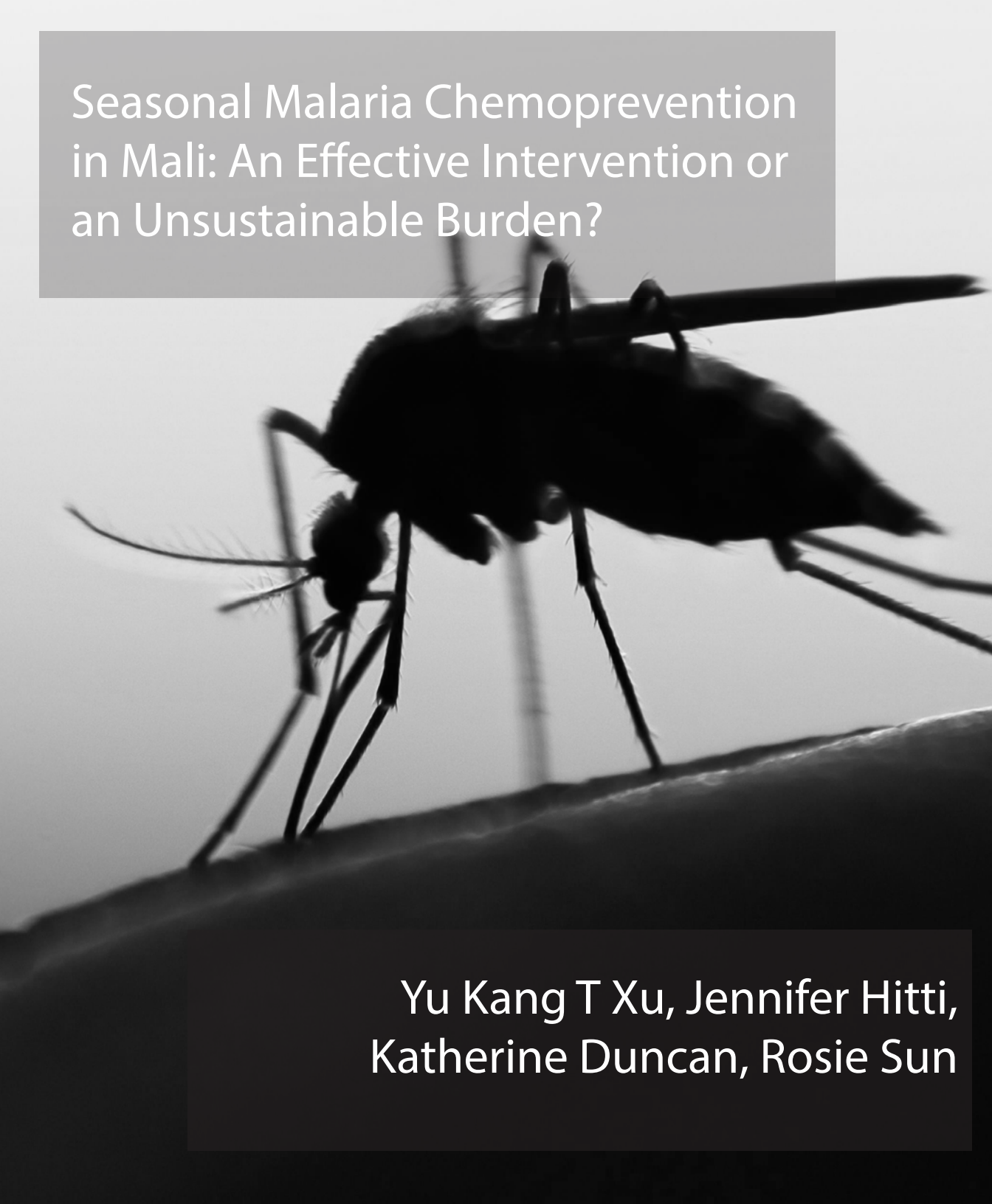
Seasonal Malaria Chemoprevention in Mali: An Effective Intervention or an Unsustainable Burden?



