but there was no association with vomiting or other adverse events, and no evidence that treatment efficacy was impaired. The CYP2C8*3 variant that was found to be associated with more marked reduction in AQ metabolism is uncommon in Africa[6]. The frequency of the CYP2C8*2 allele has been estimated to be 0.115 in Burkina Faso[7] and 0.168 and 0.179 in Ghana[8,9,10], with homozygote frequencies of 1%-3%. Stevens-Johnson syndrome is strongly associated with the human leukocyte antigen (HLA) genes HLA-B*1502 and HLA-B*5801 in Chinese, and HLA-A*3101 but not HLA-B*1502 in Caucasians and Japanese[11,12,13,14]. A genome-wide association study on a sample of 424 European cases and 1,881 controls found six single nucleotide polymorphisms (SNPs) located

[2] http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf?ua=1
[3] http://www.access-smc.org/
[4] Li Xue-Qing, Bjorkman A, Anderson TB, Ridderstrom M, and Masirembwa CM (2002) amodiaquine Clearance and Its Metabolism to NDesethylamodiaquine Is Mediated by CYP2C8: A New High Affinity and Turnover Enzyme-Specific Probe Substrate. The Journal of Pharmacology and Experimental Therapeutics 300:399–407.
[5] Parikh S, Ouedraogo J-B, Goldstein JA, Rosenthal PJ, Kroetz DL (2007) amodiaquine Metabolism is impaired by Common Polymorphisms in CYP2C8: Implications for Malaria Treatment in Africa. Clinical Pharmacology & Therapeutics 82:197-203
[6] Gil JP (2012) the Pharmacogenetics of the Antimalarial amodiaquine, in: Clinical Applications of Pharmacogenetics, Dr Despina Sanoudou (Ed.), InTech. Downloaded from: http://www.intechopen.com/books/clinical-applications-of-pharmacogenetics/the-pharmacogenetics-oftheantimalarial-amodiaquine
[7] Parikh S, Ouedraogo J-B, Goldstein JA, Rosenthal PJ, Kroetz DL (2007) amodiaquine Metabolism is impaired by Common Polymorphisms in CYP2C8: Implications for Malaria Treatment in Africa. Clinical Pharmacology & Therapeutics 82:197-203
[8] Röwer S, Bienzle U, Weise A, Lambertz U, Forst T, Otchwemah RN, Pfützner A, Mockenhaupt FP (2005) High prevalence of the cytochrome P450 2C8*2 mutation in Northern Ghana. Trop Med Int Health. 10(12):1271-1273.
[9] Adjei GO, Kristensen K, Goka BQ, Hoegberg LC, Alifrangis M, Rodrigues OP, Kurtzhals JA (2008) Effect of concomitant artesunate administration and cytochromeP4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria. Antimicrob Agents Chemother. 52(12):4400-4406.
[10] Kudzi W, Dodoo AN, Mills JJ (2009) Characterisation of CYP2C8; CYP2C9 and CYP2C19 polymorphisms in a Ghanaian population. BMC Med Genet. 10:124.
[11] Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC et al.(2004) Medical genetics: a marker for Stevens Johnson syndrome. Nature 2004; 428:86.
[12] Chung WH and Hung SI (2010) Genetic Markers and Danger Signals in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Allergology International. 2010; 59:325-332
[13] Génin et al. (2011) Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in EuropeOrphanet Journal of Rare Diseases 2011, 6:52
[14] Shi Y W, Min FL, Qin B, Zou X, Liu XR, Gao MM, Wang Q, Zhou JQ, Liao WP (2012) Association between HLA and Stevens–Johnson Syndrome Induced by Carbamazepine in Southern Han Chinese: Genetic Markers besides B*1502? Basic & Clinical Pharmacology & Toxicology, 2012, 111, 58–64.

in the HLA region were risk factors with odds ratios in the range 1.53-1.74[15]. To better understand geographical variation in the risk of adverse reactions to SMC drugs, consent for blood sampling in the surveys of molecular markers of *P. falciparum* resistance was designed to include permission for human genetic testing to determine the frequency of the markers associated with reactions to AQ and SP.

