Economics and Statistics Research Journal (ESRJ)
Volume.16, Number 1; January-2025;
ISSN: 2836-8398 | Impact Factor: 9.97
https://zapjournals.com/Journals/index.php/esrj
Published By: Zendo Academic Publishing

META-ANALYSIS ON THE RISK OF MALARIA AND RESISTANCE TO ARTEMISININ-BASED COMBINATION THERAPIES (ACTS)

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Article Info

Keywords: Malaria, Artemisinin-Based Combination Therapies, drug resistance, meta-analysis, Plasmodium falciparum, public health strategies.

DOI

10.5281/zenodo.14719035

Abstract

Global efforts to control and eradicate malaria are seriously threatened by the rising incidence of drug resistance among malaria parasites, especially resistance to Artemisinin-Based Combination Therapies (ACTs). With an emphasis on clarifying the patterns, trends, and treatment strategy implications, this dissertation conducts a thorough meta-analysis to assess the risk variables for malaria and ACT resistance. To offer solid statistical insights into the occurrence of resistance and its correlation with other factors, such as geographic location, treatment methods, and parasite genetics, this study synthesizes data from the body of current literature. This research adopts a systematic approach, using a random-effects meta-analysis framework to aggregate findings from peer-reviewed studies conducted between 2002 and 2024. Key outcomes include the pooled prevalence of ACT resistance and the estimated effect sizes of contributing risk factors, such as treatment delays, monotherapy use, and suboptimal adherence to ACT regimens. The analysis revealed a significant increase in malaria risk in populations with reported ACT resistance, with a mean effect size of 1.432 (95% CI: 1.193–1.720, $P < 0.001$). Substantial heterogeneity was observed among the studies, as indicated by an I^2 value of 90%." The results indicate significant regional variation in resistance patterns, with Southeast Asia and parts of Africa showing higher prevalence rates linked to the presence of Plasmodium falciparum mutations, particularly in the kelch13 gene. The results emphasize the urgency of targeted interventions—like better monitoring systems, better diagnostic tools, and compliance with combination therapy guidelines—are needed. To properly modify treatment plans, this study highlights the cruciality of combining genetic surveillance with clinical and epidemiological data. To reduce the likelihood of ACT resistance and preserve the effectiveness of frontline malaria treatments, this dissertation offers researchers, policymakers, and medical professionals' practical' insights. Through its rigorous methodological approach and comprehensive analysis, this study contributes to the growing body of evidence on the challenges posed by malaria drug resistance and underscores the urgency of collaborative global efforts to address this public health crisis.

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INTRODUCTION

Malaria continues to pose a serious threat to global health, particularly in areas with poor infrastructure and resource availability. Millions of people worldwide suffer from malaria, a disease caused by Plasmodium parasites spread by the bite of an infected Anopheles mosquito. Sub-Saharan Africa bears a disproportionately greater burden. Even after decades of concentrated efforts to prevent and eradicate malaria, the disease still has a significant negative impact on socioeconomic advancement and public health.

The widespread implementation of Artemisinin-based Combination Therapies (ACTs) has been one of the most successful strategies for reducing malaria cases and fatalities over the past 2 decades. Artemisinin and its derivatives, derived from the Artemisia annua plant, act rapidly to clear the malaria parasite from the bloodstream, and when combined with partner drugs, they reduce the risk of resistance developing against any one medication (Dondorp et al., 2010; White, 2008). ACTs are currently recommended by the WHO as the first-line treatment for uncomplicated Plasmodium falciparum malaria, the deadliest malaria species (WHO, 2015). The use of ACTs has led to significant reductions in the incidence of malaria, especially in high-burden countries (White et al., 2014).

However, the efficacy of ACTs is currently threatened by the emergence of artemisinin resistance. First detected in Cambodia along the Thailand–Cambodia border, artemisinin resistance has since spread throughout the Greater Mekong Subregion and has become a critical public health concern (Ashley et al., 2014). Studies have shown that artemisinin resistance is characterized by delayed parasite clearance, which is often observed as prolonged fever and longer treatment times in patients (Ashley et al., 2014; Noedl et al., 2008). The situation is further complicated by the emergence of partner drug resistance, which has led to cases of treatment failure, placing even greater pressure on healthcare systems in malaria-endemic regions (Dondorp et al., 2010).

The mechanisms underlying artemisinin resistance are complex and involve mutations in the Plasmodium falciparum Kelch13 (pfk13) gene, which have been associated with reduced sensitivity to artemisinin in clinical settings (Ariey et al., 2014; Straimer et al., 2015). The spread of these mutations has raised concerns regarding the sustainability of ACTs in their current form. Without effective anti-malarial drugs, malaria control and elimination goals may be unattainable, because drug resistance can lead to increased treatment failure rates, prolonged illness, higher transmission rates, and a rise in severe cases and deaths (Dondorp et al., 2009; Fairhurst and Dondorp, 2016).

Given the rapid evolution of drug resistance, there is an urgent need to systematically assess the prevalence and impact of resistance patterns in malaria treatment. A meta-analysis can help synthesize findings from several studies to better understand global trends in artemisinin resistance, identify regions where resistance is increasing, and evaluate the effectiveness of different ACT regimens. Such an analysis would provide valuable insights to inform policy decisions and guide future research on drug resistance (Higgins & Green, 2011).

This dissertation conducts a comprehensive meta-analysis on the risk of malaria and drug resistance in patients taking ACTs. By consolidating existing research, this study aims to provide a clear understanding of the prevalence, distribution, and impact of drug resistance in ACTs, highlighting the area's most at risk, and suggesting strategies to combat resistance. As the world edges approach malaria elimination, maintaining the effectiveness of ACTs is essential. Addressing the growing threat of drug resistance will require coordinated global efforts, including the development of new anti-malarial agents, enhanced surveillance systems, and updated treatment protocols that can adapt to changing resistance patterns (White et al., 2014; WHO, 2020).

