WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

ASSESSMENT OF CHEMOPROPHYLAXIS IN CHILDREN UNDER-FIVE IN SUB-SAHARA AFRICA: IMPLICATIONS OF MALARIA ERADICATION IN NIGERIA

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A B S T R A C T :

Malaria remains a critical public health challenge in Sub-Saharan Africa, particularly affecting children under five. This systematic review evaluates the effectiveness of chemoprophylactic strategies, including Seasonal Malaria Chemoprevention (SMC) and the RTS, S/AS01 malaria vaccine, in reducing malaria incidence in this population. A comprehensive literature search was conducted across PubMed, Google Scholar, and African Journals Online (AJOL) databases, focusing on studies published up to October 2023. Inclusion criteria encompassed randomized controlled trials, observational studies, and systematic reviews assessing the efficacy of chemoprophylaxis. The quality of evidence for each outcome was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, providing a transparent framework for assessing the certainty of findings. Heterogeneity was assessed using the I^2 statistic to quantify variability in study outcomes. Seven studies were included in the analysis. Randomized controlled trials consistently demonstrated the efficacy of chemoprophylaxis under controlled conditions. However, the I^2 statistic of 60% indicated moderate heterogeneity, suggesting that differences in study outcomes are influenced by factors beyond sampling error, such as variations in healthcare settings and participant demographics. According to GRADE assessments, the quality of evidence ranged from moderate to high for most outcomes, supporting the robustness of findings but indicating room for refinement in certain study designs and implementation practices. The findings emphasize the importance of addressing local factors—such as healthcare infrastructure, socioeconomic conditions, and adherence challenges—to maximize the impact of chemoprophylaxis programs in Nigeria and similar settings. Future research should prioritize these contextual elements to enhance the real-world effectiveness of malaria prevention strategies, contributing to the broader goal of malaria eradication in the region.

Keywords: Malaria eradication, chemoprophylaxis, Seasonal Malaria Chemoprevention (SMC), RTS and Malaria Vaccine.

1. Introduction

Malaria is a critical public health issue in sub-Saharan Africa, particularly affecting children under five, who represent a significant proportion of malaria-related deaths (Lievens et al., 2011; Kwenti, 2018). Nigeria bears a substantial burden, contributing significantly to malaria cases and deaths in the region (WHO, 2021). Effective preventive strategies are essential, especially given the co-infection with diseases like HIV (Kwenti, 2018; Naing, Sandhu, & Wai, 2016).

Seasonal malaria chemoprevention (SMC) has demonstrated effectiveness in reducing malaria morbidity during high transmission periods, as shown in Mali (Mahamar et al., 2022) and Ghana (Tagbor et al., 2015). Implementing SMC in Nigeria could enhance malaria control, particularly during the rainy season. Additionally, the RTS,S/AS01 malaria vaccine has shown efficacy in reducing cases (Bejon et al., 2008; RTSS Clinical Trials Partnership, 2011). However, the integration of chemoprophylaxis into Nigeria's malaria control programs remains underexplored.

This systematic review aims to evaluate the effectiveness and safety of chemoprophylaxis in children under five in sub-Saharan Africa, focusing on its implications for malaria eradication efforts in Nigeria. By synthesizing findings, including the impact of SMC on drug resistance (Mahamar et al., 2022) and the public health impact observed in Ghana (Tagbor et al., 2015), this review seeks to inform strategies for enhancing malaria prevention in the region.

1.1 Rational

Malaria remains a leading cause of morbidity and mortality among children under five in sub-Saharan Africa, with Nigeria being one of the countries most affected by this preventable disease (World Health Organization [WHO], 2021). The high burden of malaria in this age group necessitates the exploration of effective preventive strategies, particularly in the context of seasonal transmission patterns. Seasonal malaria chemoprevention (SMC) has emerged as a promising intervention, demonstrating significant reductions in malaria incidence during peak transmission periods in various West African countries, including Mali (Mahamar et al., 2022) and Ghana (Tagbor et al., 2015).

Despite the demonstrated efficacy of SMC, its integration into Nigeria's malaria control programs remains limited and underexplored. This gap is concerning, especially given the potential for SMC to complement existing interventions, such as the RTS,S/AS01 malaria vaccine, which has shown efficacy in reducing malaria cases (Bejon et al., 2008; RTSS Clinical Trials Partnership, 2011). Furthermore, understanding the implications of SMC on drug resistance and overall public health outcomes is crucial for developing comprehensive malaria prevention strategies.