As with all public health programmes, it was important that effective monitoring and evaluation was put in place for ACCESS-SMC to ensure that the intervention was delivered effectively, reaching the children that need it, and that it remained safe and effective, and to measure the public health impact. As SMC is a new strategy for malaria control in West Africa, it was particularly important to monitor delivery carefully to be able to optimise distribution, it was also necessary to develop monitoring tools that could be used by national programmes as part of their routine monitoring in the future.

The incidence of severe adverse events to SMC drugs had been reported to be very low, but when SMC was implemented on a very large scale these are expected to occur and, hence it is important these are recognised and properly managed and documented.

Safety monitoring was part of a wider evaluation of the ACCESS-SMC project, which had the objectives to:

1. Measure the efficacy of SMC treatments in each year of the project
2. Monitor the frequency of molecular markers of resistance to SMC drugs in the general population and in children under 5 years, in order to detect any important changes before and after two years of SMC
3. Measure the coverage of SMC treatments at the end of each year
4. Measure the impact of SMC on the incidence of outpatient malaria cases, malaria inpatients, and child deaths
5. Monitor the safety of SMC through targeted spontaneous reporting and event cohort monitoring, to measure the incidence of adverse drug reactions and their association with SMC

These studies and monitoring and evaluation activities were planned to ensure that the findings would help national control programmes to manage SMC programmes effectively, provide tools that could be used by national programmes in future, and contribute to the evidence needed by policy makers to inform planning of SMC and other malaria interventions. This summary report presents an update on objective 5 during the 2015 and 2016 SMC campaign seasons. This report was jointly prepared by Malaria Consortium the London School for Hygiene and Tropical Medicine (LSHTM) in April 2017, based on project research and implementation data and reports.

2. Methodology

Within the ACCESS-SMC project partnership framework, the SMC evaluation was implemented as a collaborative study between the LSHTM, National Malaria Control Programmes in each of the seven countries, local research institutions, the National PV Centres, the ACCESS-SMC country and regional teams, the Universite Cheikh Anta Diop (UCAD) in Dakar, the WARN/CARN SMC Working Group, WHO-TDR, WHO and the WHO collaborating centre in Morocco. LSHTM and Malaria Consortium developed the protocol, and LSHTM led the scientific coordination in consultation with ACCESS-SMC project partners. UCAD and WHO-TDR contributed to project coordination, communication and data

[15] Génin et al. (2011) Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in EuropeOrphanet Journal of Rare Diseases 2011, 6:52

analysis. An independent advisory committee on safety monitoring was established to provide oversight and approval of the protocol. The ACCESS-SMC project Technical Committee, co-chaired by Malaria Consortium and LSHTM, held teleconferences or face-to-face meetings periodically to monitor progress and advise on the technical aspects of the study.

2.1 Study sites

The study sites were the ACCESS-SMC project implementation districts or local government authorities (LGAs) in Burkina Faso, Chad, Guinea, Mali, Niger, Nigeria and The Gambia.

2.2 Approaches to PV

Multiple approaches were used to detect adverse reactions to SMC drugs included:

i) Passive detection with a focus on the known side effects of SP and AQ was used (Targeted Spontaneous Reporting). The severe adverse effects monitored at health facilities included severe skin reactions (Stevens Jonson syndrome[16] and Lyle's syndrome[17]), liver injury, extra-pyramidal syndrome (neurological effects causing movement disorders), severe vomiting, and agranulocytosis (low white cell count).
ii) Active follow-up of all children after SMC at one month from previous treatment by community health workers at the time of each subsequent SMC cycle, who asked caregivers if the child had experienced any severe side effects after the previous cycle.
iii) The end-of-cycle rapid assessments conducted in 2016 were also used to detect any incidence of drug reactions. A copy of the pertinent PV sections of the data collection tools for these assessments is annexed to this report.
iv) In Nigeria, there was a follow-up of a cohort of 10,000 children one week after each SMC cycle to ask about side effects, and to assess the frequency of mild and moderate side effects that may not be reported to the health facility.
v) In Mali, mobile phone short text messages (SMS) reminders about PV reporting were circulated to health staff during monthly campaigns.
vi) In each country, research groups involved in evaluation of ACCESS-SMC provided technical support to the PV centre.