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Abstract

Malaria presents an enormous health challenge for children and pregnant women around the world. In Mali, malarial infections were the leading cause of premature death from 2005 - 2016. The high incidence of malaria in Mali is partially attributable to its location within the Sahel region of Africa, where the annual rainy season correlates with peaks in malaria transmission. In 2012, Seasonal Malaria Chemoprevention (SMC) was recommended by the World Health Organization (WHO) to combat this seasonal spike in infections. As SMC interventions are now undergoing a major transition in funding, we believe that this a crucial time to evaluate the cost-effectiveness and sustainability of this project. Through our evaluation, we find that SMC interventions in Mali achieved their 80% coverage goal and reduced the incidence of malaria by 49%, all while maintaining a cost-effective price per round of SMC for each child (under US$5). Major obstacles that persist for this intervention are the lack of integration with local health systems and potential effects on adaptive immunity. Overall, SMC is a successful short-term strategy for combating malaria, however, the verticality of funding, logistical burden of annual treatments, and risk to adaptive immunity pose serious challenges to the sustainability of the project.

Introduction

Malaria is a devastating disease that contributes immensely to morbidity and mortality worldwide. In 2017, there were an estimated 219 million cases of malaria around the world, representing a slight increase from 2016, when 217 million cases were observed. Children and pregnant women were most vulnerable to the disease, as 61% of global malaria deaths in 2017 occurred in children under 5, and both children and pregnant women were found to be at an increased risk for malaria-related anemia (1). In particular, malaria has posed a significant public health challenge in Mali, consistently emerging as the leading cause of premature death and disability in this country from 2005 to 2016 (2). In the 2016 Global Burden of Disease Study, Mali had the highest probability of death from malaria for children under 5 in the world (Figure 1). In addition, Mali has the highest mortality rate from malaria (232.8 deaths / 100,000 people), and the highest number of years of healthy life lost due to malaria (19, 328.2 years / 100, 000 people) in Africa (3).

The high incidence of malaria in Mali is partly due to the country's geographical location. 90% of Mali's population resides in central and southern Mali, which falls within the Sahel region of Africa (4). In this area, malaria transmission is exacerbated by the short annual rainy season (5). Given that peaks of malaria transmission correlate predictably with the rainy season, the implementation of Seasonal Malaria Chemoprevention (SMC) was proposed to combat the high burden of malaria in Mali.

SMC is the "intermittent preventive treatment of malaria in children" using a monthly administration of two drugs (sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ)) during the rainy season. Several studies have shown that SMC is highly effective and safe (6,7), and

a pilot study conducted by Médecins Sans Frontiėres (MSF) showed that this is also true in the context of Mali (8). Furthermore, in a Cochrane meta-analysis, populations receiving SMC interventions saw a reduction of 75% in clinical and severe malaria episodes. This reduction was also observed in regions which, like Mali, have high long-lasting insecticide-treated bed net (LLIN) usage (9,10). Given the positive evidence for SMC treatments, in March 2012, the World Health Organization (WHO) recommended that SMC targeting children under 5 should be integrated into malaria prevention programs in the Sahel (11). With this recommendation, the National Malaria Control Program (NMCP), under Mali's Ministry of Health, adopted SMC as a policy in 2012 and scaled up the program nationally in 2016 (12).

As the SMC intervention in Mali is currently undergoing a transition in major funding partners (13), we believe this is a crucial time to evaluate the cost-effectiveness and sustainability of the project. Although studies have evaluated the sustainability of other malarial programs (14), no such studies have extensively explored the sustainability of SMC after transitioning to scale. Our case study will address this gap in information by critically appraising the efficacy and sustainability of the SMC program in Mali. Our discussion considers: (1) the effectiveness of the intervention in reaching its initial coverage, efficacy, and finance goals; (2) the strategic successes of the project, including the ability to coordinate international funding and utilize existing community healthcare worker (CHW) infrastructures; and (3) the strategic problems that challenge the sustainability of the project, including the verticality of funding, the logistical burden of annual treatments, and unforeseen consequences on adaptive immunity.

Goals and Strategy

Following the incorporation of SMC interventions into the NMCP policy in Mali in 2012, SMC distribution was scaled up to 42 districts in 2015, and to all 65 districts nationally in 2016. We established three core objectives to evaluate the efficacy of SMC interventions based on goals announced by funding partners (12, 13).