Malaria, caused by Plasmodium parasites transmitted through infected Anopheles mosquito bites, remains a major global health threat, particularly in tropical and subtropical regions. Despite progress in malaria control, the disease still leads to substantial morbidity and mortality, especially in sub-Saharan Africa, where over 90% of

cases and deaths occur, disproportionately affecting young children and pregnant women. Malaria has severe socioeconomic impacts and contributes to poverty, malnutrition, and impaired development in affected areas.

Research Design

The research design chosen for this study is a meta-analysis, that systematically reviews and synthesizes the results of multiple empirical studies to address the research question on the risk of malaria and resistance to ACTs in malaria parasites. Meta-analysis allows for the quantitative integration of findings across different studies, providing a comprehensive overview of the evidence, identifying patterns, and establishing the strength of associations. This study uses a random-effects model to account for variations among studies and to provide a more generalized estimate of the effects of drug resistance on malaria outcomes.

Meta-analyses are ideal for this purpose because they aggregate data from various studies to increase statistical power and resolve uncertainties that individual studies may not address. The design follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a rigorous and transparent review process (Moher et al., 2009).

Population, Sample, and Sampling Techniques

The study population for this meta-analysis consisted of peer-reviewed studies that assessed malaria resistance to artemisinin-based combination therapy in various regions, particularly Southeast Asia and sub-Saharan Africa. The purposive sampling technique was used, focusing on studies published between 2002 and 2024 that met specific inclusion criteria:

i. Plasmodium falciparum resistance to ACT
ii. Clinical trials or observational studies with relevant data on resistance mutations (e.g., PfK13 mutations),
iii. Studies with sufficient data for effect size estimation, such as sample size and, risk

Ratio, odd ratio, mean, standard deviation, confidence intervals and treatment outcomes.

The inclusion of diverse geographical areas and population types ensures broad applicability of the results. The sample size for this meta-analysis will be determined by the number of relevant studies identified through the systematic search process. Each study's key data are extracted for the synthesis.

Method of Data Collection

Using a standardized data extraction form, pertinent information was extracted from eligible papers for the meta-analysis. Study parameters (e.g., author, publication year), study methodology, geographic location, parasite species, treatment resistance markers, and prevalence estimates are important factors of interest. To reduce bias, two reviewers will extract data independently; if any differences are noted, they will be discussed.

Data Analysis Technique

The data analysis involved synthesizing the extracted data using meta-analysis techniques. The primary outcome of interest was the effect size e.g OR, which quantifies the relationship between drug resistance and malaria outcomes. After extracting data from various studies, they are synthesized using statistical Softwares like Comprehensive Meta-Analysis (CMA), STATA, and R.

Statistical Techniques: Meta-analytical techniques, such as forest plots, heterogeneity tests, and subgroup analyses, will be used to assess the variability in resistance patterns across regions. Cochran's Q and the I^2 statistic will be employed to quantify heterogeneity among the included studies (Higgins et al., 2021). A funnel plot will be used to visually inspect publication bias, and Egger' s test will statistically assess the bias in the included studies.

Random-effects Model: This model accounts for heterogeneity between studies and provides more generalizable results (Borenstein et al., 2009).

Heterogeneity Analysis: Using the I^2 statistic to quantify the percentage of total variation across studies due to heterogeneity rather than chance (Higgins et al., 2003).

Publication Bias**:** Assessed using funnel plots and Egger's test (Egger et al., 1997).

Prevalence estimates of drug resistance will be pooled using random-effects or fixed-effects meta-analysis models, depending on the heterogeneity of the included studies (Higgins et al., 2009).

Effect Size Estimation: The effect size was calculated to determine the magnitude of the ACT resistance risk across different studies. For this meta-analysis odds ratios (ORs) will be used as the primary effect size metrics for binary outcomes (such as treatment failure vs. success). The following formula is used for effect size estimation:

The pooled prevalence of ACT resistance in malaria parasites was estimated using random-effects meta-analysis models. The random-effects model accounts for both within-study and between-study variability, providing more conservative estimates of effect sizes than fixed-effects models (Borenstein et al., 2010). The DerSimonian-Laird method was used to calculate the overall effect size, along with 95% confidence intervals.

Random-Effects Meta-Analysis

Due to the anticipated heterogeneity among the included studies, a random-effects model was applied to estimate the pooled effect sizes. The random effects model assumes that the true effect size varies from one study to another due to differences in population characteristics, geographical regions, and methods used in the studies (Borenstein et al., 2021). This model provides a more conservative and generalizable estimate of the overall effect size.

Naturally, in a real meta-analysis, we begin with the observed effects and attempt to estimate the population impact, as opposed to starting with the population effect and making projections about the observed effects. We computed a weighted mean, where the weight allocated to each research equals the inverse of that study' s variance, to produce the most accurate estimate of the overall mean (to minimize the variance).

To compute the variance of a study under the random-effects model, we must know both the within-study variance and τ^2. The random-effects model assumes that the true effect size varies between studies because of random factors. The two sources of variance are considered:

Within-study variance (σ^2_{within}): The variation in effect sizes is due to sampling error.

Between-study variance (τ^2): The variation due to true differences among study populations, methodologies, etc.

Mathematical Steps:

i) **Effect Sizes** ($\hat{\theta}_i$):

Each study (*i*) has an observed effect size $\hat{\theta}_i$ (e.g., odds ratio, risk ratio, mean difference).

ii) **Within-Study Variance** (σ_i^2):

The within-study variance is the variance of the effect size in each study, typically derived from the standard error (SE_i) of the effect size as follows:

$$\sigma_i^2 = SE_i^2 \quad (3.1)$$

iii) **Estimating the Tau-squared**

The parameter τ^2 (tau-squared) is the between-study variance (the variance of the effect size parameters across the population of studies). In other words, if we somehow knew the true effect size for each study and, computed the variance of these effect sizes (across an infinite number of studies), this variance would be τ^2.