2.3 Training for strengthening of safety monitoring system

An initial consultation with PV experts and representatives from SMC countries, at the WHO Geneva, was organised by WHO/TDR and LSHTM to plan the PV strategy for SMC. This led to organisation of training workshops for national coordinators and PV focal persons from national malaria programmes, run in collaboration with the WHO collaborating centre for PV in Morocco, WHO/TDR, and WHO Safety and Vigilance, including all countries with SMC programmes. These workshops provided refresher training on the principles of PV and how to coordinate an effective PV system, familiarised participants with the known side effects of SMC drugs and the recommended approaches to safety monitoring of SMC drugs, and shared practical experiences of PV for SMC. Each country's plans for monitoring safety of SMC were reviewed and country teams assisted to prepare a detailed action plan for coordination of PV for SMC. Training materials and job aids for health facility workers, were developed. Subsequent workshops trained PV staff to enter reports in Vigiflow for inclusion in the international drug monitoring database, Vigibase.

ACCESS-SMC project safety monitoring process included activities meant to strengthen national PV monitoring capacity in all seven countries in order to ensure that any severe adverse drug reactions are properly investigated. Strengthening initiatives included training programmes to raise awareness

[16] Stevens-Johnson syndrome is an immune-complex–mediated hypersensitivity complex that typically involves the skin and the mucous membranes. Although several classification schemes have been reported, the simplest classification breaks the disease down as follows [1], *Source; http://emedicine.medscape.com/article/1197450-overview*

[17] Toxic epidermal necrolysis is a rare condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below. A reaction to a medication is the primary cause.

on the importance of safety monitoring, explain the use of key tools and systems, and ensure good coordination so that reporting forms are available and are collected each month.

PV staff were involved in the cascade training on SMC delivery organised each year for health facility staff and community health workers, to ensure key messages about PV were covered in this training. A job-aid for health facility staff to help them recognise the known severe adverse reactions to SMC drugs was developed and distributed to all health facilities, highlighting the known severe reactions to SMC drugs, severe skin reactions, neurological side effects, hepatitis, severe vomitting, and agranulocytosis. PV reporting forms were printed and distributed.

Workshops for strengthening PV country expertise were conducted in Geneva (October 2014) and Rabat (May 2015 and February 2016) and Ouagadougou (Sept 2016). Workshop participants included national PV coordinators, PV focal people from national malaria control programmes, and members of the ACCESS-SMC project management team in country and regional level, in order to familiarise trainees and project staff with the known side effects of SMC drugs and to assist countries to develop plans for PV for SMC.

A training manual and field guide on SMC developed as implementation standard operating procedures for ACCESS-SMC integrated modules on PV for CHWs, health facility workers (HFW) and district medical officers. Such trainings had reached over 50,000 between CHWs and health workers by 2016, and included skills such as how to recognize SMC drug adverse reactions, clinical care of affected patients, and how to investigate and document the event. The training emphasised that all medicines, including traditional medicines taken in the two weeks prior to the adverse event, were to be documented including the name of the medicine, dosage, and timing of intake, and any other predisposing factors such as concurrent illness. Annexed to this summary is the section in the standard ACCESS-SMC job aid on adverse reactions.

2.4 Data management

Safety monitoring was integrated into the SMC routine monitoring systems and tools, from the tally sheets, to the registers and referral forms, which were used by the CHWs distributing the drugs and administering the first treatment dose to the beneficiaries through directly-observed treatment. The referral forms tracked patient names, date, age, gender, and the name of the health facility, and described reason for referral. Additionally, the national PV reporting forms were replicated and made available at all health facilities in SMC areas before the start of SMC and additional forms were distributed with the SMC drugs. Linked to the training, each facility involved in SMC delivery had to submit a report on SMC delivery each month, including a checklist for reporting adverse drug reactions that were seen. All completed PV reporting forms were then forwarded after each monthly cycle to the regulatory authority and entered into the relevant database.

