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What to Know About the Cost-Effectiveness of Seasonal Malaria Chemoprevention in Endemic Countries: A Systematic Review

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Abstract:-

Introduction: Over the past 20 years, malaria incidence and prevalence has fallen in sub-Saharan Africa, mainly thanks to intensified vector control. Seasonal malaria chemoprevention (SMC) for children under five is one of the strategies producing significant results in endemic countries. We synthesized studies on cost and cost-effectiveness of SMC intervention.

Methods: Preliminary searches were conducted to identify keywords to be searched across five databases: PubMed, EMBASE, EconLit, Centre for Reviews and Dissemination, and AJOL. Screening was conducted independently by two researchers. Costs data, cost effectiveness estimates, and contextual information were extracted using a standardized form by three reviewers. An analysis and qualitative assessment were performed using the CHEERS checklist. Costs and cost-effectiveness ratios were adjusted to common year (2022) and currency (US Dollar).

Results: The initial search identified 1,517 publications; 17 were retained for full-text review. Cost-effectiveness and incremental cost-effectiveness (ICER) ratios were presented in 53% (n=9) of the studies. Three ICERs were provided with a ratio ranging from 19 to 128 USD (2020) per malaria case averted and a ratio of 3,938 USD per malaria death averted. Cost-effectiveness ratios provided were from 1 to 146 USD per uncomplicated malaria case averted and 11 to 241 USD per severe malaria case averted.

Conclusion: Investments in implementation of SMC are cost-effective, and the evidence is relatively strong. Very few studies have been conducted in the highly endemic countries of the WHO African Region, receiving significant funds for malaria control.

Keywords:- *Cost, Cost-Effectiveness, Seasonal Malaria Chemoprevention, Systematic Review, Mali.*

I. INTRODUCTION

Since 2012, the World Health Organization (WHO) has recommended the use of seasonal malaria chemoprevention (SMC) in the endemic countries of malaria in sub-Saharan Africa. This recommendation has led to the roll out of SMC in many countries. SMC consists of the administration of a full treatment course of an antimalarial drug repeatedly during periods of high malaria transmission, used to maintain therapeutic concentrations of antimalarial drugs in the blood and thereby clear any infections and provide prophylaxis against malaria infection during high risk periods of the year [1, 2] . SMC was historically called intermittent preventive treatment in children (IPTc) or in infants (IPTi), as in initial studies the intervention targeted pregnancy women and children under five years of age. Currently, some countries, such as Senegal and Mali, have started to extend SMC to children under 10 years of age [1, 3]. It is important to note that there has been an explosion of chemoprophylactic application to specific targeted groups, including chemoprevention for children and pregnant women, post-discharge chemoprophylaxis and chemoprophylaxis to travellers with occupational hazards, as well as people in the malaria elimination areas. In many cases, WHO recommendations for chemoprophylaxis are not followed [4, 5].

According to WHO, in 2017 more than 29.3 million children were eligible for treatment of SMC across the 12 countries implementing SMC worldwide; however, only 15.7 million of these children received SMC treatment [6]. In 2021, at least one dose of SMC per course was administered to approximately 40.4 million children in the 11 countries in the WHO West Africa Region implementing SMC [7]. In several countries, SMC has been scaled up to cover all regions, and extended from children under five to all children under ten. This important step in malaria control must be accompanied by a review and synthesis of the published SMC studies carried out in different contexts worldwide.

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The purpose of this review is to synthesize available data on the cost or cost-effectiveness of SMC. There have been very few systematic reviews published in the peer-reviewed literature on cost or cost-effectiveness of SMC as a malaria control intervention in the most endemic countries [8, 9]. The approach for this systematic review is similar to that of White et al., who selected all studies related to cost estimation for malaria control interventions [8]. However, in this case, we are only interested in articles regarding the costs and cost-effectiveness of one type of intervention: SMC. In this study, when referring to SMC, we mean all preventive treatments used against malaria in children (SMC, IPTi, IPTc).

This review will contribute to improving allocative efficiency in malaria control programs by providing synthesis of the available data on the costs and cost-effectiveness of SMC in sub-Saharan Africa [10].

II. METHODS

➢ *Data sources and search strategy*

We carried out a preliminary search that identified several electronic databases used by different authors for systematic reviews. Among these, five were used five bibliographic databases were searched: PubMed, Excerpta Medica Database (EMBASE), EconLit, Centre for Reviews and Dissemination of University of York (NiHR-CRD), and African Journals Online (AJOL). The search was conducted in May 2019 and updated in January 2021.