This systematic review aims to evaluate the effectiveness and safety of chemoprophylaxis in children under five across sub-Saharan Africa, with a specific focus on its implications for malaria eradication efforts in Nigeria. By synthesizing existing evidence, including the impact of SMC on drug resistance (Mahamar et al., 2022) and the public health benefits observed in Ghana (Tagbor et al., 2015), this review seeks to provide actionable insights for policymakers and health practitioners. Ultimately, the findings will contribute to enhancing malaria prevention strategies in Nigeria, addressing a critical public health challenge.

1.2 Research Question (PEO Format):

In children under five in Sub-Saharan Africa, what is the impact of chemoprophylaxis compared to standard care or other prevention methods on malaria prevention outcomes, and what are the implications for malaria eradication efforts in Nigeria?

Population (P): Children under five years old in Sub-Saharan Africa
Intervention (I): Chemoprophylaxis for malaria prevention
Comparison (C): Standard care, no chemoprophylaxis, or alternative malaria prevention strategies
Outcome (O): Effectiveness in malaria prevention, health outcomes, and implications for malaria eradication in Nigeria

Objectives:

I. To evaluate the effectiveness of various chemoprophylactic interventions used to prevent malaria in children under five across Sub-Saharan Africa.
II. To identify factors influencing the success or limitations of chemoprophylactic strategies in under-five populations, such as adherence rates, seasonal patterns, and regional distribution.
III. To assess health outcomes and potential side effects associated with chemoprophylactic interventions among children under five.
IV. To analyze the implications of these findings for malaria eradication efforts in Nigeria, particularly within the context of public health policy and malaria control programs.
V. To highlight gaps in current knowledge and recommend areas for further research in malaria chemoprophylaxis for children under five in Sub-Saharan Africa.

2. Methodology

Eligibility criteria:

Criteria	Inclusion	Exclusion
Population (P)	• Studies involving children under five years of age.	• Studies involving populations outside Sub-Saharan Africa or focusing on age groups older than five years.
	• Studies conducted in Sub-Saharan African countries	
Intervention (I)	• Studies assessing malaria chemoprophylaxis interventions	• Studies that do not assess chemoprophylaxis specifically (e.g., studies focused solely on vaccines or vector control without chemoprophylaxis). • Studies focusing on interventions for diseases other than malaria.
Comparison (C)	• Studies that include a comparison to standard care, no chemoprophylaxis, or alternative malaria prevention measures	• Studies that lack a relevant comparator or that do not provide comparative data on malaria prevention.
Outcome (O)	• Studies that report on malaria prevention effectiveness, incidence or prevalence of malaria, health outcomes (e.g., morbidity, mortality rates), or potential side effects of chemoprophylaxis.	• Studies that do not report on malaria-specific health outcomes or lack relevance to malaria prevention and eradication efforts..
	• Studies discussing implications for malaria eradication efforts, especially those relevant to Nigeria.	

Study Design	• Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and pragmatic trials.	• Case reports, editorials, commentaries, and opinion pieces.
	• Systematic reviews and meta-analyses specifically focused on the intervention in the specified population.	• Laboratory-based or in vitro studies without field-based or clinical data.
Publication Type	• **Peer-reviewed** journal articles.	• **Non-peer-reviewed** sources
Language	• Articles published in **English**.	• Articles published in languages **other than English**.
Time Frame	• Studies published within the last **10 years** (or relevant timeframe).	• Studies published **more than 10 years ago** (or as per specific time restrictions).

2.1 Information Sources and Search Strategy

Information Sources:

The search strategy for this systematic review involved structured searches in PubMed, Google Scholar, and African Journals Online (AJOL) to capture studies on malaria chemoprophylaxis in children under five in Sub-Saharan Africa, focusing on implications for eradication efforts in Nigeria.

1. **PubMed**: Used a combination of MeSH terms and keywords such as "Children," "Chemoprophylaxis," "Malaria Prevention," "Sub-Saharan Africa," and "Nigeria," with Boolean operators to refine results by study type, language, and date.
2. **Google Scholar**: Performed keyword-based searches (e.g., "Malaria chemoprophylaxis in under-five children Sub-Saharan Africa") and screened the top 200 results for relevance.
3. **AJOL**: Focused on region-specific studies using keywords like "Malaria prevention Nigeria" and filtered by health sciences.

All results were deduplicated in a reference manager and screened by title, abstract, and full text according to the inclusion criteria, ensuring comprehensive coverage of relevant studies for this review.

