Seasonal Malaria Chemoprevention (SMC) Deep Dive synthesis report

Introduction

The World Health Organization (WHO) defines Seasonal Malaria Chemoprevention (SMC) as intermittent administration of full treatment course of antimalarial medicine (a combination of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ)) during peak malaria transmission seasons to asymptomatic children belonging to age groups high at risk of malaria, regardless of whether the child is infected with the malaria parasite. It establishes antimalarial drug concentrations in the blood that clear existing infections and prevent new ones during the period of greatest malaria risk (ref).

WHO recommendations regarding the seasonal malaria chemoprevention strategy is explained in the video: Malaria: New WHO recommendations for seasonal malaria chemoprevention in young children (SMC)

After the first WHO recommendation on SMC in 2012, the intervention was implemented in 13 countries (Benin, Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Togo). Recently in 2021, Mozambique, Uganda and South Sudan have also adopted and implemented SMC campaigns followed by Mauritania in 2022 and Ivory Coast in 2023 (ref, ref). In 2022, updates to the WHO recommendation on SMC made the intervention less restrictive, paving the way for its broader use among young children at high risk of severe malaria in areas with both seasonal and year-round transmission. However, obstacles to the rapid scale-up of SMC persists. One of the major challenges identified is mobilizing the required resources in time, before the start of the next malaria transmission season (ref).

Relevance

The first SMC field guide produced by the WHO Global Malaria Programme (GMP), recommended SMC in areas with highly seasonal malaria transmission throughout the Sahel sub-region. It included a complete treatment course of SP plus AQ given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, up to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy) (ref). However, SMC has also been shown to reduce the incidence of clinical malaria in children over 5 years old. Studies suggested substantial reductions in malaria incidence and prevalence and moderate reductions in severe malaria and prevalence of any anemia among children < 5 years of age and children ≥ 5 years (ref). Also, children < 5 years old and children ≥ 5 years old showed similar effect sizes for the incidence of uncomplicated and severe malaria during the transmission season, as well as for malaria prevalence and prevalence of any anaemia at the end of the transmission season, indicating that the latter group may benefit from SMC just as much as the former (ref). Hence, the recent WHO guidelines for malaria offer flexibility in recognizing age-based risk among children at high risk of severe malaria (ref). Although the safety and effectiveness of a number of other drug combinations have been assessed, there is currently insufficient

data on the possible hazards of cumulative toxicity and the influence on drug resistance due to the lack of widespread implementation as suggested by the WHO guidelines (ref).

Pilot projects are ongoing for expansion of SMC beyond the Sahel to Eastern and Southern Africa. Also, the expansion of the strategy to other regions and the risk of emergence of drug resistance have opened up new avenues of exploration in the chemoprevention sphere against malaria. A study in Senegal suggested SMC substantially reduced the incidence of outpatient cases of malaria and of severe malaria in children, but found no difference in all-cause mortality in children under 10 years of age (ref). Studies comparing modalities of SMC delivery suggest a possible role community health workers could play in the strategy. A study in Mali reported that door-to-door delivery achieved significantly higher coverage than fixed-point delivery (ref). Studies found similar SMC coverage in children given directly observed treatment compared to non-directly observed treatment (ref).

The purpose of this Deep Dive is to map SMC projects across various countries, identify the research areas being explored and the key stakeholders involved, analyze the allocated funds, and provide an overview of the existing gaps and future priorities in SMC delivery and timelines of the emerging body of evidence on this strategy.

This Deep Dive was developed in collaboration with the Malaria Consortium.

Objectives

1. To map out the geographical scale and scope of ongoing SMC research.
2. To provide an overview and analysis of SMC related research.
3. To outline the investments in SMC research and the institutions involved in them.
4. To describe the research areas being explored by the projects.
5. To identify knowledge gaps.

Methodology

The collation and categorization of research projects on SMC are outlined below:

- Systematic project searches in the MESA Track Database of malaria projects were conducted in 2021 and revised in 2023. The projects in MESA Track were complemented by other projects identified by scanning diverse grant databases for projects and investments (Dimensions, NIH RePORTER, Europe PMC, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform, European & Developing Countries Clinical Trials Partnership, GrantNav, etc). The following search terms were used: SMC AND malaria, seasonal AND malaria, chemoprevention AND malaria, chemoprophylaxis AND malaria.
- For each project, the information sought was the Project title; Project objective(s); Abstract and rationale; Start and end date; Project site; Principal investigator (PI); Principal institution; Funding institution; Partner institution; and Funding amount.

Eligibility criteria

The criteria used were:

- Research projects related to SMC
- Research projects that began/active ≥ 2012
- Research projects in/translated to English

Information verification

Once a project was identified and included in the MESA Track database, the principal investigator was contacted via email. (S)He was given a link to the project information in the MESA Track database of malaria projects and asked for additional information, if indicated, and verification. Projects for which we did not get a response to our verification request were still included in the Deep Dive.

Categorization of projects

The projects that fulfilled the eligibility criteria for the Deep Dive were categorized into different research areas based on the research objectives the projects had in common.

Results

A total of 1,977 projects were identified from the keyword search. Out of which 1,937 projects were excluded as they did not fulfil the eligibility criteria or for duplication. 40 projects were added to MESA Track which already had 29 projects on SMC. This Deep Dive therefore has 69 projects in total to date. This is an active Deep Dive; as such, some details in this report may be subject to change as and when new information on projects or new investments are tracked.