We employed three separate search strategies for the various databases. To search in PubMed, Embase, and EconLit, we used a series of cost or assessment-related terms with the Boolean operator 'or', which included:

cost OR "cost-effective" OR "cost effective" OR cost-effectiveness OR "cost effectiveness" OR "economic evaluation" OR "impact evaluation" OR "health economic evaluation" OR "study costs" OR capital OR overheads OR price OR "cost benefit analysis" OR "cost-benefit analysis" OR "economic analysis" OR "sensitivity analysis" OR "health economics" OR "health resource allocation" OR "health resource utilization" OR "cost analysis" OR "health expenditures"

in combination with a series of SMC-related terms (using the Boolean operator 'or'), including:

AND ("seasonal malaria chemoprevention" OR IPTi OR IPTc OR "intermittent preventive treatment" OR "intermittent preventive therapy" OR (malaria AND chemoprophylaxis)).

Thus, the article must include at least one of the cost or assessment terms and at least one of the SMC terms.

For other databases, we employed a different search approach, based on the database search options. The phrase *"(malaria AND children) AND cost NOT (bednets OR HIV)"* was used in the NiHR-CRD database and *"seasonal malaria chemoprevention"* in the AJOL database.

A secondary search was conducted by searching for relevant references of articles already found in bibliographic databases to identify and review additional publications.

No publications were eliminated based on the publication language, the geographic location of the study, or the date of publication.

➢ *Selection criteria*

A study was included if: (i) it presented primary cost or cost-effectiveness data; (ii) it presented cost-effectiveness analysis (CEAs) for SMC or IPT interventions for children and infants; or (iii) it was an economic study comparing the invested funds in SMC with the results obtained. We did not include studies that: (i) only discussed SMC but did not include economic evaluation; (ii) only mentioned cost or cost-effectiveness in the discussion; (iii) targeted populations over 10 years of age; or (iv) that were not from the provider's perspective.

The first step of screening consisted of examining the titles and abstracts of all publications found during the search of the five databases to verify the relevance of these publications. In the initial screening, an article was deemed relevant if (i) the study appeared to focus on cost analysis and/or cost-effectiveness analysis of SMC (including IPTi and IPTc); (ii) if the study highlighted or identified publication gaps on cost analysis and cost-effectiveness analysis of SMC for future research; or (iii) if the study provided an evidence base for decisions on the use of SMC as a malaria control intervention. Separate inclusion criteria were applied in the initial screen verses after a full text review to allow the authors to review, in full, texts that related to cost-effectiveness of SMC, even if they did not provide primary data. During initial screening, the authors also determined the existence of information suggesting other databases or keywords. This step allowed us to identify additional publications on other search engines, such as Google Scholar, which were not among the databases searched. This review was conducted by two independent researchers. When the two researchers' decisions on the

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inclusion of an article differed following the first review, that article was included for a full-text review.

The second round of screening included a full text review of relevant articles by the two authors (Y.T. and R.K.). The selection was made using three main inclusion criteria, established prior to beginning the systematic review. Two additional researchers (H.M. and M.M.) were involved in making the final decision to exclude or include when the article was under discussion or when the decision was not unanimous between Y.T. and R.K.

➢ *Data extraction and management*

All articles identified through the search were imported into the EndNote 20.5 (Bld 16860) reference management software. The data extraction plan was developed in Excel using chosen items from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, a tool used to determine whether authors are including key information that should be included in an economic evaluation [11]. Three members of the systematic review team extracted data into the standardized Excel spreadsheet, focusing on the following variables: title, first author name, year of study, year of publication, country of study, and the following CHEERS methodology items: measure of cost, the effectiveness outcome measures, study perspective, time horizon, discount rate (currency, pricing period, and conversion), cost-effectiveness estimation, and Incremental Cost Effectiveness Ratio (ICER).

When a study did not provide data on one or more of the fields (variables) in the table, the study was not removed from the analysis; rather, the cell in the table was left blank and the information is not presented in the results. When a variable is presented with multiple data or with a range of data, it is presented in the results as such. All SMC implementation costs were converted to the cost per dose of SMC administered and were adjusted to common year (2022) and currency (US Dollar) and compared using a discount rate of 3% to compare studies. When the number of doses was not explicit, the WHO standard of three doses per month for four months was used. Some studies were conducted over several years (up to three years for time horizon), with sample sizes varying from year to year. In this case, the mean of the sample size was used for analysis purposes.