Goals

- 80% coverage of eligible children under five with the full course of treatment
- 70% reduction in the number of malarial cases during the rainy season
- Achieve cost-effectiveness: maximum US$5.00 for each round of SMC annually per child

Strategy

What: SMC involves preventatively administering intermittent doses of antimalarial drugs to children aged 3 to 59 months during the rainy season when malaria transmission is highest. The objective is to maintain high levels of antimalarial drugs in the body throughout the duration of the rainy season to reduce morbidity and mortality from P. falciparum malaria in these children. The treatment regimen consisted of an AQ tablet daily for three days, with a SP tablet on the first day only. Since SP and AQ confer a high degree of protection for only four weeks, the 3-day cycle was repeated 4 times at

monthly intervals (11).

Where: Targeted areas had extremely high burden of malaria, with more than 10 cases in every 100 children during the transmission season. Additionally, these regions exhibited strong seasonality effects: more than 60% of annual cases of malaria occurred within 4 months (11). In Mali, the target season for SMC administration was composed of August, September, October, and November (4).

How: CHWs were used for the delivery of SMC due to the strict timing required for the regimen and the vast number of individuals that needed to be reached. As well, mobile delivery through CHWs was shown to be more effective at achieving high coverage than stationary delivery through health facilities (15). In this case, CHWs either visited families door-to-door or gathered children at an agreed fixed-site in the neighborhood (12). CHWs administered the first dose and instructed the caregiver to administer the second and third doses of AQ over the following two days (16).

Impact evaluation

Coverage

In Mali, coverage goals were generally met despite geographical challenges. According to the WHO annual report in 2016, the intervention reached 93% of its targeted 3,702,724 recipients in Mali (10). The cooperation of districts was also high, with 89% of targeted districts implementing the full 4-course SMC treatment (10). According to ACCESS-SMC's final report, however, the implementation of SMC in their programs only reached the 80% coverage goal in 2015, but not 2016 (This discrepancy in data reporting, between the WHO and ACCESS-SMC's reports, is further discussed in subsection "Strategic Challenges: Caveats of Data"). Notably, this failure in 2016 for ACCESS-SMC's interventions in Mali contrasted with the success of similar interventions in other Sahel countries in both years. Upon more critical examination of the data, however, it is reasonable to associate this failure partially to the enormous increase in eligible individuals in 2016 (from 2.8 million to 4.6 million) due to the national upscaling of the program. Thus, we conclude that although coverage in ACCESS-SMC programs did not reach their 2016 goal, there was still a sizeable increase from 2015 in the number of interventions offered (13). Overall, SMC interventions made significant progress in attaining their coverage goals.

Reduced incidence of malaria

Anecdotal evidence reported a 49% decrease in cases of malaria throughout the rainy seasons in Mali after implementation of SMC from 2015 - 2017 (13). The Malaria Consortium also found a 50% reduction of mortality in areas with SMC implementation throughout the Sahel region (17). Importantly, however, these studies represent only a correlational finding between SMC deployment and reduced malaria incidence, as other interventions may have been introduced during the same period that may confound the benefit attributable to SMC alone. The only study that provides comparative causal analysis is presented by Diawara et al. In this study, researchers compared the efficacy of SMC de-

ployment in the Kita district to a socio-demographically matched Bafoulabe district that received no SMC intervention. They found that SMC reduced malaria infection from 24.1% to 18.0% in the Kita region, whereas the Bafoulabe region saw an increase in malaria incidence from 30.5% to 46.0%. Thus, SMC helped reduce malaria incidence by 61% when accounting for the increase in baseline mortality in the control group (Figure 2) (16). Overall, evidence suggests that implementation of SMC did significantly reduce malaria incidence in Mali.

Effects on adaptive immunity

A case-specific consideration for evaluating the efficacy of SMC treatments, and other interventions that do not permanently interrupt transmission, is the potential that they may reduce the adaptive immune response of children to malaria and prompt an age-shifted delay in morbidity (18, 19). This can occur if access to the treatment regimen is ever disrupted, leaving a population with a lower immunity towards malaria and prompting a possible resurgence in morbidity and mortality. This is also known as the "rebound effect" (18, 19). Before transitioning to scale, studies reported conflicting evidence on the impact of SMC on adaptive immunity a year following treatment (18-21). However, none of those trials followed children through all 5 years of SMC treatment. More recently, after deploying the intervention across the Sahel region, a few controlled studies support a correlative relationship between SMC interventions and reduced adaptive immunity. A study in Ouelessebougou, Mali, found that children who received SMC, regardless of the number of years they received it, had lower levels of antibodies towards both blood and liver-stage malarial antigens (22). Although it is currently unclear whether these findings correlate with more severe clinical infections, similar results were found in a study in Southern Senegal (3). These findings must be considered when discussing the long-term sustainability of SMC programs.