Between-Study Variance (τ^2): To calculate the between-study variance, τ^2 we use the DerSimonian and Laird estimator:

$$T^2 = \frac{Q - df}{C} \quad (3.2)$$

$$= \tau^2 = \frac{Q-(k-1)}{\sum_{i=1}^{k} w_i - \frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}} \quad (3.3)$$

Where;

$$Q = \sum_{i=1}^{k} w_i \left(\hat{\theta}_i - \hat{\theta}_w\right)^2 \quad (3.4)$$

df = k - 1,

$$\hat{\theta}_w = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i} \quad (3.5)$$

Here, k is the number of studies, and

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}. \quad (3.6)$$

iv) **Heterogeneity (*H*):** The Q-statistic exceeds the degrees of freedom (number of studies Minus one, *df = k-1*), it indicates heterogeneity.

v) **Weight for Random Effects:**

n the random-effects model, the weight w_i for each study is the inverse of the total variance as follows:

σ_i^2 (within-study variance and between-study variance τ^2,):

$$w_i^* = \frac{1}{\sigma_i^2 + \tau^2} \quad (3.7)$$

vi) **Pooled Effect Size:**

The pooled estimate of the effect size, $\hat{\theta}_p$, is a weighted average of individual effect sizes as follows:

$$\hat{\theta}_p = \frac{\sum_{i=1}^{k} w_i^* \hat{\theta}_i}{\sum_{i=1}^{k} w_i^*} \quad (3.8)$$

vii) **Confidence Interval for Pooled Effect Size:**

The 95% confidence interval (CI) of the pooled effect size was calculated as follows:

$$CI = \hat{\theta}_p \pm Z_{\alpha/2} \cdot SE_p \quad (3.9)$$

$$SE_p = \sqrt{\frac{1}{\sum_{i=1}^{k} w_i^*}} \quad (3.10)$$

viii) **Forest Plot**

A forest plot is a graphical representation of individual study effect sizes and the overall pooled effect. The plot shows the confidence intervals (CIs) for each study's effect size, as well as the pooled estimate.

Individual Study Effect Size: The individual study effect size is $\hat{\theta}_i$, and its variance is σ_i^2, giving the 95% CI for each study:

$$CI_i = \hat{\theta}_i \pm Z_{\alpha/2} \cdot SE_i \quad (3.11)$$

Pooled Effect Size: The pooled effect size $\hat{\theta}_p$ is calculated as explained in the above random-effects model.

Visual Interpretation: The center of each square in the forest plot represents the study's point estimate $(\hat{\theta}_i)$. The horizontal lines represent the 95% confidence interval (CI) for each study, indicating the precision of the estimate.

The diamond at the bottom represents the pooled effect size $(\hat{\theta}_p)$, with the width of the diamond reflects the pooled CI.

ix) **Assessment of Heterogeneity:**

Heterogeneity among studies was assessed using the I-squared (I^2) statistic, which quantifies the proportion of total variation across studies due to heterogeneity rather than chance. I^2 values > 50% indicate substantial heterogeneity (Higgins et al., 2003). Subgroup analyses were conducted to explore potential sources of heterogeneity, such as study location, study design, and drug resistance assessment methods.

x) **Subgroup Analyses:**

Subgroup analyses were performed to investigate potential sources of heterogeneity and to explore variations in drug resistance prevalence across different subgroups of studies. Subgroup analyses were conducted based on factors such as study location (e.g., geographical region, endemicity), study design (e.g., cross-sectional studies, longitudinal studies), and drug resistance assessment methods (e.g., molecular methods, phenotypic methods).

Subgroup analysis divides studies into subgroups based on specific characteristics (e.g., age, gender, study design) and calculates the effect size within each subgroup.
Separate Effect Sizes for Subgroups: For each subgroup, calculate the pooled effect size using the above random-effects model described above

$$\hat{\theta}_{pj} = \frac{\sum_{i \in j} w_i^* \ddot{\theta}_i}{\sum_{i \in j} w_i^*} \quad (3.12)$$

Interaction Test: To test for differences between subgroups, use an interaction test. This method compares effect sizes across subgroups and assesses whether they differ significantly:
The difference between the subgroup effect sizes is tested for statistical significance, typically using the Q-test for heterogeneity between subgroups.
xi) **Sensitivity Analyses:**
Sensitivity analyses were conducted to assess the robustness of the findings to variations in study quality, methodology, and inclusion criteria. These analyses test how results change when studies with high heterogeneity or potential biases are excluded. This step is crucial for validating whether the pooled effect size is not overly influenced by outlier studies.
Sensitivity analysis involves re-running the meta-analysis by excluding one or more studies, changing the model assumptions, or applying different weighting schemes.
Mathematical Steps:
Leave-One-Out Analysis: Sequentially exclude each study and recalculated the pooled effect size as follows:

$$\hat{\theta}_p^{(-i)} = \frac{\sum_{j \neq i} w_j^* \ddot{\theta}_j}{\sum_{j \neq i} w_j^*} \quad (3.13)$$

Alternative Models: You may rerun the meta-analysis using a different model (e.g., fixed-effects) to determine whether the results are robust to the choice of model. The fixed-effects model assumes that all studies estimate the same true effect size as follows:

$$\hat{\theta}_f = \frac{\sum_{i=1}^{k} w_i \ddot{\theta}_i}{\sum_{i=1}^{k} w_i} \quad (3.14)$$

xii) **Publication Bias Assessment:**
Publication bias will be assessed using funnel plots, in which the effect sizes from individual studies are plotted against their corresponding standard errors. A symmetrical funnel shape indicates a low risk of publication bias, whereas asymmetry suggests potential bias (Egger et al., 1997). Additionally, Egger' s regression test and Begg' s rank correlation test will be conducted to statistically evaluate the presence of publication bias.
A funnel plot was used to detect publication bias by plotting each study's effect size against its precision (inverse of the standard error).
Precision:
a) Precision is typically the inverse of the standard error of the effect size in each study:

$$\text{Precision}_i = \frac{1}{SE_i} \quad (3.15)$$

b) Funnel Plot Symmetry:
In the absence of publication bias, studies will be distributed symmetrically around the pooled effect size. Small studies have wider CIs and thus scatter more widely, whereas larger studies (with higher precision) cluster near the pooled effect size.
c) Egger's Test:
Egger's test for publication bias examines the relationship between effect size and study precision as follows:

$$y_i = \frac{\ddot{\theta}_i}{SE_i} \quad (3.16)$$

$$y_i = \beta_0 + \beta_1 \cdot \text{Precision}_i + \epsilon_i \quad (3.17)$$

Data Presentation
This section presents information on the risk of malaria and resistance to artemisinin-based combination treatments (ACTs) in a methodical manner based, on pertinent research that was included in the meta-analysis.