Finally, in this review, we have attempted to examine how publications have addressed the distributional effects and equity in the effectiveness measure.

III. RESULTS

Through searches in five different databases, 1,517 publications were identified. The articles were published between 1948 and 2021. After initial screening, 37 publications that met the inclusion criteria were retained. Of the 37 articles, a full text version for four articles was not found, despite extensive efforts to access the article. A total of 33 full text articles were reviewed; 16 were excluded based on the pre-determined inclusion and exclusion criteria and 17 were deemed eligible for inclusion in the final review. A summary of the inclusion and exclusion process for publications is provided in the PRISMA diagram below.

➢ *Overview of Results*

The selected studies were all published in sub-Saharan Africa between 1992 and 2021. Some publications were multi-country studies (n=6, 35%), four (24%) were in Ghana, two (12%) in Tanzania, two (12%) in Gambia, two (12%) in Senegal, and one (6%) in Mali. Most of the single-country studies were conducted at the health district level (n=10, 59%), most studies (87%) were conducted in rural or semi-urban areas. The area of coverage was not specified in four studies (24%). The number of children targeted and treated with SMC was reported in 13 studies (77%) and ranged from 250 children to 25 million children. The steps and process for including and excluding publications are summarized above in the PRISMA flow diagram.

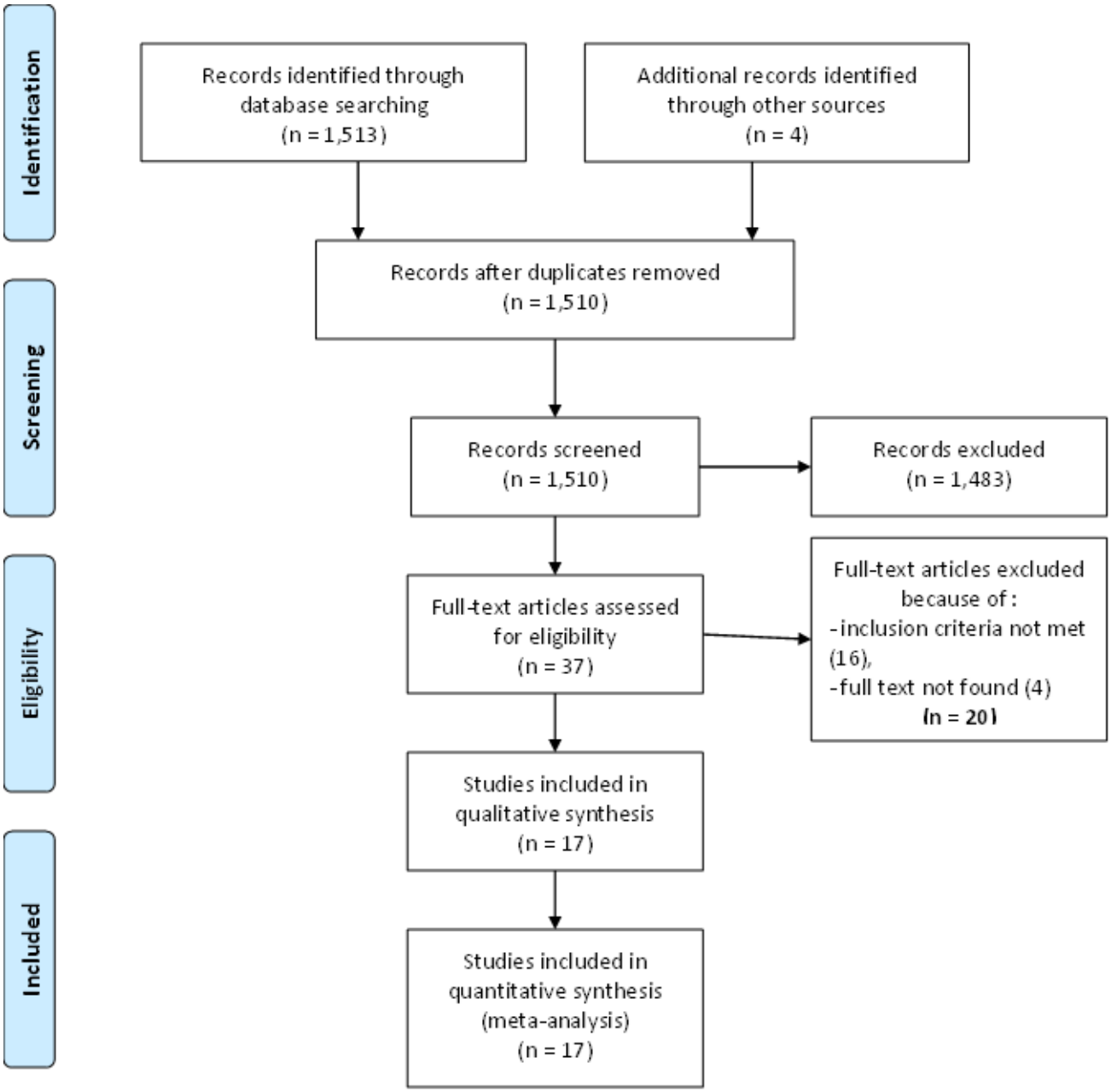

Fig 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

➢ *Study perspective, discounting, and time horizon*

The synthesis shows that 59% (n=10) of the studies adopted the provider perspective and 18% (n=3) adopted both the provider and societal perspectives, while 24% (n=4) did not specify the study perspective. However, the unit of cost measurement allowed us to determine that the perspectives of these four studies was that of the provider [12-15]. The period covered by the studies ranged from three months to four years [12, 13, 16-20]. Discounting of costs and effect performed with rate were specified in only two studies. The currency used in 12 of the 17 studies was the United States Dollar (USD); the other five studies only provided costs in dollars, with no further mention of the currency.

➢ *Costs measured in the selected studies*