Financing

The NMCP has been able to finance SMC projects primarily through partnerships with various international organizations. The pilot project in 2012 was funded by MSF, and subsequent projects were funded by WHO, UNICEF, Save the Children, the President's Malaria Initiative (PMI), the World Bank, and the Global Fund (4, 12, 13, 16). The scaling up of SMC in 2015 and 2016, conducted by ACCESS-SMC, was funded primarily by UNITAID, which has donated US$67 million for ACCESS-SMC's work in seven Sahel countries (4, 12). ACCESS-SMC is a consortium composed of 6 charities, including the Malaria Consortium (MC) and Christian Relief Services (CRS) (4, 13). In 2017, Global Fund replaced UNITAID as the primary funder of ACCESS-SMC (13), although other aid organizations, such as UNICEF and the World Bank, continued to play a role in funding SMC interventions (12).

Altogether, the pilot project in 2012 cost MSF a total of US$815,548 to reach 159,317 children in a single district (8). In 2014-2016, PMI spent US$314,000 for its work in covering 77,497 children in another district (12). The cost dis-

tribution is shown in Figure 3, with the majority of funding going towards staff, supplies, and transport. (8, 13).

A maximum US$5.00 target was established for the cost of a four-round cycle of SMC for a single child (13). The initial pilot project performed by MSF cost US$1.44 for each round, implying a cost of US$5.76 for a full four-round course (8). By 2015, however, the cost for a child's complete annual four-round treatment of SMC was brought down to only US$4.05. This was accomplished, in part, by securing drug prices at 27 cents per dose with the manufacturer Guilin (13).

Overall, the cost for each disability-adjusted life year (DALY) saved has been calculated to be US$39. According to the WHO, a highly cost-effective intervention costs no more than US$724 per DALY, making SMC a cost-effective intervention. In terms of cost per DALY, SMC is comparable to other preventative malaria interventions, such as LLIN (US$29/DALY) and Indoor Residual Spraying (US$31/DALY). Compared to malaria case treatment (US$9/DALY), however, SMC is less cost-effective (13).

Strategic Successes

Effective partnerships

Partnerships between the NMCP, district and local health authorities, and various international organizations were key to the success of the SMC program (16). The NMCP's partnerships with multiple international organizations allowed it to acquire the technical and financial support required for the project. Additionally, local actors, such as the Malaria Research and Training Center, were also involved in contributing skills and knowledge to the project (8). This transfer of knowledge allowed for local capacity building that created hundreds of jobs in healthcare and improved supply chain management tactics, among other benefits (12, 13). Despite the large number of players involved, the NMCP was largely successful in coordinating these actors to efficiently implement SMC (13). These connections have been critical in allowing Mali to become the only country to adopt SMC nationwide. For example, MC was instrumental in securing a low cost for SMC drugs through effective partnership with Guilin. As well, CRC used its prior relationship with Global Fund to attract funding for the 2017 and 2018 seasons (13).

Use of pre-existing local CHWs and distributors

Another reason for SMC's success is the use of existing health care networks. For example, SMC was delivered in combination with previously implemented malaria prevention strategies, such as LLIN (8). Furthermore, the local distributor, Pharmacie Populaire du Mali, was used for the transportation of the SMC drugs (4). The Ministry of Health (MoH) had also trained 2,377 CHWs between 2010 and 2016 to address the shortage of healthcare workers in Mali (12), and these workers were effectively adopted for the delivery of SMC treatments (4, 16). Overall, the use of these established local resources allowed for smoother implementation of the SMC intervention.

Monitoring and adaptability

The monitoring and responsiveness of key players was a highlight for the SMC intervention that allowed the project to adapt and improve its implementation strategies over time. For example, in 2015, fixed-point distribution was used as the primary method of drug delivery. However, when this strategy was found to provide poor coverage results, ACCESS-SMC tested and switched to a door-to-door delivery method. After the success of the change, the 2016 strategy was altered to include a combined fixed-point and door-to-door approach (13). The ability to quickly identify and adapt to problems was key to the success of SMC interventions in Mali.