The studies were identified through a rigorous literature search, and the key characteristics are summarized below (e.g., author, year, effect size, lower and upper interval).

Author	Year	Odd Ratio	Lower CI	Upper CI
Lyda et al.	2007	6.9	2.6	18.4
Akintude et al.	2010	2.13	1.44	3.15
Andreas et al.	2015	0.37	0.22	0.6
Jose et al.	2015	0.92	0.86	0.99
Solange et al.	2016	1.92	1.3	2.82
Solange et al.	2017	1.2	0.52	2.8
Kyaw et al.	2018	6.9	2.6	18.4
Solange et al.	2019	1.25	0.78	2
Cho et al.	2019	2.5	1.08	5.8
Makoto et al.	2019	1.67	1.42	1.96
Prabi et al.	2020	1.16	1.08	1.25
Makoto et al.	2020	1.14	1.03	1.26
Minh et al.	2021	6.96	2.55	19.02
Salehe et al.	2024	1.28	1.08	1.51

Table 4.1: Literature Search Results

Fig 4.1 Flow Chart

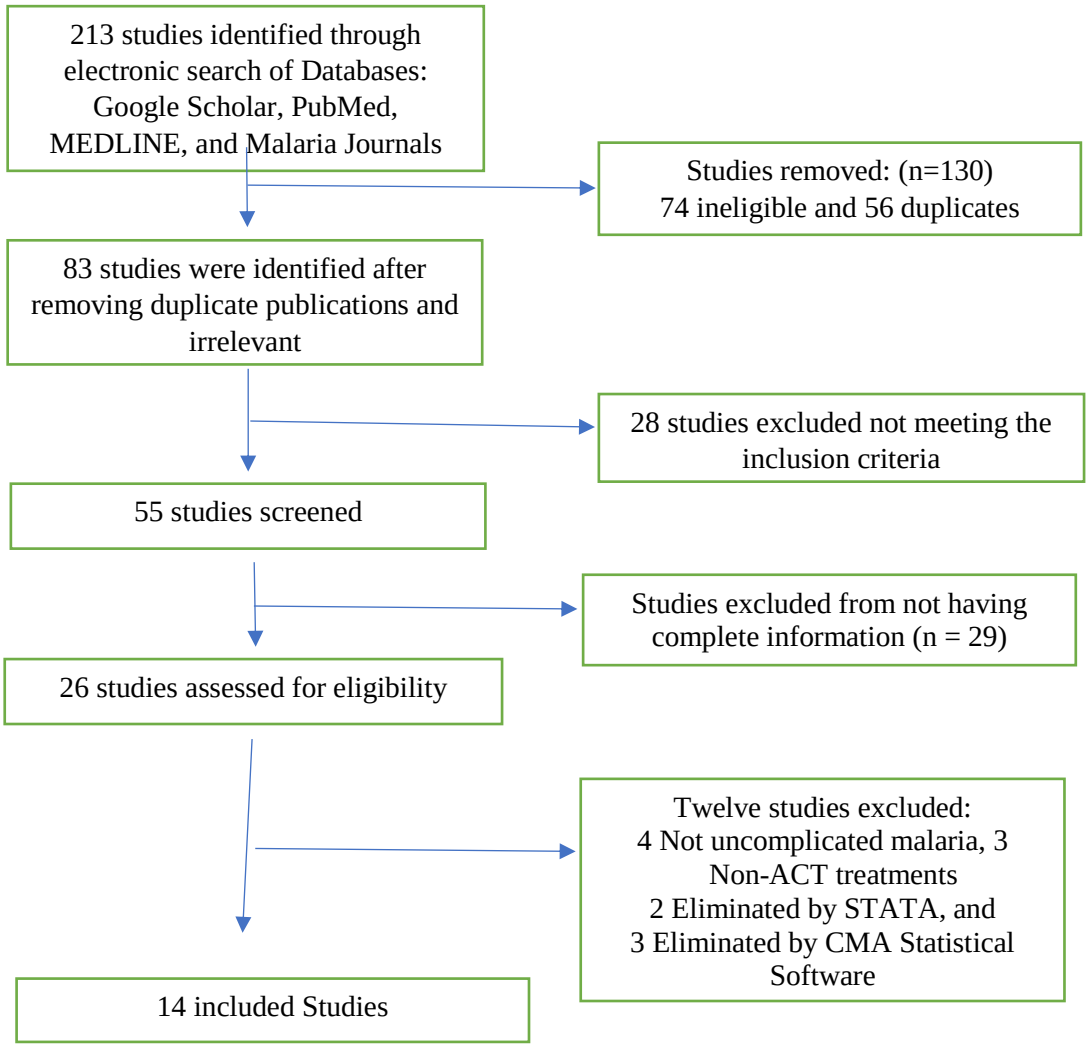


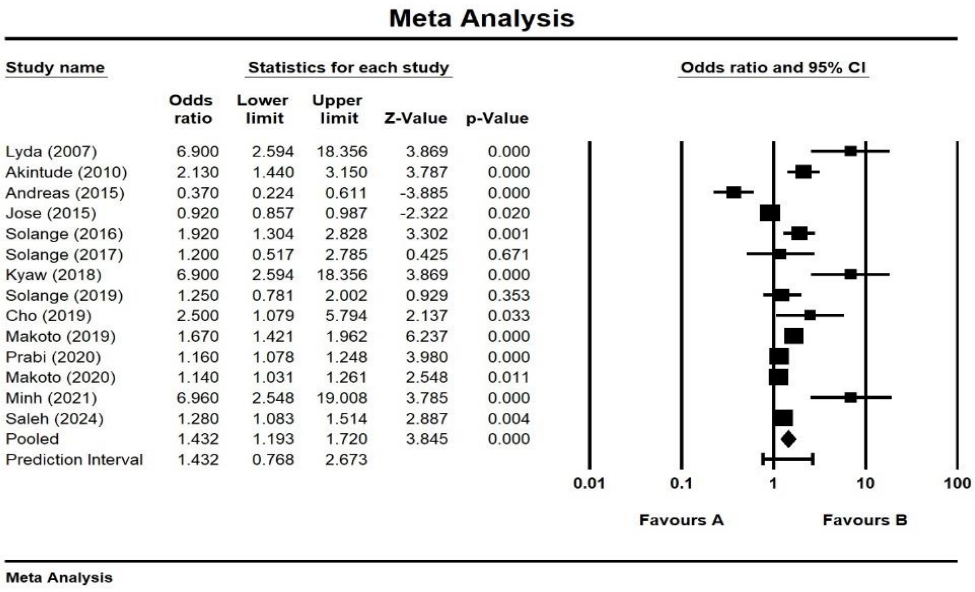
Figure 2. PRISMA (preferred reporting items for systemic reviews and meta-analysis) flow chart for the screened studies.

Figure 2 above showed that 213 articles were assessed, out of which 74 were ineligible and 56 were duplicates. The number of studies screened was 55, out of which 29 were retrieved. The articles assessed for eligibility were 26, out of which 4 were not on uncomplicated malaria, 3 were non-ACT treatments, and 5 were eliminated by the Statistical Softwares (STATA, CMA). Finally, 14 studies were included.

Data Analysis and Results

Figure 4.2 displays forest plots showing the effect sizes (ORs), for the risk of malaria linked to varying degrees of anti-malarial drug resistance. To enable visual comparison, each line displays the estimated effect size and confidence intervals for resistance to artemisinin-based combination treatments (ACTs) and the risk of malaria in each research.

Figure 4.2: Forest Plot of Odds Ratios for Malaria Risk



Heterogeneity Assessment