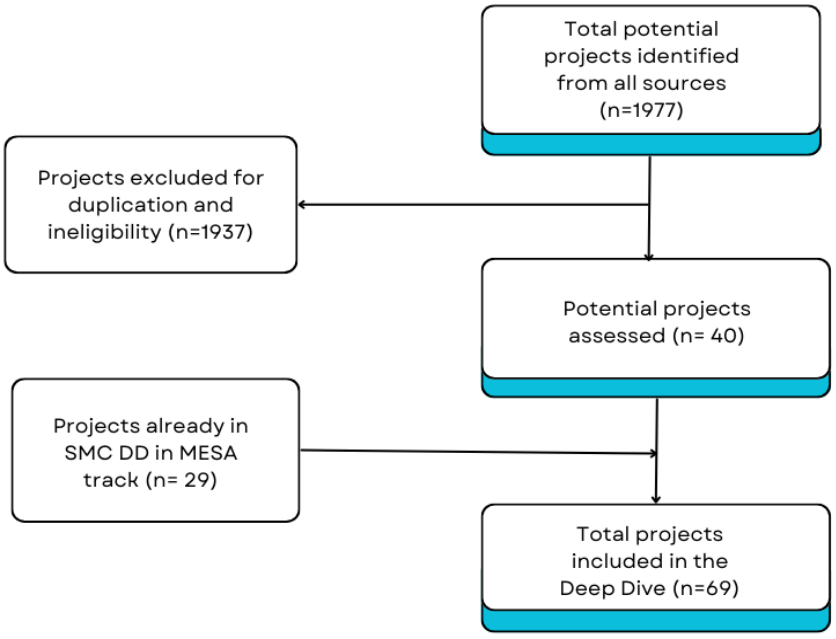

Figure I: Project search flowchart

Project Overview

The projects included in the Deep Dive are led by a host of institutions from different parts of the world. The chart below gives a snapshot of where the principal institutions are located. The majority of the institutions leading the projects are from the United Kingdom followed by Mali, Senegal, Burkina Faso and the USA. Other lead institutions are based in Switzerland, Ghana, Cameroon, The Gambia, Uganda, China and Benin.

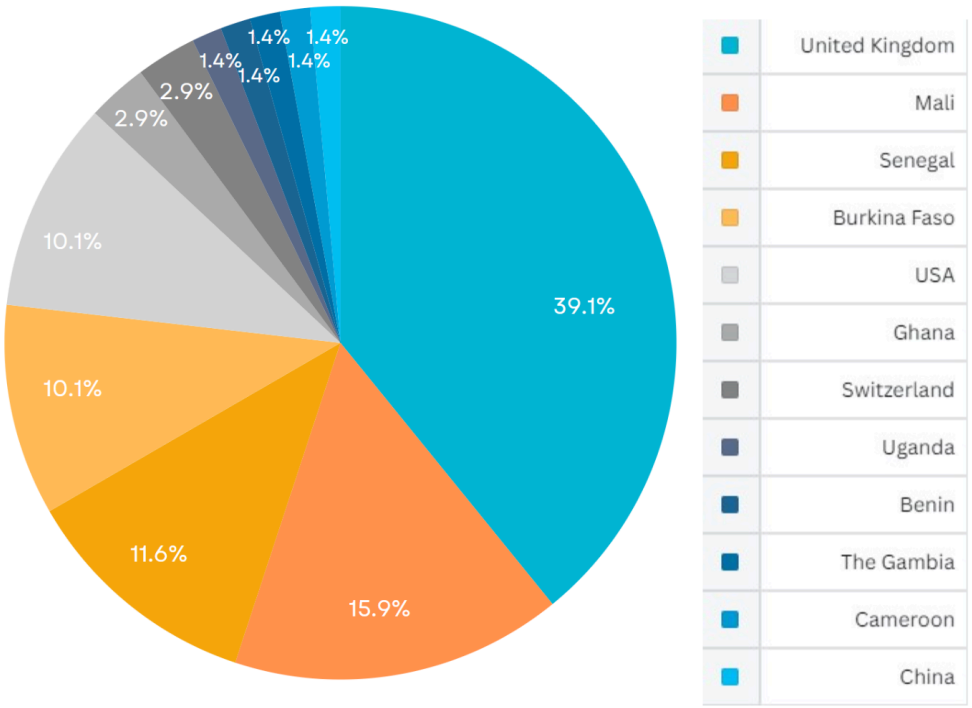

Figure II: Proportion: Lead principal institutions per country

The main institutions leading SMC research are illustrated with figure III below:

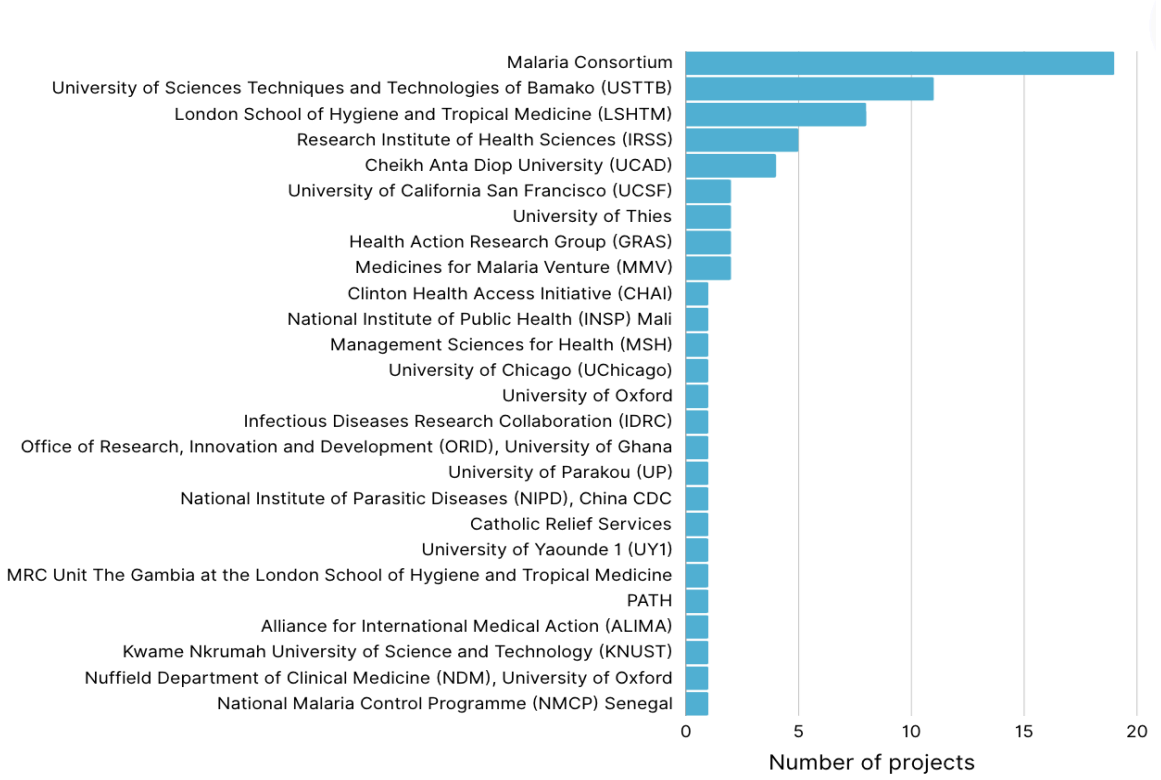

Figure III: Number of projects led by Principal Institutions

Categorising projects by their initiation date shows one project each starting in the year 2007, 2010 and 2011. These include evaluation study on the effectiveness of seasonal intermittent preventive treatment and feasibility study for SMC. A gradual increase in the number of projects in subsequent years followed by WHO recommendation of this strategy can be observed with the highest number of projects initiated in the year 2021. (Figure IV)

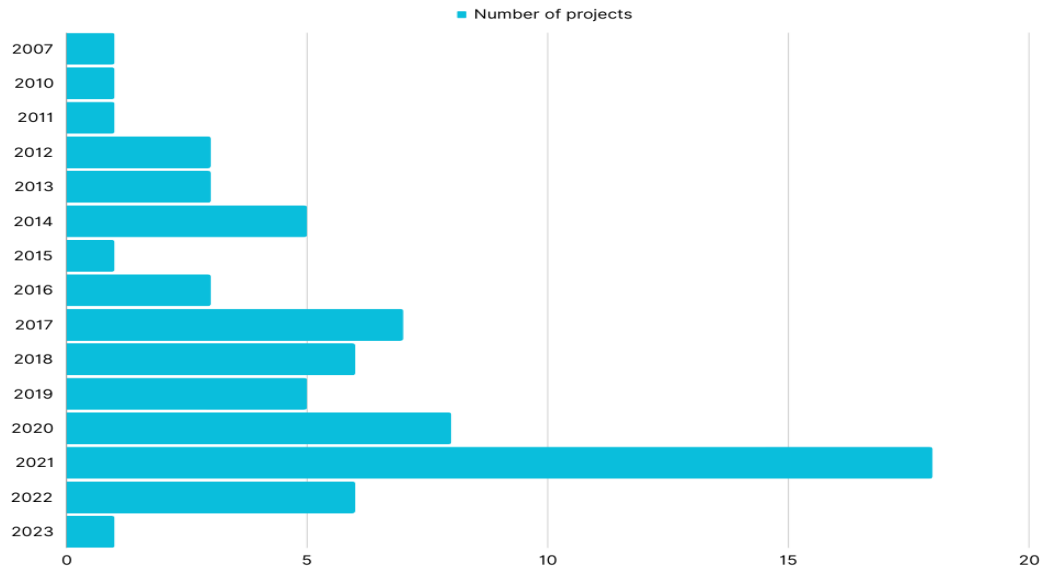

Figure IV: Number of projects by start date

Malaria Consortium and London School of Hygiene and Tropical Medicine in the UK are leading the majority of SMC projects. However, implementation of the projects are found to be spread across the continent of Africa, specifically West Africa. The map below shows the geographical distribution of the projects. Out of the total 69 projects included in the Deep Dive, there are 19 projects taking place in Mali followed by Burkina Faso with 15 projects and Nigeria with 10. Eight projects are in Senegal and 5 in the UK. Ghana and Mozambique follow with 4 projects each. Uganda, USA and Chad have 3 projects each followed by Switzerland, Benin and The Gambia with 2 projects each. The rest of the countries highlighted in the map are housing a single project each.

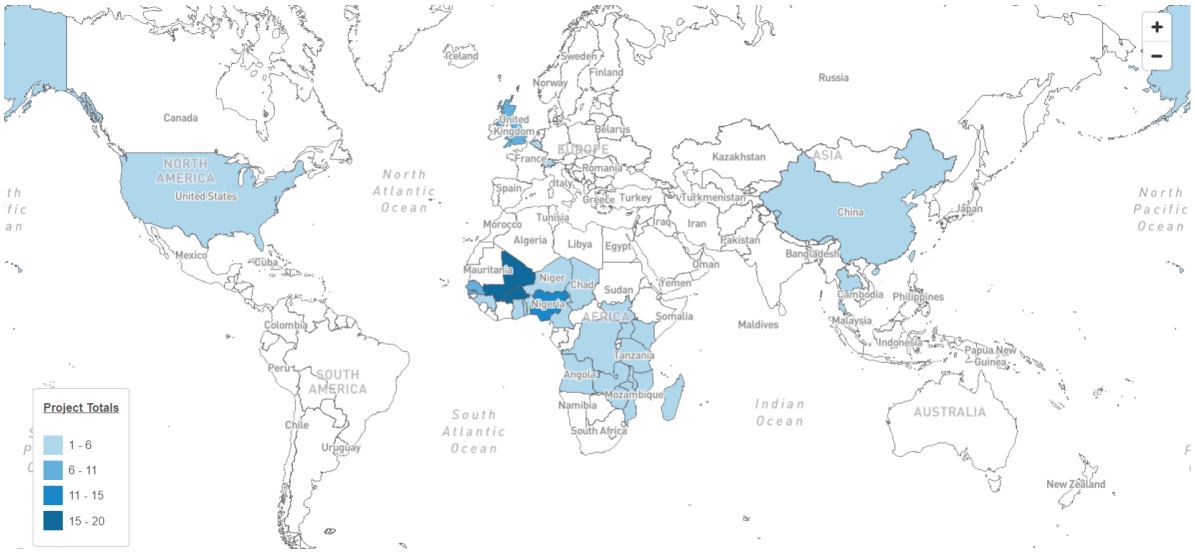

Figure V: Geographical project distribution

*Projects that state regions as operational sites instead of specific countries are not shown in the map.