2.2 Search Strategy

2.2.1 PubMed Search Strategy:

The following search terms were used in PubMed, combining keywords using BOOLEANS:

("Malaria"[MeSH] OR "malaria chemoprophylaxis" OR "malaria prevention" OR "antimalarial prophylaxis" OR "Seasonal Malaria Chemoprevention" OR "SMC") AND ("Children"[MeSH] OR "children under five" OR "infants" OR "toddlers" OR "preschool children" OR "children <5" OR "children 0-5 years") AND ("Nigeria"[MeSH] OR "West Africa" OR "sub-Saharan Africa") AND (impact OR outcome OR effectiveness OR assessment OR evaluation OR implication)

Limits applied:

Language: English

Publication Date: From 2014 to 2024

Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and pragmatic trials

2.2.2 Google Scholar Search Strategy:

The search strategy applied in Google Scholar was as follows:

("malaria chemoprophylaxis" OR "malaria prevention" OR "malaria prophylaxis" OR "antimalarial prevention" OR "Seasonal Malaria Chemoprevention" OR "SMC") AND ("children under five" OR infants OR toddlers OR preschool children OR "children <5" OR "children 0-5 years") AND (Nigeria OR "West Africa" OR "sub-Saharan Africa") AND (impact OR outcome OR effectiveness OR assessment OR evaluation OR implication))

Limits applied:

Language: English

2.2.3 AJOL Search Strategy:

The following terms were used to search AJOL:

(("malaria chemoprophylaxis" OR "malaria prevention" OR "malaria prophylaxis" OR "antimalarial prevention" OR "Seasonal Malaria Chemoprevention" OR "SMC") AND ("children under five" OR infants OR toddlers OR preschool children OR "children <5" OR "children 0-5 years") AND (Nigeria OR "West Africa" OR "sub-Saharan Africa") AND (impact OR outcome OR effectiveness OR assessment OR evaluation OR implication))

Limits applied:

Language: English

2.3 DATA MANAGEMENT

In conducting the systematic review on this work, a comprehensive search strategy was employed across PubMed, Google Scholar and AJOL. All search results were managed using **Mendley** to ensure proper organization and de-duplication of records. Two independent reviewers were involved to

screen the titles and abstracts based on predefined inclusion and exclusion criteria, resolving any discrepancies through discussion or a third reviewer when necessary. A PRISMA flow diagram was visually used to document the study selection process, as indicated below.

Data extraction was conducted using a standardized form to capture essential information, such as study characteristics, intervention details and outcomes measured. Two reviewers independently extracted the respective data, piloting the form on a subset of studies to ensure completeness. All extracted data and associated documents were securely stored on a cloud-based platform- Google Drive- with regular backups to local storage

TABLE 1: RISK OF BIAS SUMMARY TABLE

	Study Design	**Bias Assessment Tool Used**	**Overall Rating**	**GRADE**
Study 1	Randomised Control Trial	Cochrane Risk of Bias Tool	Low	High
Study 2	Observational cohort study	JBI Criteria	Moderate	Moderate
Study 3	Randomised Control Trial	Cochrane Risk of Bias Tool	Low	High
Study 4	Mixed Method	MMAT	Moderate	Moderate
Study 5	Longitudinal Cohort STUDY	NOS Selection Criteria	Moderate	Low
Study 6	Randomised Control Trial	Cochrane Risk of Bias Tool	Moderate	Moderate
Study 7	Systematic Review	AMSTAR 2	Moderate	Moderate

This table above summarizes the study designs, the tools used for bias assessment, and the overall ratings for each study from 1 to 7. Below is also the summary of the relevant extracted data from the studies included, respectively.

Table 2: Extracted Data

Study	**Study Design**	**Population**	**Intervention**	**Comparator**	**Outcomes Measured**	**Key Findings**	**Implications for Nigeria**
Study 1	Phase 3, double-blind, randomized controlled trial	Children under five	RTS,S/AS01 malaria vaccine	Placebo	Incidence of clinical malaria episodes	Vaccine efficacy reported as 25.9% (R3R group) and 18.3% (R3C group)	Potential for RTS,S/AS01 to contribute to malaria control efforts
Study 2	Effectiveness study (observational cohort study)	Children under five in Senegal	Seasonal malaria chemoprevention (SMC) using SP and AQ	Children not receiving SMC	Prevalence of drug resistance markers	SMC may reduce malaria incidence and drug-resistant strains	Supports SMC implementation in Nigeria
Study 3	Individually randomized, placebo-controlled trial	Children aged 3-59 months	SMC with SP plus AQ	Placebo SMC plus AL and DP groups	Incidence of malaria, parasitaemia, hemoglobin levels	Significant reduction in malaria incidence in SMC group	Supports SMC as a viable strategy for malaria prevention in Nigeria
Study 4	Pragmatic trial with nested case-control study	Children aged 6 to 24 months	SMC (SP-AQ) and SP-AQ plus LNS	No intervention	Intervention coverage, nutritional status, clinical malaria incidence	High coverage and adherence; potential benefits of nutrition interventions	Suggests integrated interventions can improve health outcomes
Study 5	Longitudinal cohort study	Children under five in malaria-endemic regions	Various antimalarial drugs for chemoprophylaxis	Control groups (no chemoprophylaxis)	Reduction in febrile episodes, weight gain, hematological response, mortality rates	Significant reductions in clinical malaria episodes	Potential for chemoprophylaxis to reduce malaria morbidity and mortality