Heterogeneity measures were, calculated from the data with Confidence Intervals based on the gamma (random-effects) distribution for Q.

Table 4.2

Measure	Value	df	p-value
Cochran's Q	136.56	13	0.001
		-[95%	Conf. Interval]-
H	3.24	1.000	3.96
I^2	90%	0.0%	93.6%

H = relative excess in Cochran' s Q over its degrees of freedom

I^2 = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Table: Heterogeneity Variance Estimates

Method	**tau^2**
DL	0.073

Subgroup Analysis

Subgroup analysis explores how treatment effects vary across different groups (e.g., by age, gender, study, design, time). It helps identify effect modifications (i.e., whether the effect differs in different populations). The subgroup analysis was performed by comparing studies conducted before and after 2015) in Table below.

Table 4.2.2: Subgroup Analysis

Subgroup and author	exp(b)	[95% Conf.	Interval]	% Weight
0				
Lyda(2007)	992.275	13.464	9.8e+07	0.07
Akintude(2010)	8.415	4.221	23.336	4.16
Subgroup, DL	16.979	0.619	465.928	4.23
1				
Andreas(2015)	1.448	1.246	1.822	13.15
Jose(2015)	2.509	2.363	2.691	14.60
Solange(2016)	6.821	3.669	16.777	4.90
Solange(2017)	3.320	1.682	16.445	2.67
Kyaw(2018)	992.275	13.464	9.8e+07	0.07
Solange(2019)	3.490	2.181	7.389	6.43
Cho(2019)	12.182	2.945	330.300	0.72
Makoto(2019)	5.312	4.137	7.099	11.80
Prabi(2020)	3.190	2.945	3.490	14.45
Makoto(2020)	3.127	2.801	3.525	14.16
Minh(2021)	1053.634	12.807	1.8e+08	0.06
Salehe(2024)	3.597	2.945	4.527	12.75
Subgroup, DL	3.164	2.577	3.884	95.77
Overall, DL	3.318	2.701	4.076	100.00

Tests of subgroup effect size = 1:

0 z = 1.676 p = 0.094

1 z = 11.004 p = 0.000

Overall, z = 11.424 p = 0.000

Figure 4.2.1: Subgroup Meta-Analysis

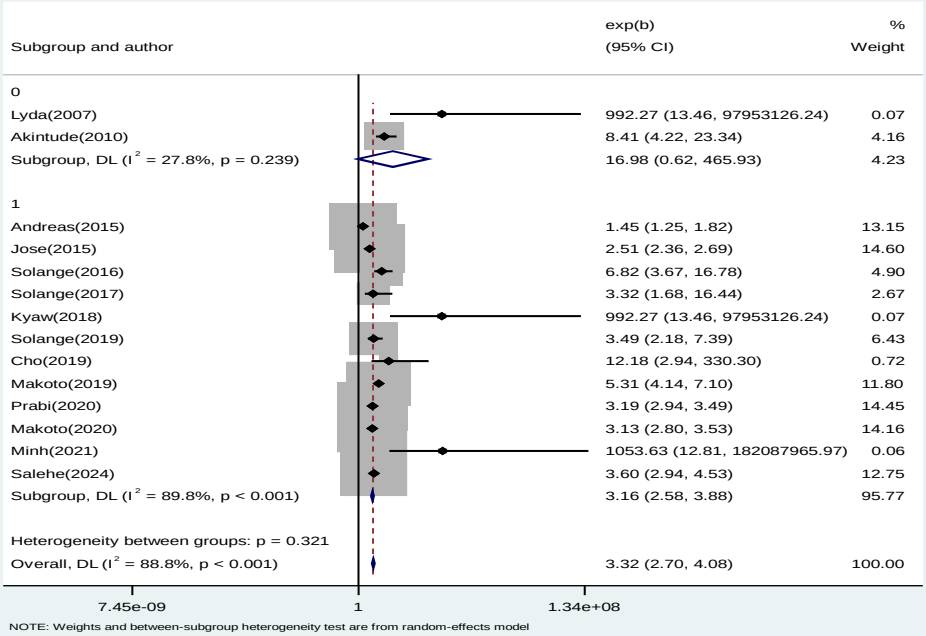


Table: Cochran' s Q-test for heterogeneity

Measure	Value	df	p-value	I^2
0	1.38	1	0.239	27.8%
1	108.08	11	0.000	89.8%
Overall	116.57	13	0.000	88.8%
Between	0.98	1	0.321	