Active projects

There are 12 active projects in the Deep Dive as of July 2024, with 3 projects ongoing in Mali, 2 in Nigeria and 1 project ongoing in the rest of the locations as shown in figure VI.

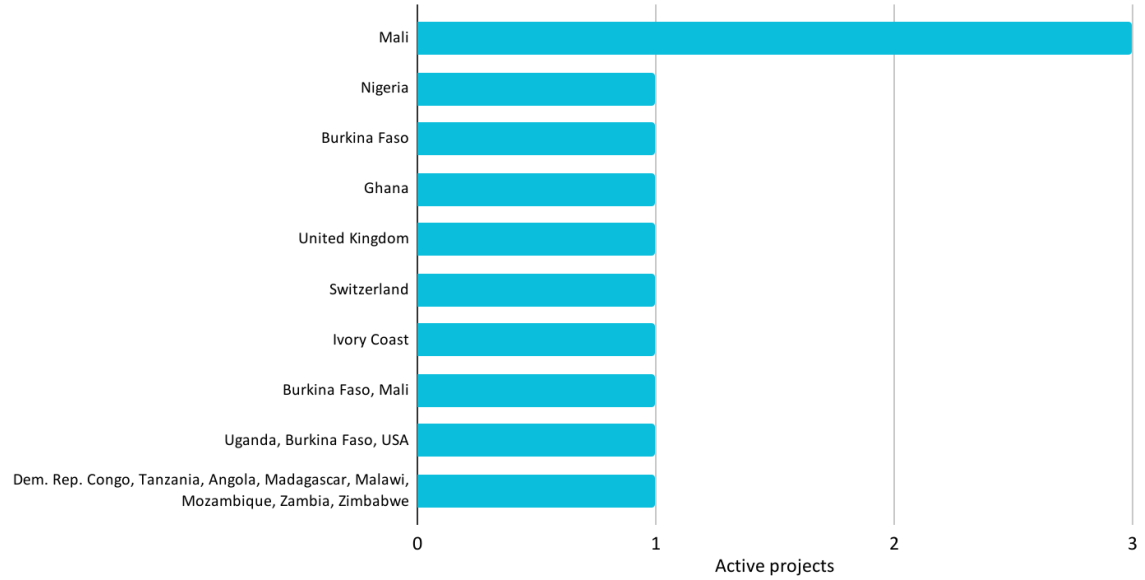

Figure VI: Active projects by location

The active projects explore the rebound effects of SMC, the age-specific impact of seasonal malaria chemoprevention on malaria incidence, antibody responses; parasite reservoirs, referral and management of severe disease. Some notable ongoing project activities include:

- Rapid assessments for the deployment of SMC in new geographies of east and southern Africa.
- Exploration of association between drug levels, malaria transmission, and antimalarial resistance in the setting of SMC.
- Assessment of opportunity costs of SMC in Sub-Saharan Africa.
- Optimisation of SMC and seasonal vaccination in childhood to address the resurgent malaria burden in Africa.

Funding

The projects included in the Deep Dive amount to a total investment of $357.79 million. Out of the total funding amount, active projects garner $254 million. The highest proportion of contribution comes from Bill & Melinda Gates Foundation (BMGF) which accounts for 69.70% of the total funding, followed by the Medical Research Council (MRC) which garners 3.1%, and the National Institute of Allergy and Infectious Diseases (NIAID) which captures 1.7%. Besides, important contributions by philanthropic donations for SMC research can be observed in the funding landscape. All the institutions and the amount contributed are given in table I. Fifteen projects (21.7%) in the Deep Dive have not stated the funding amount and two projects lack the information about the funding institution itself. These projects are being followed up by MESA with the Principal Investigator and the information will be updated as soon as it is acquired.

Table I: Funding institution/s and contribution in USD ($)

Funding Institutions	Amount in USD ($)	Percentage (%)
Bill & Melinda Gates Foundation (BMGF)	249,343,818	69.70
UNITAID	71,573,020	20.00
Medical Research Council (MRC)	11,012,470	3.08
National Institute of Allergy and Infectious Diseases (NIAID)	5,926,880	1.66
Good Ventures, Give Well, Effective Altruism, The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Department for International Development (DFID)	5,040,880	1.41
European & Developing Countries Clinical Trials Partnership (EDCTP)	4,272,770	1.19
Korea International Cooperation Agency (KOICA)	3,571,450	1.00
Philanthropic donations by GiveWell	1,766,000	0.49
Wellcome Trust	1,897,477	0.53
Expertise France, French Initiative 5%	950,225	0.27
Department for International Development (DFID)	756,080	0.21
U.S. President's Malaria Initiative (PMI)	629,000	0.18
Malaria Consortium	550,000	0.15
MAlaria Research CApacity Development in West & Central Africa (MARCAD)	385,977	0.11
Open Philanthropy	103,911	0.03
World Health Organization (WHO)	15,000	0.004
TOTAL	357,794,958	100

**Only the projects where funding amounts was stated are included in this table*

Geographical funding distribution

Out of the 69 projects included in the Deep Dive, there are 19 projects operating in Mali with a cumulative funding of $77.7 million. Burkina Faso follows with 15 projects and total funding of $79.6 million. Nigeria has 10 projects with $79.6 million funding while Senegal has 8 projects with a total funding of $7 million. The UK has 5 projects with $9.35 million funding. Ghana and Mozambique follow with 4 projects each with a total funding of $56.7 million and $3.18 million respectively. The United States is involved in 3 projects with an investment of $56.9 million while China has a project with $200,000 funding. The full distribution is illustrated in the figure below:

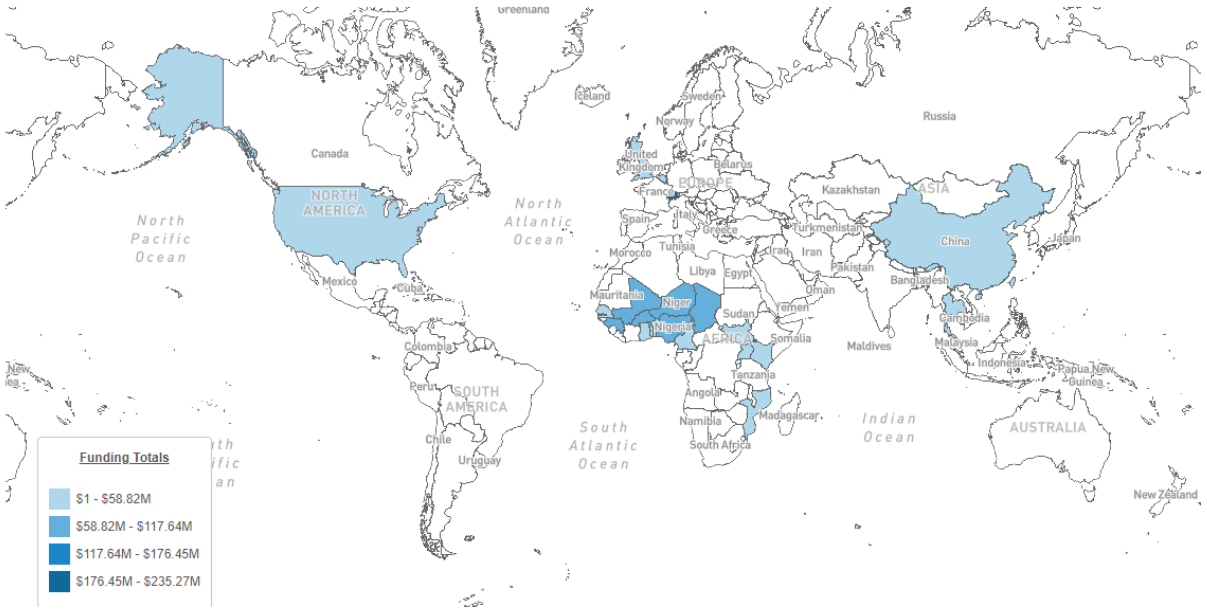

Figure VII: Geographical funding distribution

Research Areas in focus

The projects included in the Deep Dive were classified into 7 different research categories. The research areas in focus encapsulate the general theme of the projects on what is being done. Some projects overlap between different research areas while some are encapsulated by a single category. The research areas are liable to expand as more projects are added to the Deep Dive.

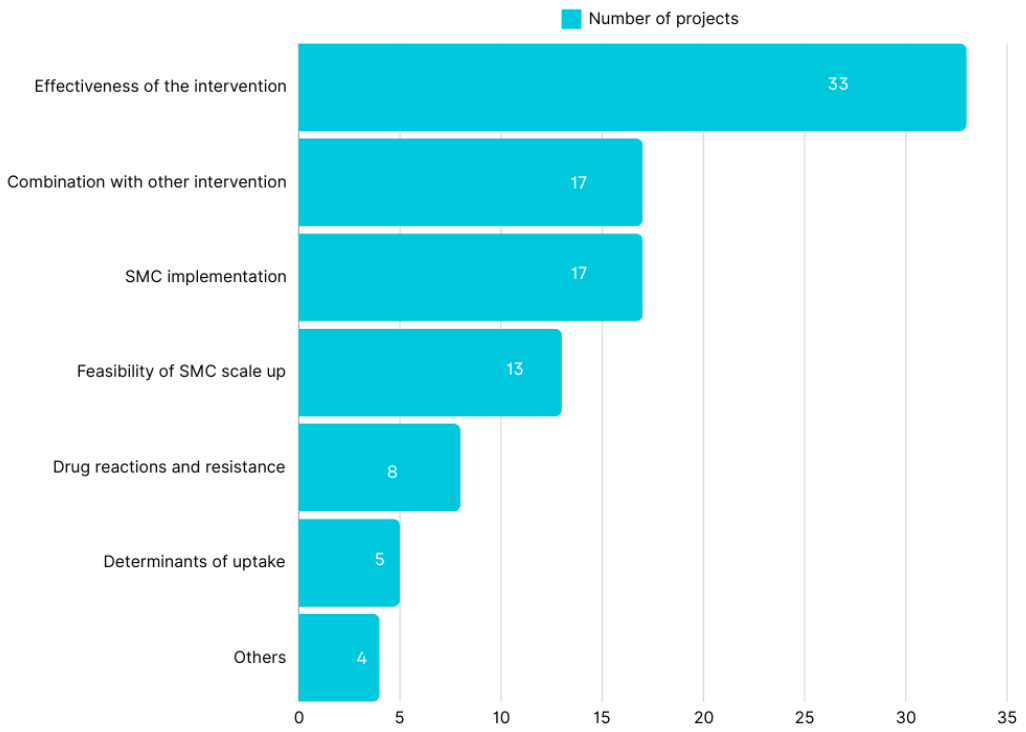

Figure VIII: Projects per research area

I. Effectiveness of the intervention

Effectiveness of the intervention includes projects that assess the effectiveness, efficacy and impact of SMC. Projects investigating but not limited to the rebound effects, age-specific impact on malaria incidence, impact on the build-up of protective immunity, etc. are included in this category. This research area consists of thirty-three projects which is the highest number of projects included in the Deep Dive. Some of the projects are: A study exploring the effectiveness and chemoprevention efficacy of implementing SMC in Karamoja Region, Uganda via a hybrid effectiveness-implementation study design which intends to inform malaria policy in high-burden countries, specifically on the utility of SMC outside the Sahel, and contribute to progress in malaria control (ref), A MRC tropical epidemiology group project led by London School of Hygiene and Tropical Medicine (LSHTM) evaluating the effectiveness of SMC delivery through routine health services to determine the effectiveness of adding SMC to existing control strategies for malaria, A project assessing the effectiveness, feasibility and acceptability of SMC in Aweil South district in Northern Bahr el Gazal, South Sudan which concluded that SMC using SPAQ was highly effective in reducing malaria during the high transmission season in children aged 3-59 months (ref), etc.