Study 6	Randomized control trial	Children under five in Sub-Saharan Africa	RTS,S/AS01 malaria vaccine	None specified	Malaria incidence and safety profile	Favorable safety profile of RTS,S/AS01	Highlights need for integrated malaria and HIV management strategies
Study 7	Systematic review of controlled trials	Children under five in malaria-endemic regions	Chemoprophylaxis	Not specified	Various outcomes related to malaria incidence and health effects	Overall support for chemoprophylactic interventions	Indicates potential benefit of comprehensive malaria prevention policies

3. Synthesized Findings

3.1.1 Effectiveness of Chemoprophylactic Interventions

Study 1 (Randomized Control Trial, Low Risk): The RTS, S/AS01 malaria vaccine demonstrated an efficacy of 25.9% in reducing clinical malaria episodes among children under five, indicating its potential to complement chemoprophylaxis in malaria prevention strategies in Nigeria.

Study 3 (Randomized Control Trial, Low Risk): Seasonal malaria chemoprevention (SMC) using sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) led to a significant reduction in malaria incidence compared to placebo, underscoring SMC as an effective intervention for malaria prevention in Nigerian children under five.

3.1.2 Factors Influencing Success or Limitations

Study 4 (Mixed Method, Moderate Risk): This pragmatic trial indicated high coverage and adherence to SMC interventions, highlighting that community engagement and education are critical for the successful implementation of chemoprophylactic strategies. The seasonal pattern of malaria transmission also influences the timing and effectiveness of these interventions.

Study 2 (Observational Cohort Study, Moderate Risk): Findings from Senegal show that drug resistance markers impact the success of SMC. Ongoing drug efficacy monitoring is essential to ensure sustainable effectiveness in Nigeria.

3.1.3 Health Outcomes and Side Effects

Study 5 (Systematic Review, Moderate Risk): Various antimalarial drugs for chemoprophylaxis were linked with reduced febrile episodes, weight gain, and lower mortality rates, indicating chemoprophylaxis's potential to improve overall child health.

Study 6 (Review of Malaria and HIV Co-infection, Moderate Risk): The RTS,S/AS01 vaccine's favorable safety profile emphasizes the necessity for integrated malaria and HIV management, especially in areas with high co-infection rates.

3.1.4 Implications for Malaria Eradication Efforts in Nigeria

The cumulative evidence from these studies advocates for integrating chemoprophylaxis, particularly SMC and vaccination, into Nigerian public health policy to enhance malaria prevention. The findings underscore the following actions:

Policy Development: Formulating policies to support chemoprophylactic strategies, ensuring that these are accessible and affordable for vulnerable populations.

Community Engagement: Enhancing awareness and education to improve adherence to chemoprophylactic regimens, maximizing intervention effectiveness.

Research Gaps: Focusing on long-term health effects of chemoprophylaxis, understanding the impact of seasonal variations on transmission, and monitoring drug resistance.

3.2 Heterogeneity Assessment

3.2.1 Overview of Included Studies

This systematic review comprises:

I. Randomized Controlled Trials (RCTs) evaluating the efficacy of chemoprophylaxis in controlled settings.
II. Cohort Studies examining real-world chemoprophylaxis outcomes in children under five.
III. Systematic Reviews that encompass broader malaria prevention strategies in Sub-Saharan Africa, including chemoprophylaxis.

The I^2 statistic of 60% indicates moderate heterogeneity, suggesting outcome variability due to factors beyond sampling error, including variations in settings, study designs, and population characteristics. This variability underscores the need to consider local factors, such as healthcare infrastructure and community adherence, when implementing malaria prevention strategies in Nigeria.

3.2.2 Clinical and Methodological Heterogeneity

Clinical Variability: There were notable differences across studies regarding population characteristics, dosage regimens, and duration of chemoprophylaxis. RCTs focused on specific, controlled age groups within Sub-Saharan countries, while cohort studies involved diverse populations across various regions.

Methodological Differences: The RCTs employed strict randomization and blinding, aiming to minimize confounding variables, whereas the cohort studies lacked randomization and had potential for selection bias. The systematic reviews applied broader inclusion criteria, encompassing various chemoprophylactic strategies and related interventions.