Strategic Challenges

Sustainability

Verticality of funding: Despite meeting the goal for cost-effectiveness based on costs per DALY, SMC is not a financially sustainable intervention in the long-term. This is evident when considering that (a) unlike a vaccine, this intervention must be repeated indefinitely to reduce incidence of malaria, and (b) the funding to support SMC is presently sourced almost exclusively from international institutions. This sustainability problem is further exacerbated when considering that national funding for SMC programs is currently out-of-reach for the Malian Ministry of Health. Although the government of Mali allocates a budget of US$2.5 million annually towards malaria control (12), this is only a small fraction of the > US$18 million that would be necessary to provide SMC for all of Mali's 4.6 million eligible children (13). This unreasonable demand for resources means that, for the conceivable future, funding for SMC interventions in Mali must continue to rely largely on international donors. Thus, despite successfully utilizing local health care infrastructure to deliver SMC drugs, the lack of local funding prevents the full integration of SMC interventions. Additionally, as with all top-down funding, the unreliability of donor support presents severe risks to the future sustainability of SMC interventions in Mali.

A shift towards more horizontal funding requires the successful integration of various strategies at the national and local levels. Integrated community case management (iCCM), for example, has been shown to improve access to preventive care and treatment for children in underserved communities by allowing interventions to integrate with existing local and horizontal infrastructures (1). While full integration with iCCM has not been achieved by the SMC intervention, a highlight of the 2015-2017 fiscal years is that the funding per person at risk for Malaria in Mali has increased by approximately 20% from the periods 2012-2014 (1).

Logistical burden: Logistically, employing SMC anywhere is complicated. To sustain suppression, CHWs must deliver multiple rounds of SMC therapeutics each year. This continuous requirement for SMC drugs greatly increases the burden of funding and human resources, and potentially leads to incomplete coverage (24). Furthermore, the eligibility of children presents an ongoing logistical problem for SMC

interventions. Currently, there are no monitoring mechanisms set in place to ensure the health of children aging out of the program each year or to ensure adherence of children to the drug regimen. As well, the number of new children added to the program annually presents an administrative challenge.

The implementation of SMC in Mali, specifically, also faces unique logistical challenges. Geographically, many of the target areas that would benefit most from the intervention are rural and difficult to access due to poor infrastructure (24). As well, in the rainy season, flooding can impair SMC drug delivery (25). These geographic and infrastructure barriers can have a large impact on coverage, as shown in a study in Kita, Mali, in which travel-associated difficulties accounted for 43% of drop-outs between SMC treatment rounds (16). Violent conflict, particularly in Northern areas of Mali, also occasionally contributed to preventing SMC delivery (12, 13). Additionally, local health authorities were often inexperienced in supply chain management, which led to sporadic stock-outs of SMC drugs in certain districts (13). Lastly, orchestrating the large number of international stakeholders in Mali posed certain bureaucratic and communication difficulties. For instance, on some occasions, when approval was required from multiple actors, decision-making was delayed due to disagreements (13).

These logistical concerns pose a serious challenge to the sustainability of SMC interventions in Mali. Currently, 35% of the cost for SMC interventions is solely devoted to the transport of drugs and supplies (Figure 3) (8, 13). Innovations to decrease costs in delivery of care and increase integration with local funding are required to build the capacity for local governments to handle these logistical problems on their own.

Considerations for long-term sustainability: The finding that SMC interventions rely heavily on vertical funding, face logistical burdens, and pose risks to adaptive immunity calls for a reassessment of the sustainability of this intervention. Although the delivery of SMC drugs successfully reduced disease burden and suffering in the short-term, the inability for local governments to independently fund this initiative poses a risk: a sudden lapse in international funding could result in a collapse of the program and the "rebound effect," whereby malaria resurges due to reduced immunity. In light of this risk, and given little evidence that SMC interventions can or will be integrated sustainably in the future, we argue for a move towards a more integrative approach, where multiple interventions, like SMC, vaccination, LLIN, indoor spray, rapid diagnosis and treatment ect… are deployed as an integrated initiative that utilizes resources to improve the sustainability of any one intervention.