II. Combination with other intervention

This research area encapsulates the SMC related projects which are either being implemented in conjunction with other interventions, as a part of a study with a wider scope or testing some new intervention modality combining multiple approaches to enhance the efficacy. Some of the examples include projects combining SMC and vaccination to address the resurgent malaria burden, incorporating helminth control and vitamin-A supplementation with SMC, etc. These include 17 projects currently in the Deep Dive. Example: A project assessing effects of including lipid-based nutritional supplements (LNS) together with SMC on SMC coverage, child nutrition and health in northern Nigeria which stated that the addition of bulky LNS had no impact on coverage attained through SMC campaigns and recommended including different products to existing campaigns to enhance the efficiency of improving child health, such as vaccines and essential medicines (ref). Similarly, a research brief from the project improving coverage of vitamin A supplementation through integration with seasonal malaria chemoprevention delivery which is included in this research category stated that the coverage of Vitamin A supplementation (VAS) surged from 1.1 % at baseline (without SMC integration) to 82.3 % at endline (with SMC integration) in the two study sites in northeast Nigeria while the cost of integrating VAS into the usual SMC cycle introduced a minimal additional unit cost of $0.24 per child (ref).

III. SMC implementation

This category deals with projects that focus on specific impacts of SMC implementation. This research area overlaps with the effectiveness of the intervention in several instances. Projects dealing with launching and executing SMC programs, evaluation of impact of SMC, supporting the SMC digitization campaign, supporting malaria endemic countries to optimise the delivery of SMC to local contexts, etc. It currently includes 17 projects in the Deep Dive. A case control study which was a part of the project "Evaluation of the impact of Seasonal Malaria Chemoprevention delivered by district health services in Southern Senegal" concluded in 2018 stated that SMC offered a protective effectiveness of 89% (OR= 0.12 (CI 95%=0.04-0.28)) hence, it is an effective strategy in the control of malaria in children. An article reporting on the formative phase of a three-phased intervention development study as a part of a project led by Malaria consortium which worked on optimising the role of lead

mothers during Seasonal Malaria Chemoprevention campaigns in Kano state, Nigeria stated that lead mothers (LM) have influence over caregivers to adopt healthy malaria prevention behaviours during SMC campaigns because of their strong community relationship but LMs lack adequate knowledge and skills to deliver targeted health messages highlighting the need for training and supporting materials (ref). A study measuring the impact of seasonal malaria chemoprevention as part of routine malaria control in Kita, Mali, highlighted the substantial reduction in malaria and anaemia by routine implementation of SMC, with reductions of similar magnitude to those seen in previous RCTs and recommended improving coverage to strengthen SMC coverage. U.S. President's Malaria Initiative (PMI) funded project leading to this output is included in this category. Also, this category houses a project supporting the digitization of the 2021 SMC campaign in Benin, one which enables malaria prevention packages to be optimised according to the local epidemiology to address the resurgent malaria burden in Africa which began in 2021 and is expected to operate until 2026.

IV. Feasibility of SMC scale up

This category consists of the projects that deal with the expansion of existing SMC projects nationally, regionally and to parts where SMC has not been implemented before. It includes 13 projects in the Deep Dive. A fairly recent study that commenced in March 2023 is conducting rapid assessments for the deployment of seasonal malaria chemoprevention in new geographies of East and Southern Africa. The assessment was scheduled to begin in the Democratic Republic of Congo, Malawi and Mozambique in early 2024. Some of the key questions this project seeks to answer are:

- How effective is SMC with SPAQ at preventing clinical malaria among children aged 3–59 months in these new locations?
- What is the chemoprevention efficacy of SMC with SPAQ at preventing malaria infections among children aged 3–59 months in these new locations?
- What is the prevalence of the molecular markers associated with SPAQ resistance in these new geographies?
- What model can best predict the suitability of SMC in these new geographies?
- How feasible and acceptable is SMC with SPAQ in these new geographies?

There are other projects that focused on expanding the existing SMC programmes to the districts or regions in the countries which initially lacked them.

V. Determinants of uptake

This category includes projects that assess the acceptability of certain cycles of SMC, addressing the barriers to SMC implementation to maximise the efficacy and reach the population in need in an effective manner. There are 5 projects in this research category. The UNITAID funded ACCESS- SMC project included in this category led to a cost-effectiveness and cost-saving analysis of SMC which concluded that it indeed is a cost saving and effective strategy in the seven countries it was evaluated in (ref).

VI. Drug reactions and resistance

This research area focuses on studies that delve into the emergence of resistance related to the drug regimen and reactions related to them. There are 8 projects in this category. An article published in January 2024 as a part of the project assessing the efficacy of Dihydroartemisinin-Piperaquine (DHA-PQ) compared to Sulfadoxine-Pyrimethamine associated to Amodiaquine in SMC in school aged children from 6-15 years in Mali

concluded that children in DHA-PQ arm reported less adverse events compared to the SP-AQ arm (ref). Also, a case-control study aiming to determine the association between SMC drug levels, drug resistance markers, and presentation with malaria stated rare (0%–1%) prevalence of mutations mediating high-level SP resistance which was similar between cases and SMC-ineligible control and cited that high malaria incidence in SMC eligible children despite scale-up of the strategy in Burkina Faso could be attributed to suboptimal concentrations of SMC drugs, likely due to missed SMC cycles, rather than increasing resistance to SP-AQ (ref).