A national level PV review panel was constituted in each country with the role of assessing each event for severity and relatedness to SMC drugs. The PV centres were supported to submit reports to the WHO international monitoring centre in Uppsala (Uppsala Monitoring Centre (UMC), a WHO collaborating centre on safety monitoring (https://www.who-umc.org/#) and if necessary, to join the WHO monitoring system. All national PV coordinators and the PV focal persons from each National Malaria Control Programme were oriented and trained to help them to establish effective safety monitoring for SMC and to ensure any confirmed severe adverse events were reported to the UMC through the Vigiflow system, to be included in the WHO safety monitoring database (Vigibase).

2.5 Ethical considerations

ACCESS-SMC implementation standing operating procedures required that any suspected case of Stevens Johnson Syndrome was to be referred immediately to the nearest hospital. All severe events

had to be reported immediately to the relevant district medical officers. All serious adverse events had to be reported within 15 days to the regulatory authority. Moreover, CHWs were trained to ask if the child had any severe illness since the previous SMC treatment (that required a visit to a health facility), and this was marked on the tally sheet; children with history of adverse effects were excluded from receiving SMC, and were referred for follow-up to the health centres. Regional hospital laboratories capacity was assessed with regards to their ability to perform assays that may be required in the investigation of adverse drug reactions, including liver function tests and whole blood counts. However, the strengthening of the laboratories and of the management of any severe adverse events was not supported by the ACCESS-SMC (with a few ad-hoc cases), and it was agreed that this was the role of the national health systems.

3. Results: progress update

The aim of the PV component of ACCESS-SMC was to support countries to strengthen spontaneous reporting, with an emphasis on the known severe side effects of SMC drugs. At project baseline, the PV systems in the seven countries were assessed as very weak, having reported very few PV reports of any kind in the past. Chad and The Gambia had never submitted PV reports, and Chad was not a member of the WHO safety monitoring system. Through the activities of ACCESS-SMC, all countries are now reporting events, with most countries reporting through the UMC VigiBase, the international drug safety database. Chad has become an associate member of the WHO system, so that now all SMC countries are members or associate members of WHO safety monitoring network.

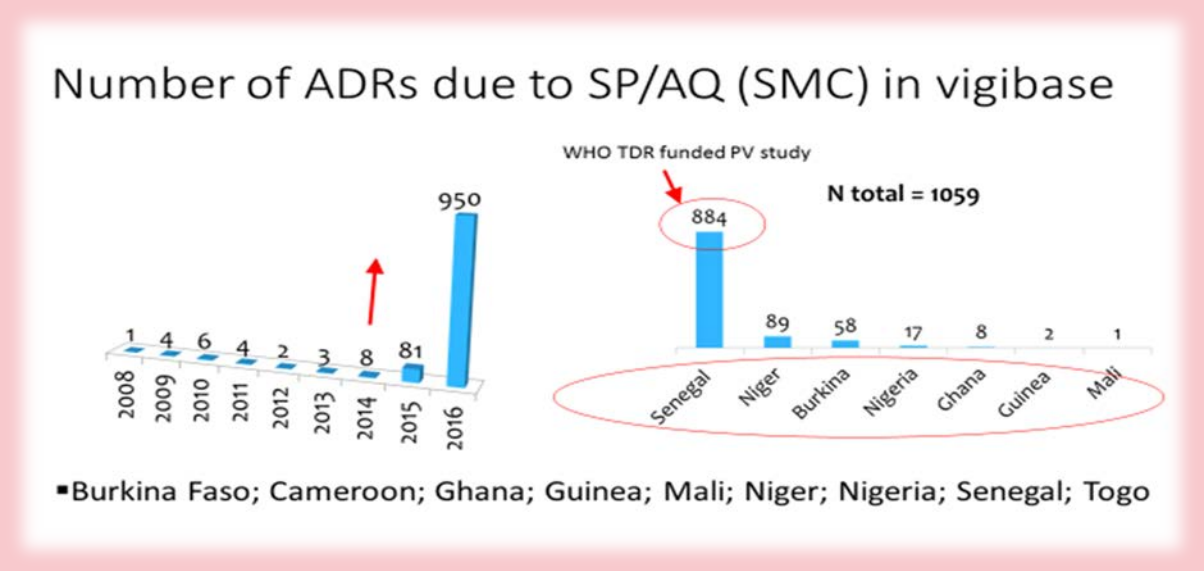
The project has also been able to catalyse support for PV for SMC from other agencies. WHO-TDR, supported training workshops in 2014, 2015 and 2016, WHO Safety and Vigilance, developed training materials for PV for SMC and organised a workshop on PV for SMC in Burkina Faso in 2016 for PV coordinators and a further training which will take place in July 2017 in Rabat. An international SMC safety committee has been established, under the auspices of WHO Safety and Vigilance, in collaboration with LSHTM, WHO-TDR, ACCESS-SMC partners and the WHO collaborating centres for PV in Morocco and Ghana. This committee reviews safety of SMC annually and reports to the WHO Advisory Committee on Safety of Medicines and Medicinal Products.