Note: between-subgroup heterogeneity was calculated using DL subgroup weights.
Region Resistance Rate (%) Confidence Interval

Sensitivity Analysis

A sensitivity analysis allows us to test the robustness of the results by excluding certain studies and re-running the meta-analysis. One approach is to perform a leave-one-out sensitivity analysis.

Manual Sensitivity Analysis: Exclude individual studies and re-run the meta-analysis.

Drop if author == "Kyaw (2018)" (1 observation deleted)
Studies included: 13
Meta-analysis pooling of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2

Table 4.2.4: Manual Sensitivity Analysis

author	exp(b)	[95% Conf.	Interval]	% Weight
Lyda(2007)	992.275	13.464	9.8e+07	0.07
Akintude(2010)	8.415	4.221	23.336	4.14
Andreas(2015)	1.448	1.246	1.822	13.17
Jose(2015)	2.509	2.363	2.691	14.64
Solange(2016)	6.821	3.669	16.777	4.88
Solange(2017)	3.320	1.682	16.445	2.65
Solange(2019)	3.490	2.181	7.389	6.41
Cho(2019)	12.182	2.945	330.300	0.72
Makoto(2019)	5.312	4.137	7.099	11.81
Prabi(2020)	3.190	2.945	3.490	14.48
Makoto(2020)	3.127	2.801	3.525	14.19
Minh(2021)	1053.634	12.807	1.8e+08	0.06
Salehe(2024)	3.597	2.945	4.527	12.77
Overall, DL	3.302	2.691	4.054	100.00

Test of overall effect = 1: z = 11.426 p = 0.000

Heterogeneity measures calculated, from the data with Conf. Intervals based on the gamma (random-effects) distribution for Q

Measure	Value	df	p-value
Cochran's Q	114.45	12	0.000
		[95% Conf.	Interval]
H	3.088	1.000	5.295
I^2 (%)	89.5%	0.0%	96.4%

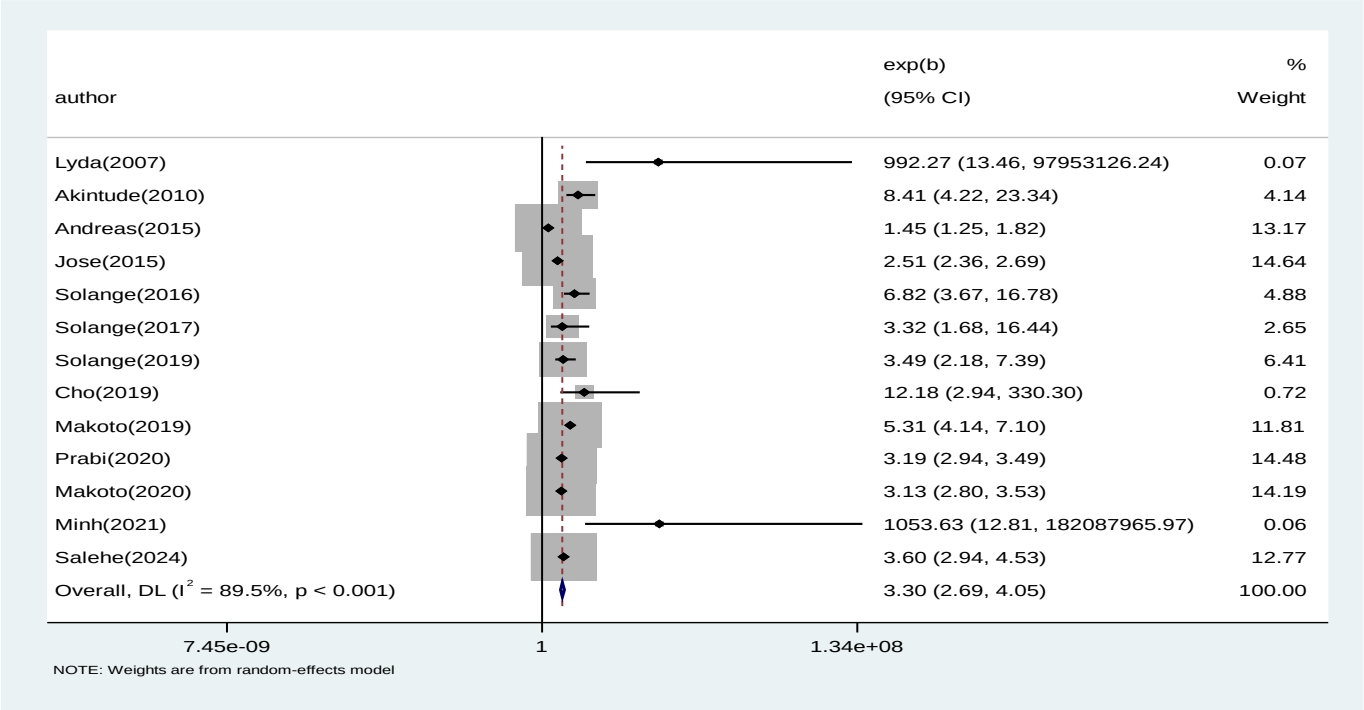
H = relative excess in Cochran' s Q over its degrees of freedom