VII. Others

Projects that do not fit into any other categories are placed in this one. It consists of 4 projects in the Deep Dive. A project studying the amplification of impact of Seasonal Malaria Chemoprevention (SMC) through simultaneous screening and treatment of SMC-children's roommates in Burkina Faso is included in this category. This project promises to respond to a major public health concern by providing evidence of the efficacy of an innovative strategy to boost the impact of SMC intervention (ref). A drug discovery, translation, and development project led by Medicines for Malaria Venture (MMV) which aims at developing new seasonal malaria chemoprevention/mass drug administration (SMC/MDA) regimen is also included in this category.

**When more projects are encountered with time then new research areas will be added as per the need with subsequent update of the Deep Dive.*

Funding by research area

Funding by research area ranges from $2 million to $181 million. The research area "Others" garners the highest funding amount i.e. $181 million for which a single project from Medicines for Malaria Venture (MMV) is responsible for $180 million. Projects included under the category "Effectiveness of the intervention" despite encapsulating the highest number of projects accounts for $79.3 million of the total funding. The research category "Combination with other interventions" accounts for $65.9 million. It covers projects that are carried out in combination with helminth control, vitamin A/zinc supplementation, vaccination with the RTS,S/AS01, etc. Moreover, $82.4 million is attributed to the research area "Feasibility of the scaling-up". These projects mainly are all about expansion of SMC either by geography, age-group or the drugs. Besides, "Determinants of uptake", "SMC implementation" & "Drug reactions and resistance" account for $71.9 million, $29.4 million and $2 million respectively. **It is important to note that some projects have been categorised into more than one research area and the funding associated is contemplated in each research category.*

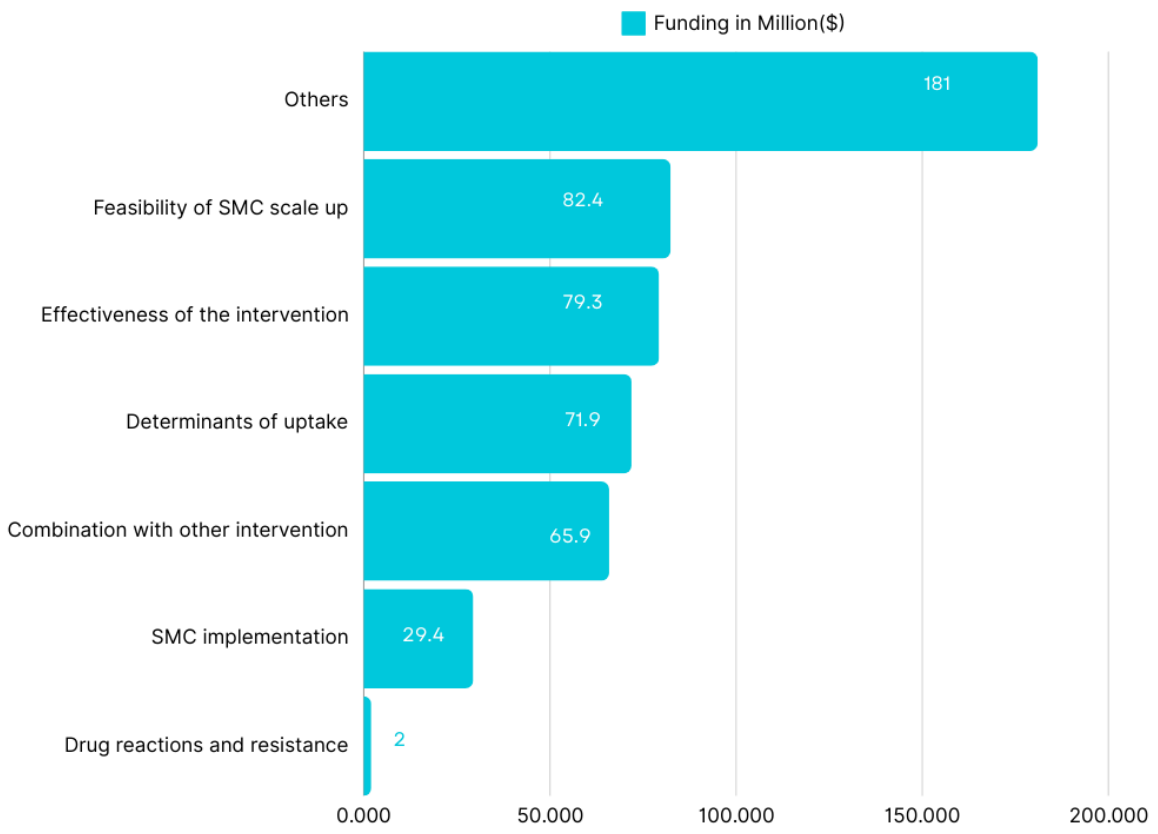

Figure IX: Funding per research area

The figure below highlights the number of projects and investments per research category. Although the categories combination with other intervention and SMC implementation have the same number of projects, there seems to be some degree of dissonance in funding.