Table 1: Severe adverse events reported to date[18] from 12 SMC implementing countries in West Africa

Countries	Serious Adverse Events reported so far	Treatment outcome
Burkina Faso	Three (1 oedema, 1 dyspnea and 1 drowsiness)	Recovered
Chad	One (oedema)	Recovered
Cameroon	Zero	
Gambia	One (extrapyramidal syndrome), Two cases of jaundice	Recovered
Ghana	Zero	
Guinea Bissau	Zero	
Guinea Conakry	Zero	
Mali	One (oedema)	Recovered
Niger	Twenty one (with one extrapyramidal syndrome)	Recovered
Nigeria	Six	Recovered
Senegal*	Seven (2 Stevens Johnson Syndrome, 1 Lyell Syndrome, 1 extrapyramidal syndrome, 3 allergic shock)	Recovered
Togo	0	
Based on approximately 95 million SMC treatment administered		

[18] 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*

Table 2: Number of ADRs due to SP+AQ in UMC/WHO VIGIBASE[19]



In considering the PV study in Senegal supported by WHO-TDR, it's interesting to note both the catalytic role of ACCESS-SMC (WHO-TDR funding specific PV work for SMC) and the positive results from the study, in that it demonstrated the value of sentinel sites where PV can be more closely supervised, the feasibility of reporting using simple smart-phone apps, and of using community health workers for active follow-up of cohorts of children. Reassuringly, while enhanced surveillance produced a large number of reports (all of which are entered in Vigibase), these were mild in intensity and the enhanced PV did not reveal any hidden burden of more severe cases.

Interestingly, some personal choices of beneficiaries may be at play. The 10,000 children cohort in Nigeria produced only five PV reports, and it seems to be linked to some reluctance to report by beneficiaries. The ACCESS-SMC team joined the PV team on door to door visits during the cohort follow-up, and the interpretation seems to be that families perceive the drugs to working, they may be reluctant to report adverse effects, in case this might detract from the programme. On the other hand, this may also point to a low frequency of severe adverse events, since such events would be more difficult to go unreported. The five events that were detected were not serious.

Table 3 details examples of adverse event reports from Burkina Faso. In investigation of these adverse events, SMC administration errors were noted. These reports highlight the difficulty of attributing symptoms to drug intake. There is no confirmed link between medication errors and the symptoms observed.

Table 3: Case study PV in Burkina Faso, 2017

Case 1: Adverse event occurred on 1 August 2015 in the Zorgho health district in a 32-month-old child (born 14/10/2012), weighing 12 kg. Clinical signs included vomiting, generalized pruritus, puffiness of the face and oedema of the eyelids, which occurred 3 hours after the administration of SP+AQ (lot No: LP150417, expires on April 22, 2018). The parents went immediately to the health center for better care. The child recovered without sequelae.
Case 2: An adverse event that occurred on July 25, 2016 in the health district of Séguénéga, following a medication administration error (two amodiaquine tablets on day 1, instead of 1 tablet of SP+AQ to an infant of 3 months). Preliminary investigations found that the child took both AQ tablets at 8 am and consulted with the health center at 6 pm for coughing, refusal of breastfeeding and breathing difficulties. The child was cared for at the health center and then referred to the

[19] 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*

district pediatrician the same day. The child was hospitalized and then discharged on 28th July with a favorable clinical picture.