All 17 studies reported data on the cost per dose (n=9, 53%) or per treatment administered to children (n=8, 47%). All costs were converted to cost per dose of SMC and adjusted into common currency of 2022. The costs per dose administered to children ranged from 0.03 to 1.83 USD, with an average of 0.52 USD (95% CI: 0.29 – 0.75) per dose per child. The median cost of SMC dose per child was 0.36 USD (IQR: 0.50), that is 4.32 USD per child for full SMC treatment. Of the included studies, nine (53%) reported costs of SMC per dose administered or per course [13, 14, 18-24]. All other studies (n=8, 47%) reported costs per season of three to four months of SMC [12, 15-17, 25-28]. Twelve of the 17 (71%) studies reported a second unit cost, and some reported tertiary unit costs that were used to analyse the secondary and tertiary health outcomes of their interventions. Shared costs were not reported in any of the studies included in this review.

➢ *Health outcomes and effectiveness outcomes considered*

In 13 of the 17 studies (17%), health outcome measures were reported [12, 13, 15, 16, 18, 19, 22-28]. These measures were

expressed in terms of malaria incidence, number of malaria cases averted, reduction in parasitaemia, number of years of life lost, number of quality-adjusted life years (QALYs) gained, or disability-adjusted life years (DALYs) averted. The remaining studies did not specify health outcomes in their results. Where possible, the aim was to assess the reduction in the incidence or prevalence of malaria in the treatment areas compared to the control areas when there was a comparator. In some studies (n=3), DALYs were used to capture the effectiveness of the intervention. In several of the selected studies, secondary, tertiary, or even supplementary measures of effectiveness were reported in addition to the primary measure of effectiveness.

➢ *Cost-Effectiveness and Incremental Cost-Effectiveness*

The cost-effectiveness ratio (CER), incremental cost-effectiveness ratio (ICER), incremental health outcome, or incremental cost was calculated in 53% (n=9) of the studies.

Table *1* below shows the main indicators provided or not provided (yes/no) in the included studies and

The other eight studies did not perform these types of analyses [12-17, 20, 21]. In the studies selected, three ICERs were provided, including two for cases of malaria averted (with a ratio ranging from 19 to 128 USD) and one for deaths averted, with a ratio of 3938 USD [19, 26]. CERs were also provided in three studies for uncomplicated and severe malaria cases averted, with scores ranging from 1 to 146 USD and 11 to 241 USD, respectively [24, 25, 28]. In four studies (24%) incremental costs and incremental health outcomes were calculated. These incremental costs and health outcomes analyses focused on comparisons between different types of treatment (dihydroartemisinin-piperaquine versus artemether-lumefantrine) or different types of agents and methods of administering treatments (health workers, outpatient departments, EPI outreach clinics, outpatient departments) [22, 24, 25, 27].