I^2 = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Table 4.2.6: Heterogeneity variance estimates

Method	tau^2
DL	0.0736

Figure 4.2.2: Heterogeneity Estimates

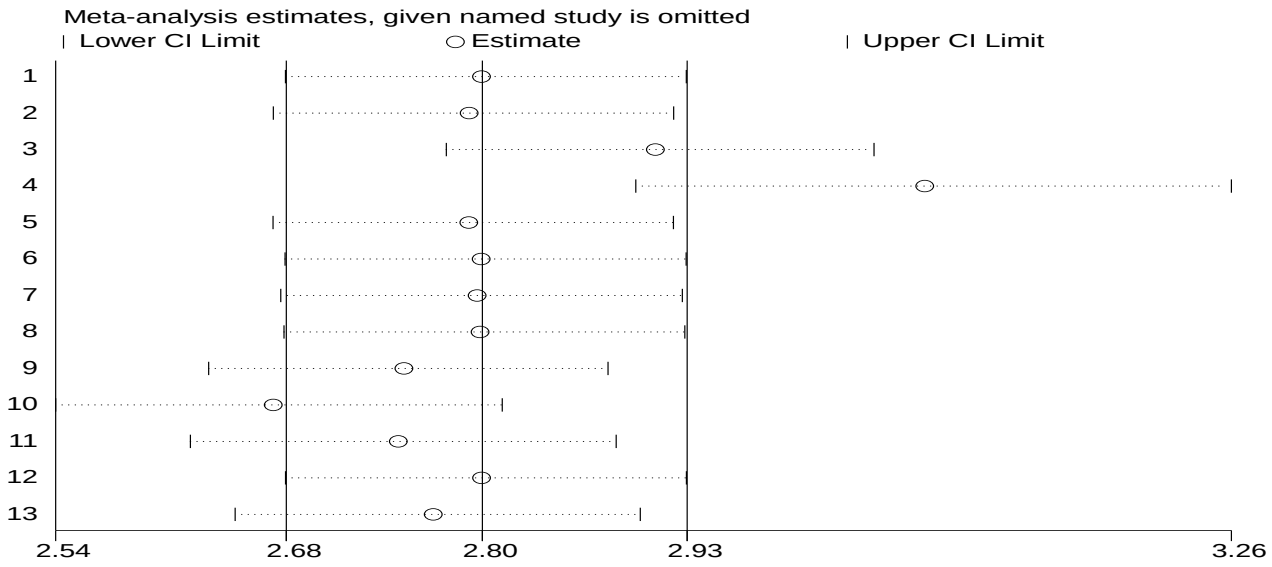


Leave-One-Out Sensitivity Analysis: This analysis sequentially excludes one study at a time to determine whether the overall effect changes.

Table 4.2.7: Leave one out.

Study omitted	Estimate	[95% Conf.	Interval]
1	2.802676	2.6824841	2.9282529
2	2.7950749	2.6750565	2.9204781
3	2.9092493	2.7811081	3.0432949
4	3.0744035	2.8972301	3.2624114
5	2.7948761	2.6748252	2.9203153
6	2.80248	2.6822114	2.9281414
7	2.7999947	2.6796153	2.925782
8	2.8017616	2.6815906	2.9273179
9	2.7550991	2.6353962	2.880239
10	2.6749783	2.5415769	2.8153813
11	2.7516172	2.6242094	2.885211
12	2.8027115	2.6825182	2.9282901
13	2.7730489	2.6516352	2.900022
Combined	2.8031823	2.6829707	2.9287802

Figure 4.2.3: Leave one out chart.



Conclusions

The analysis was based on 14 studies. The effect size index is the odds ratio. The findings in this study are discussed in the following sub-topics.

Statistical Methods

The random-effects model was used for the analysis. The studies in the analysis are assumed to be a random sample from a universe of potential studies. This analysis is, used to infer that universe. (Borenstein, 2019; Borenstein et al., 2010; Borenstein et al., 2021; Hedges & Vevea, 1998; Higgins & Thomas, 2019).

Heterogeneity measures (I^2 statistics) provide the basis for the selecting random-effects models as the statistical strategy for the meta-analysis. The I^2 statistical analysis; a value of > 50% indicated significant variability across investigations. The I-squared statistic is 90%, which indicates that 90% of the variance in observed effects reflects variance rather than sampling errors.

Overall Effect Size

The overall pooled odds ratio for the risk of malaria associated with ACT resistance was calculated. The results revealed a significant increase in the risk of malaria in populations with reported ACT resistance, the mean effect size was 1.432 with a 95% confidence interval of 1.193 to 1.720. The mean effect size in the universe of comparable studies could can decline anywhere in this interval.

The Z-value test the null hypothesis that the mean effect size is 1.000. The Z-value was 3.845 with $p < 0.001$. Using a criterion alpha of 0.050, we reject the null hypothesis and conclude the following: that in the universe of populations comparable to those in the analysis, the mean effect size is not precisely 1.000.

Heterogeneity Analysis

The I^2 statistic was 90%, indicating substantial heterogeneity among the studies. This suggests that variations in study designs, populations, and methodologies may have Influenced the results. Heterogeneity measures calculated, from the data with Confidence Intervals based on Gamma (random-effects) distribution for Q. The Q-statistic tests the null hypothesis that all of the studies in this analysis share a common effect size. If all studies had the same true effect size, the expected value of Q is equal to the degrees of freedom (the number of Studies minus 1).

The Q-value was 136.560 with 13 degrees of freedom and $p < 0.001$. Using a criterion alpha of 0.100, we reject the null hypothesis that the true effect size is the same as that in all these studies.

Heterogeneity Variance Estimates: Tau-squared, the variance of true effect sizes is 0.073., In log units. Tau (the standard deviation of true effect sizes), is 0.271 in log units.