Case 3: Another administration error was identified in the health district of Djibo (double dosage of two amodiaquine tablets administered by the mother on the second day of, instead of issuing just one tablet) to a 4-year-old child. Clinical signs observed were: somnolence, redness of conjunctival mucosa. The care offered was observation at the hospital. The child healed without sequelae.

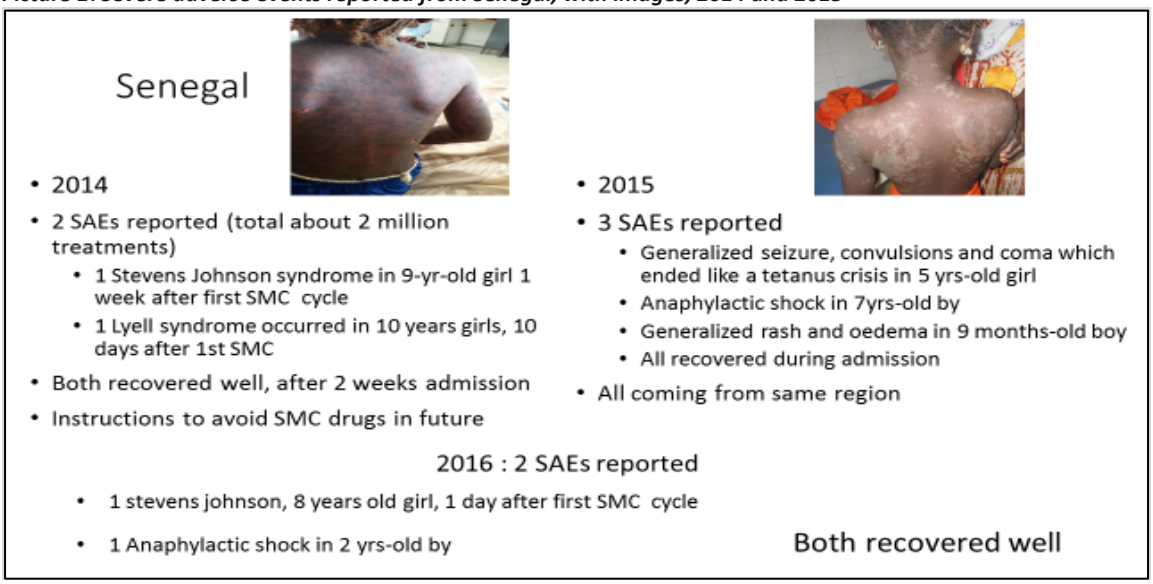
The seven ACCESS-SMC project countries have had no cases of severe skin reactions in children under 5 years of age to date. Though three cases of necrotic skin reactions were reported in Senegal, all are in older children. There have been two cases of extrapyramidal syndrome (in Niger and Gambia), two cases of jaundice (The Gambia), three cases of oedema (Burkina Faso, Chad and Mali). As of April 2017, there are a total of 1,333 reports in VigiBase in children under 5 years of age related to SMC for all SMC-eligible countries (not just ACCESS-SMC), from the years 2015-2016. Vomiting, diarrhoea and abdominal pain were the most common symptoms, see table 1 and 2.

From the end-of-cycle rapid assessment, there seems to be similar trends on reported severe adverse events. We present the example of Burkina Faso; further analysis will be done to compare all seven country findings.