***Table* 2** summarizes the overall CERs and ICERs reported in the various studies included in this review.

Table 1: Main indicators used and provided in the studies

First author	Shared resources	Cost provided	CER provided	ICER provided
Gilmartin, 2021 [25]	no	yes	yes	yes
Baba, 2020 [16]	no	yes	no	no
Diawara, 2019 [12]	no	yes	no	no
Winskill, 2019 [21]	no	yes	no	yes
Pitt, 2017 [17]	no	yes	no	no
Cisse, 2016 [13]	no	yes	no	no
Nonvignon, 2016 [26]	no	yes	no	yes
Pfeil, 2014 [22]	no	yes	yes	yes
Abotsi, 2012 [18]	no	yes	no	yes
Bojang, 2011 [19]	no	yes	no	no
Patouillard, 2011 [27]	no	yes	no	yes
Ross, 2011 [23]	no	yes	yes	yes
Conteh, 2011 [24]	no	yes	yes	yes
Hutton, 2009 [14]	no	yes	no	no
Manzi, 2008 [20]	no	yes	no	no
Gonzelez, 2000 [28]	no	yes	yes	yes
Picard, 1992 [15]	no	yes	no	no

Table 2: Incremental cost-effectiveness ratio estimate from different SMC interventions (ICER)

1st Author	Estimate indicators	CER/ICER
Gilmartin, 2021 [25]	Cost per malaria case averted	6.7
	Cost per severe malaria case averted	240.84
Nonvignon, 2016 [26]	Cost per additional case averted (base estimates ICERs)	127.84
	Cost per additional death averted (base estimates ICERs)	3938.44
Pfeil, 2014 [22]	Incremental Cases of uncomplicated malaria when treated with dihydroartemisinin-piperaquine versus artemether-lumefantrine	0.38
	Incremental Cases of severe malaria when treated with dihydroartemisinin-piperaquine versus artemether-lumefantrine	0.01
Abotsi, 2012 [18]	Cost per deaths averted (CE Ratio)	11.83

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Ross, 2011 [23]	Cost per uncomplicated episode averted (Lower limit)	1.49
	Cost per uncomplicated episode averted (Upper limit)	24.35
Patouillard, 2011 [27]	Incremental Saving for health workers compared to facility-based nurses working	0.96
	Incremental Saving for health workers compared to outpatient departments	0.48
	Incremental Saving for health workers compared to EPI outreach clinics	1.48
	Incremental Saving for EPI outreach clinics compared to outpatient departments	28.68
Bojang, 2011 [19]	ICR for malaria episodes averted	19.16
	ICR for child who received at least one dose	4.82
Conteh, 2010 [24]	Net Cost Effectiveness (Cost per malaria case averted)	145.90
Gonzelez, 2000 [28]	CER of Severe anaemia per DALY averted using combination of pyrimethamine, dapsone and iron)	11.26
	CER of Severe anaemia per DALY averted using combination of pyrimethamine and dapsone	12.69

IV. DISCUSSION

This study reviewed and synthesized all cost and cost-effectiveness analyses related to SMC for children and identified gaps in published studies to provide the evidence base for decision making on the use of SMC as a malaria control intervention. Methodologically, almost all the included studies did not include one or more of the important steps in an economic evaluation, despite the multiplicity and diversity of guidelines which recommend these successive steps. To facilitate comparability of results, these guidelines, such as CHEERS, High Authority of Health of France (HAS), or Professional Society for Health Economics and Outcomes Research (ISPOR), recommend that certain items be highlighted or that an explanation be provided as to why certain methodological issues are not addressed in a study [11, 29, 30].

We found an important number of publications on cost and cost effectiveness worldwide, but few have been included in our analysis compared to the previous reviews carried out in 2011 and 2021: these two reviews covered all malaria control strategies as opposed to our review, which focuses exclusively on SMC intervention [8, 9]. If a significant number of publications had been analysed after meeting the inclusion criteria, the arguments used to explain the stagnation of results observed in malaria control since 2015 could be substantiated [7, 31, 32]. In a context of scarce resources, there are increasing expectations for effective malaria control strategies to reduce the millions of malaria cases and hundreds of thousands of deaths still being recorded [7].