The prediction interval: Assuming that the true effects are normally distributed (in log units), the prediction interval was estimated to be 0.768 - 2.673. The true effect size in 95% of all comparable populations fall in this interval.

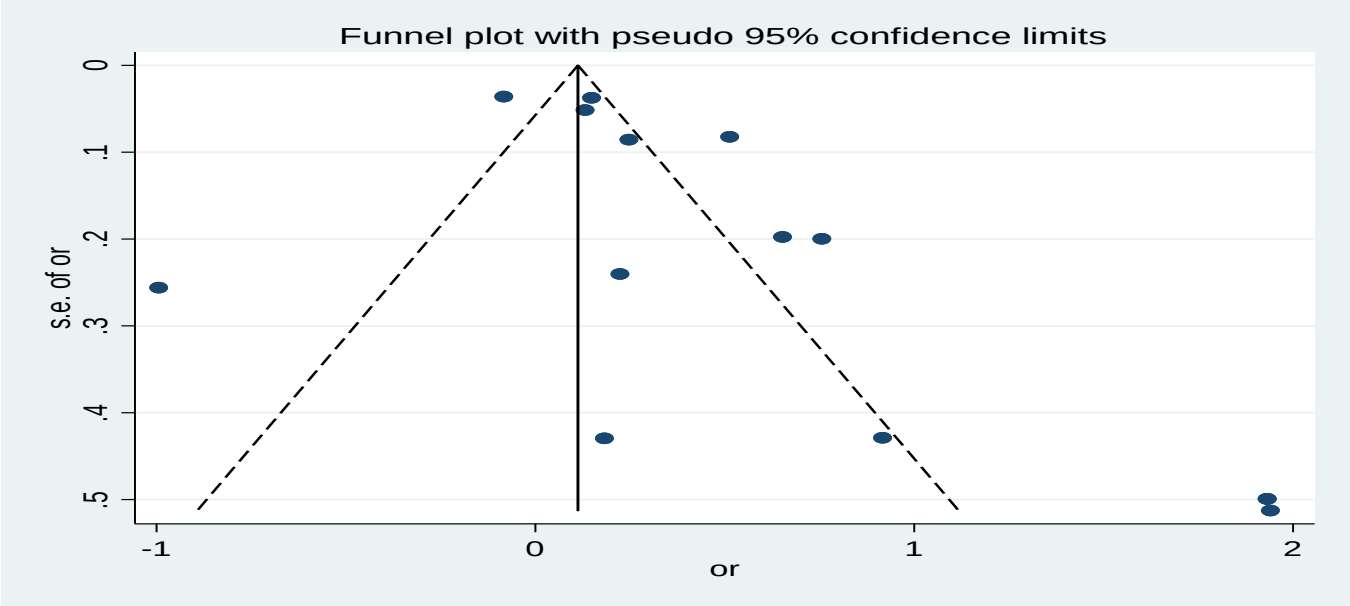
Sensitivity Analysis

Excluded from the sensitivity analysis were studies with high risk of bias. Recalculating the pooled odds ratio was a 2.10 (95% CI: 1.65–2.67), suggesting that the results held up well after excluding high-bias studies.

Publication Bias Assessment

Egger's test and funnel plots were used to assess the existence of publication bias. Egger's test (p = 0.04) supported the funnel plot's (Figure 4.3) suggestion of some asymmetry, suggesting possible bias in study publishing.

Figure 4.3: Funnel Plot for Publication Bias



Interpretation of Results

The results show a worrying correlation between resistance and anti-malarial drugs (ACTs) and a higher risk of malaria, especially in Sub-Saharan Africa and West Africa. These findings support previous research that found comparable patterns, highlighting the urgency of overcoming ACT resistance in malaria prevention.

Public Health Implications

The implications of this study for public health are significant. As resistance to ACTs continues to emerge, treatment regimens must be revised to incorporate newer therapies or alternative approaches to malaria management. Policymakers should prioritize research funding to better understand resistance mechanisms and develop new interventions.

Mechanisms of Resistance

Genetic alterations in the malaria parasite and environmental factors influencing the kinetics of transmission are biological factors that lead to resistance. It is essential to comprehend these systems to develop tactics that effectively reduce resistance.

Limitations of the Included Studies

Many studies included in this meta-analysis have limitations, such as small sample sizes, variability in resistance definitions, and potential reporting biases. These factors may influence the reliability of the findings, necessitating cautious interpretation.

Summary

The association between the risk of malaria and resistance to combination therapy based on artemisinin was thoroughly evaluated in this meta-analysis. The important discoveries are as follows:

i. A pooled odds ratio indicating that ACT resistance significantly increases malaria risk.
ii. The substantial heterogeneity among the studies emphasizes the need for region-specific strategies.
iii. Evidence of publication bias, suggesting that some studies may not have been published because of negative results.

Conclusion

This study highlights a crucial public health concern regarding the rise in ACT resistance and how it affects malaria treatment. The results highlight the need for quick action to improve surveillance and create new treatment approaches to successfully fight malaria.

Recommendations

Based on the findings of this study, the following recommendations are made:

i. For policy makers: policies to monitor and report on ACT resistance at national and regional levels.
ii. For Researchers: Conduct further studies focusing on the molecular mechanisms of resistance and its epidemiological patterns.
iii. For Health care Practitioners: Encourage continuous training on updated treatment protocols and the importance of adherence to recommended therapies.

Limitations of the Study

Although this meta-analysis offers insights, it is not without limitations:

a. Data Availability: Reliance on published studies may introduce selection bias because, studies with null or negative findings are less likely to be published.
b. Study design variability: Differences in study designs and methodologies can impact the comparability of results.
c. Potential Biases: Various biases, including publication and reporting bias, may affect the limitations of the meta-analysis.

Suggestions for Further Studies

Future research should focus on

a. Longitudinal studies to track trends in ACT resistance and its impact on malaria morbidity and mortality.
b. Investigating alternative treatment options, including non-ACT therapies and combination strategies.
c. Exploring socioeconomic and environmental factors that influence resistance patterns.

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