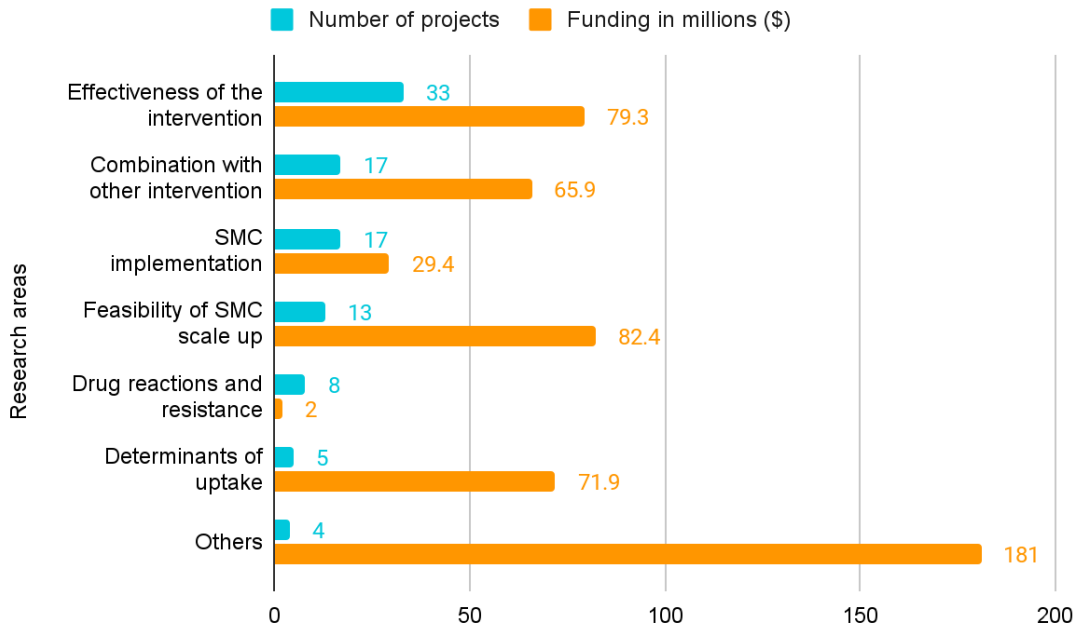

Figure X: Number of projects and funding by research category

Discussion

The majority of the projects included in this Deep Dive are carried out in the Sahel region of Africa as the first WHO recommendation for SMC was exclusively for this area. However, recent projects suggest the expansion of this low-cost and highly cost effective intervention (ref) in Eastern and Southern Africa. The research area “Others” captures a significant proportion of the funding ($180 million) which can be attributed to a single multifaceted project by MMV, apart from that projects in the rest of the research categories seem to not have a significant disparity in funding.

With the release of the updated recommendations for SMC implementation, some changes can be anticipated in the approach and investments in SMC in the coming years. Since children under 5 years old accounted for about 80% of all malaria deaths in the WHO African region in 2021 (ref) there remains a lot of work to be done to mitigate the under 5 years mortality. The decrease in mortality in this age group over the past years could be attributed to the implementation of SMC and other prevention and control measures. Issiaka et al., 2020 (ref) assessed the impact of SMC on hospital admissions and mortality in children under 5 years in Mali. Results showed that the implementation of SMC was associated with a substantial reduction in hospital admissions and reduction of all-cause mortality.

Gaps and Challenges

- **Implementation and scaling-up:** There is limited information available on the challenges faced during the implementation of SMC, especially in the new adopter countries like Mozambique, Uganda and South Sudan. Comprehensive analysis on the implementation, operational effectiveness**,** mobilisation and scaling issues could improve the effectiveness and efficiency of the strategy while applying it to a new setting.
- **Drug combination safety and resistance:**

    - **Combination safety:** While the safety and effectiveness of various drug combinations for SMC have been assessed, insufficiency of data on possible drug toxicity and development of drug resistance is evident. This warrants more research on the long-term safety and potential development of resistance.
    - **Resistance:** Exploration of emergence of resistance to SPAQ that has been used for SMC since its initiation is ongoing, however there is the necessity of new studies to assess it comprehensively which will aid in expanding the strategy to new regions and assess the need for new drug combination/s for the SMC strategy for the future.
- **Delivery modalities and role of community health workers:** As suggested by a study conducted in Mali described in the report earlier, door-to-door delivery achieves higher coverage than fixed point delivery. Further probing is necessary to understand the role of community health workers in the successful implementation of SMC.
- **Long term sustainability and programmatic considerations:** Ongoing and completed projects on SMC give a clear picture where the focus is on regarding the strategy as highlighted by the research areas in this report, there seems to be a gap in understanding the long-term sustainability of SMC programs. More information on programmatic considerations, integration with existing health systems, and community engagement is required.
- **Community acceptance and uptake:** The latest recommendation by WHO on SMC strategy saw a shift from top-down to bottom-up approach on modification and implementation of the strategy. Henceforth, the role of community cannot be overemphasised in the success of this strategy. Although several projects touch on the determinants of uptake, it is apparent that an in-depth analysis of community acceptance, understanding the barriers to implementation, and strategies for maximising community engagement would provide valuable insights.

- **Cost effectiveness:** Cost-effectiveness studies of SMC in terms of cost per reduction in Disability-adjusted life year (DALYs) lost due to malaria may provide additional motivation to open new avenues for investments in the SMC sector.

More recently, the eDELPHI study conducted by SMC Alliance aimed to identify medium-term future research priorities for Seasonal Malaria Chemoprevention in Africa. The eDELPHI study concluded that to effectively address key questions related to the implementation, impact and cost-effectiveness of SMC, increased research investments are necessary. Greater emphasis is needed on understanding drug resistance and the efficacy of chemoprevention. Additionally, future SMC activities should recognize and accommodate the differing research priorities of various stakeholders.

Conclusion

Sir Brian Greenwood's expert opinion (August 2024): The approval of the RTS,S and R21 malaria vaccines by WHO and their deployment on an increasing scale is an important advance in malaria control. It will now be important to determine how the deployment of effective malaria vaccines will impact on the overall programme of malaria control in different epidemiological situations. For example in areas where malaria transmission is highly seasonal and a high level of coverage with the currently recommended four dose regimen of RTS,S or R21 given in the first years of life is achieved, perhaps supplemented

with additional seasonal booster doses, will SMC, which is demanding to deliver when given in four or five cycles to children under five or ten years, no longer provide sufficient added benefit or be sufficiently cost effective to be sustained? Some difficult decisions may need to be made when budgets for malaria control are constrained. More research is needed to ensure that these decisions, which may also apply to some other forms of chemoprevention such as Perennial Malaria Transmission (PMC), are based on the results of sound research.

If you would like to comment on the synthesis report, or are currently involved or planning research / programmatic activities on SMC please contact MESA (mesa@isglobal.org)