We identified very few publications on cost-effectiveness analyses of SMC (24.4%, n=17). Of the five countries with the highest number of cases in the world, accounting for more than half (51.5%) of 2022 global malaria cases, these studies covered only Nigeria and Mozambique [7, 14, 25]. On this point, however, it should be remembered that the WHO has only recommended the implementation of SMC in certain malaria endemic countries, but not all [1].

No study reported on the dimension of reducing socioeconomic inequalities of interventions using distributional cost-effectiveness analyses to explore health inequality impacts into CEA [33-35]. The absence of this type of analysis and methodology in the literature may be due to it only recently appearing in economic evaluation guides.

Our synthesis showed in Table 1 that the cost-effectiveness and ICERs differed substantially from one author to another. The observed discrepancies were considerably high. These differences could be partly explained by the use of different methods of estimating the units of health outcomes measurement by the authors. Our findings showed that the measure of effectiveness was assessed differently across studies. Indeed, in most studies, the effectiveness of the intervention was measured by its capacity to prevent malaria's occurrence or death [12, 13, 15, 16, 18, 19, 22-28]. Although there are several guides for conducting economic evaluations, in most of the publications reviewed in this systematic review, the authors did not present ICERs in their abstracts [30, 36-38]. They have often simply given incremental costs and incremental health outcomes side by side, without calculating the ICERs [22, 27]. ICERs are one of the most important outcomes of an economic evaluation because they help guide and support decisions about whether or not to continue a health intervention.

The WHO recommends four rounds of SMC and three doses of SMC per round. In our review, the median cost per dose of SMC was 0.36 USD, so the median cost of SMC per child was 4.32 USD (0.36*3*4) [1]. Our results on the median cost of SMC per child (4.32 USD) were close to those of White et al. in 2011 (4.03 USD). These estimates are very different from those of Conteh et al. in 2021 (121.5 USD), for whom the cost was estimated in relation to cases averted [8, 9]. These are the only two systematic reviews found in the literature on cost-effectiveness of malaria control interventions. The differences between our findings and those of Conteh et al. could, in part, be explained by the different outcomes, denominators, and methods applied. Conteh used the US Inflation Calculator, where as we used 3% to convert as consumer price index for measures of inflation [39].

V. LIMITATIONS

Synthesis and direct comparison of all identified studies was not possible because the units of measurement of health outcomes, and thus of cost-effectiveness and incremental cost-effectiveness, were not comparable in all publications. In addition, to compare studies, we used the mean and median cost per dose of SMC, although in some cases this was not the best option. For the comparison, we referred to the WHO recommendations for SMC to make the conversion (three doses for each of the four months of treatment), although some countries used their own protocols.

VI. CONCLUSION

The results of our systematic review show that investments in the implementation of SMC as a malaria control strategy are cost-effective. In addition, the number of studies identified and analysed in this review is relatively high to consider that there is sufficient evidence to demonstrate the effectiveness of SMC. It appears from this study that very few studies have been conducted in the highly endemic countries of the WHO African Region, which are the recipients of significant financial resources for the fight against this disease. Although SMC is not recommended in all endemic countries, of the five African countries that account for more than half of the world's malaria cases, only two (a multicentre study including Nigeria and another including Mozambique) were included.

This review highlighted the limited evidence linking health outcomes to financial or economic costs. Just as Evan et al. highlighted the need to re-evaluate strategies to achieve the Sustainable Development Goals, it is time for governments and their technical and financial partners to put in place strategies that can lead to more economic evaluation [40]. This will address the challenge of funding caps identified by the WHO in its 2022 report and will help improve the effectiveness of SMC in particular, and malaria control interventions in general. A more comprehensive set of studies on SMC could help provide greater justification for resource allocation, and for the choice and adjustment of SMC strategy.

- *Author contributions*

YT, HM, MM, JOY, SD and PW conceived, designed and conducted the study. YT, RK, HM and M.M. screened and reviewed the full text review of relevant articles. YT, HM, MM, OS, MT and JOY analysed the extracted data and wrote the manuscript. KK, JOY, HS and SD supervised the study. All authors discussed, commented and approved the final results.

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- *Conflict of interest*

None to declare.

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