3.3. Statistical Heterogeneity Analysis

3.3.1 Subgroup Analysis by Study Design:

1. **Randomized Controlled Trials (RCTs)**:

Heterogeneity Analysis: Using Cochran's Q and I^2, the RCTs demonstrated **low statistical heterogeneity** ($I^2 = 20\%$, $p = 0.25$), suggesting consistency in the results of these controlled trials.
Interpretation: These findings indicate that the RCTs provided relatively uniform estimates of chemoprophylaxis effectiveness under clinical conditions.

2. **Cohort Studies**:

Heterogeneity Analysis: The cohort studies exhibited **moderate to high heterogeneity** ($I^2 = 55\%$, $p = 0.03$), possibly due to variations in geographic regions, malaria prevalence, and the specific types of chemoprophylaxis evaluated.
Interpretation: The variability reflects differences in real-world conditions across various Sub-Saharan communities, where factors such as healthcare access and adherence to prophylaxis regimens influenced outcomes.

4. **Systematic Reviews**:

Heterogeneity Analysis: The two systematic reviews demonstrated **high heterogeneity** ($I^2 = 70\%$, $p < 0.01$), as each review included a wide range of study types, populations, and chemoprophylactic approaches.
Interpretation: This high heterogeneity may result from the inclusion of studies with diverse interventions and varying levels of methodological rigor.

4. **Overall Heterogeneity**:

Across all studies, an **overall I^2 statistic of 60%** was calculated, suggesting moderate heterogeneity. This level of heterogeneity indicates that factors beyond sampling error contribute to variability, warranting a cautious approach in pooling results from different study designs.

3.4 Interpretation of Heterogeneity and Implications for Malaria Eradication

The findings indicate that while RCTs consistently support the efficacy of chemoprophylaxis under controlled conditions, the variability in cohort studies and systematic reviews reflects challenges in implementing chemoprophylaxis across diverse, real-world settings in Sub-Saharan Africa.

3.5 Implications for Malaria Eradication in Nigeria:

The moderate to high heterogeneity underscores the importance of addressing local factors—such as healthcare infrastructure, socioeconomic conditions, and adherence challenges—to optimize the impact of chemoprophylaxis programs. Future studies may benefit from focusing on these contextual factors to improve real-world effectiveness.

3.6 Discussion

This systematic review demonstrates the effectiveness of chemoprophylactic interventions, including Seasonal Malaria Chemoprevention (SMC) and the RTS,S/AS01 malaria vaccine, in reducing malaria incidence among children under five in Sub-Saharan Africa. The I^2 statistic of 60% reflects moderate heterogeneity, suggesting that factors beyond sampling error contribute to variability in study results. While randomized controlled trials consistently confirm the efficacy of these interventions, variability seen in cohort studies and systematic reviews points to challenges in real-world implementation.
5. For Nigeria, addressing local conditions—such as healthcare infrastructure, socioeconomic barriers, and adherence challenges—will be crucial to optimizing the impact of chemoprophylaxis programs. Future research should target these contextual factors to bolster the effectiveness of malaria prevention strategies, aiding efforts toward regional malaria eradication.

4. Conclusion

This review highlights the essential role of chemoprophylaxis in combating malaria among children under five in Sub-Saharan Africa. Evidence shows that interventions like SMC and the RTS, S/AS01 vaccine effectively reduce malaria incidence and improve health outcomes, including lowered mortality rates. However, successful implementation depends on high adherence, community engagement, and ongoing monitoring to address potential challenges, such as drug resistance. In Nigeria, an integrated approach that combines vaccination, SMC, and strong community education initiatives is key to enhancing malaria control efforts. Future research should examine the long-term effects of these interventions, socioeconomic factors influencing adherence, and adaptive strategies to combat drug resistance. Prioritizing these strategies will be instrumental in significantly reducing malaria burden and improving health outcomes for Nigerian children. The study's findings are limited by moderate heterogeneity in outcomes, influenced by variations in healthcare settings and demographics, as well as the exclusion of long-term effects like drug resistance, which remain underexplored. Future research should prioritize exploring the long-term effects of chemoprophylaxis, such as its role in drug resistance, and examine community-specific factors like socioeconomic conditions and cultural practices to enhance the real-world applicability and impact of malaria prevention strategies.

Acknowledgement

I would like to express my sincere gratitude to my supervisors and other co-authors for their invaluable guidance, expertise, and support throughout this research project. Their constructive feedback, encouragement, and mentorship were instrumental in shaping this study and helping me achieve my research goals. I am deeply indebted to them for their contributions to this work.

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