Table 4: Safety monitoring as reported by the end-of-cycle rapid assessment for Burkina Faso

Symptom	Number reporting	Mild	Moderate	Severe
Sore throat	0	0	1	
Vomiting	4			
Diarrhea	4			
Yellow eyes	1	0.4		
Rash	0	0		
Oedema	1	0.4	1	
Loss of appetite	0	0		
Fever	10	3	2	5
Drowsiness	0	0		
Others	0	0		
Total reported	16			
Sample size	**264**			

***Picture 1*: Severe adverse events reported from Senegal, with images, 2014 and 2015**[20]



[20] *Strengthening system for safety monitoring for SMC in the Sahel; presentation by* Rachida Soulaymani Bencheikh – Paul Milligan – Corinne Merle; Houda Sefiani on behalf of SMC working group; April 2017, Geneva

However, some problems were detected when analysing PV data, such as the duplication of cases and the limitations around the quality of completion of national PV reporting forms, yielding incomplete data. For example, the severity of cases , the time of onset of symptoms, and intake of other medications, required for causality assessment, were not consistently reported. For example, vomiting under 30minutes after medication may be related to the taste of drugs rather than drug-induced central vomitting). There is a need to improve reporting forms so that all critical data for analysis are collected; to develop methods at country level to detect duplication; and to train the PV technical committees in causality assessment.

4. Discussion and conclusion

4.1. Lessons learnt to date on SMC drug safety monitoring

Structures: Training and capacity building: workshops, in country training, individual and long term training in Rabat were very helpful and set the pace for the strengthening of PV systems in Africa. The need for systems strengthening also helped with the generating other funds from: GF (Niger), Ministry of health (Burkina). There has been investment in improved tools for collecting data: reporting form, mobile phones etc. as part of ACCESS- SMC. Some outcomes of the systems strengthening were that countries like Tchad have become associate members of the WHO programme; Niger and Burkina started reporting to VigiBase through coaching during an internship in Rabat. So capacity building enabled the strengthening of PV systems.

There were limitations related to reporting, it was noted that some districts consistently reported more SAE, than others, this could be the human factor and there was also delayed reporting in some instances. The quality of reporting was often poor, reporting forms also need improvement to include description of the event in detail including time of onset. In most countries laboratories lacked capacity for full laboratory investigations. Additionally, the analysis of data was limited in the defining of the ADR (semiology, sign, symptom, disease) and in eliminating other etiologies (dysentery, malaria for example); the grading of severity was not always clear; and causality assessment was often problematic. National PV Advisory Committees have been establishedin most countries but require additional support to function effectively. In some countries there is a need to strengthen the coordination between the National PV center and the National Malaria Programme. Nonetheless, the strengthening of PV has improved reporting and allowed SMC programmes to demonstrate that SMC drugs are safe and well tolerated.

4.2 Conclusion and recommendations

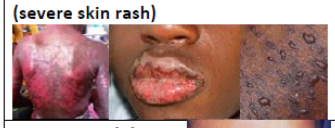
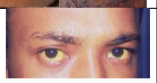
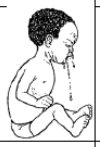
SMC drugs are safe and well tolerated, and the strengthening of PV that has been done for SMC, primarily through ACCESS-SMC, is seen as a successful model with lessons to be learned for other programmes. Successful strengthening of PV systems in Africa requires a collaborative approach and effective partnership, as the ACCESS-SMC model (WHO PV control programme and collaborative PV centers Morocco and Ghana, Malaria Consortium, CRS, UCAD, LSHTM and WHO/TDR). Since 2014 progress were done in SMC countries but more still needs to be done, recommendations:

I) Additional resources are needed for countries to adequately monitor safety during Mass Drug Administration campaigns such as SMC.
II) All public health programme budgets should include funds for PV and fund to support the work of the national PV centre.
III) Innovative approaches should be developed to facilitate effective reporting of events, such as applications to report via smartphones.
IV) Revise the National PV reporting forms to permit collection of key information necessary for analysis
V) Develop quality control methods at country level to limit data duplication
VI) Support national safety committees to improve capacity for causality assessment