Caveats of the data

Through our evaluation of SMC interventions in Mali, we also observed that the reporting and monitoring of these project faces some limitations. For example, the shortage of peer-reviewed literature on the efficacy of the intervention in Mali is worrisome. Even

more concerning is the inconsistencies in data reporting that indicate a lack of communication among key stakeholders. For example, the WHO report found that the coverage goal for SMC was reached in Mali in 2016, whereas the ACCESS-SMC report asserted otherwise (10, 13). Furthermore, data reports do not attempt to discuss or control for the effects of simultaneous interventions. For example, initiatives promoting LLINs in Mali (10) present confounding factors when considering efficacy of SMC interventions. Overall, these limitations in data reporting show how the overabundance of international aid organizations promotes the decentralization of data collection. These problems in data reporting should be addressed by increasing partnerships between international aid and research organizations in addition to increasing partnerships between local governments.

Future Implications

The most pressing issue for the continuation of SMC interventions in Mali is the need to secure future funding that will go towards supporting the long-term benefits of the project. For the 2018 season, the Global Fund will continue to fund ACCESS-SMC as part of a US$70 million grant for the prevention of malaria (12, 13). PMI will also spend over US$3.3 million to support SMC for 650,000 children in 12 districts (12). Despite these grants, certain aspects of monitoring will have to be discontinued due to insufficient resources (13). Furthermore, funding for 2019 and beyond is still uncertain (13). To address these potential future gaps in funding, the delivery of SMC drugs could be integrated with other CHW delivered interventions. For example, CHWs could administer SMC alongside nutritional interventions or deworming medications to split delivery costs between different projects (13).

The other pressing issue for the future of SMC interventions is the need to verify the effects on adaptive immunity. To date, the evidence for this effect is still controversial at best. Thus, to address this gap in knowledge, children aging out of the SMC program should be monitored for their susceptibility to malaria. As well, the adaptive immunity of new children entering into the SMC program should be monitored for the entire 5-year treatment regimen. These findings should then be incorporated into an ethics board evaluation of SMC programs to justify the continuation of this intervention.

Conclusion

Overall, the NMCP was able to cost-effectively implement a short-term SMC program in Mali. Other interventions can learn from this project with regards to the successful mobilization of local and international partners, use of CHWs, and adaptability in response to challenges. Due to precarious vertical funding and potential risks to adaptive immunity, the sustainability of SMC treatments must be seriously evaluated before committing to future funding.

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Appendix

Visual Abstract

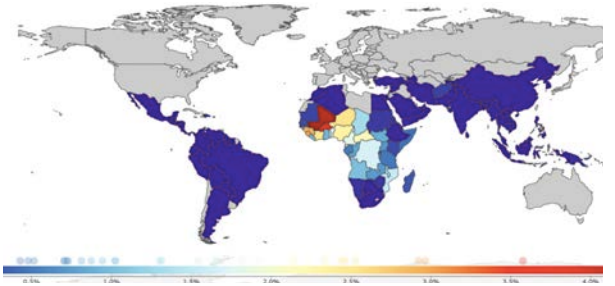

Figure 1: The probability of death from malaria in 2015 from birth to age 5 around the world. Mali is the country in red, showing that it has the highest probability of death from malaria for children under 5 in the world (4.3%) (2).

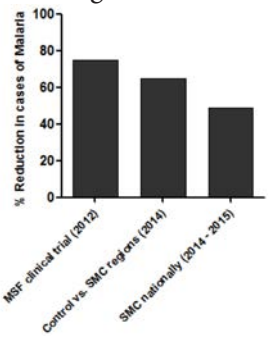

Figure 2: Comparing the efficacy (reduction in ma-

laria incidence) of three SMC interventions in Mali: the initial 2012 clinical trial by MSF, the 2014 regional case-control study in Kita, and the 2014-2015 transition to scale (8, 13, 16).

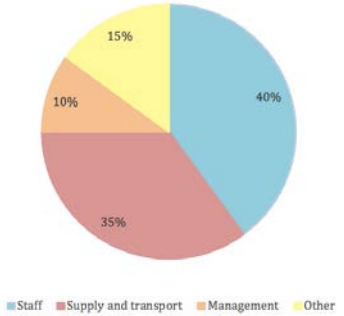

Figure 3. Distribution of SMC project costs (8, 13).