5. Appendix

5.1 SMC guide on SAE for CHWs

Safety monitoring for SMC: Guide to the rare severe side-effects of SMC drugs

Possible SAEs from SP+AQ	Description of Signs and Symptoms	Actions for Health Facility Worker
Stevens-Johnson syndrome (severe skin rash) 	▪ Painful red or purplish rash that spreads and blisters. ▪ Top layer of the affected skin dies and sheds. ▪ May begin with flu-like symptoms.	▪ **Notify and hospitalize immediately (medical emergency)** ▪ Write **"Allergy Not Eligible for SMC"** on SMC Register and Child Record Card. ▪ **Avoid SP and all sulfa-containing drugs in future.**
Hepatotoxicity (jaundice) 	▪ Yellowing of the sclera (white of the eyes). ▪ Dark coloured urine. ▪ Loss of appetite, nausea, vomiting or abdominal pain. ▪ Extreme fatigue or weakness.	▪ **Notify and refer to hospital.** ▪ Confirm with lab tests for liver function if possible. ▪ Write **"Allergy Not Eligible for SMC"** on SMC Register and Child Record Card. ▪ **Avoid AQ in future.**
Extra-pyramidal syndrome (neurological disorder)	▪ Involuntary muscle movements in the face and neck. i.e. lip smacking, tongue movements, blinking, and head or finger spasms. ▪ Restlessness and difficulty moving the arms and legs.	▪ **Notify and refer to hospital.** ▪ Write **"Allergy Not Eligible for SMC"** on SMC Register and Child Record Card. ▪ **Avoid AQ in future.**
Repeated vomiting 	▪ Repeated vomiting which begins hours after taking drug. ▪ In severe cases can persist for several days with vomiting several times per day.	▪ Eligible for SMC in the next cycle. ▪ Advise caregiver to bring the child to the health facility if symptoms recur.
Agranulocytosis (Low white cell count (neutrophils) <750/mm^3)	▪ Sudden fever and chills. ▪ Prone to infections. ▪ Severe sore throat (pharyngitis) within a week of getting SP+AQ	▪ **Notify and refer to hospital.** ▪ Diagnosis requires complete blood count. ▪ Treat infections. ▪ Write **"Allergy Not Eligible for SMC"** on SMC Register and Child Record Card. ▪ **Avoid AQ in future.**

5.2: Extract of PV questions used in SMC data collection tools- end of cycle and coverage survey

27) Has the child been unwell since the first day of this SMC cycle? |__|Y/N

28) If the response to Qn. 27 is NO, please stop here. If the response is yes, indicate the symptoms that the parent or caregiver talks about

PS: If the child is unwell, refer them to the nearest health facility

Symptom	Y/N *No. Times/Day**	Y/N *No. Times/Day**
Vomiting	|__| |__|	|__| |__|
Diarrhoea	|__| |__|	|__| |__|
Symptom	Y/N *Severity#*	Y/N *Severity#*
Sore throat	|__| |__|	|__| |__|
Yellow eyes	|__| |__|	|__| |__|
Rash	|__| |__|	|__| |__|
Abdominal Pain	|__| |__|	|__| |__|
Loss of appetite	|__| |__|	|__| |__|
Fever	|__| |__|	|__| |__|
Itching	|__| |__|	|__| |__|
Drowsiness	|__| |__|	|__| |__|
Other	_____	_____

*No of times per day on the worst day

#Severity:

1=mild, does not prevent play

2=moderate, prevents normal play

3=severe, child referred

Ask the respondent whether they have additional comments or questions, and at the *end of the interview, say,* ***'Thank you'***

5.3. Referenced documents

a) Strengthening system for safety monitoring for SMC in the Sahel; presentation by Rachida Soulaymani Bencheikh – Paul Milligan – Corinne Merle; Houda Sefiani on behalf of SMC working group; April 2017, Geneva
b) Evaluation of SMC coverage, efficacy, safety, drug resistance, and impact: Summary of progress and preliminary results, LSHTM, April 2017.
c) 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
d) Field Guide for Training & Service Delivery of Seasonal Malaria Chemoprevention in Nigeria, Malaria Consortium, 2016
e) Progress report SMC- submitted to UNITAID, September 2016
f) 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