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Research Article

CHRONIC MALNUTRITION AND ANTIMALARIAL DRUG RESPONSE IN CHILDREN: A SCOPING REVIEW OF PHARMACOKINETIC ALTERATIONS AND THERAPEUTIC IMPLICATIONS

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Abstract

Chronic malnutrition remains a significant public health concern in malaria-endemic regions and may substantially influence the pharmacological response to antimalarial therapy in children. Although both malnutrition and malaria have been extensively studied independently, their combined effects on drug pharmacokinetics and treatment outcomes are still not well understood. This gap is largely due to the limited integration of pharmacokinetic, clinical, and nutritional evidence, with only a few studies examining their interaction in shaping antimalarial responses. Malnutrition affects antimalarial pharmacokinetics and therapeutic outcomes in pediatric populations, while also identifying key research gaps. This scoping review followed PRISMA-ScR guidelines, with a systematic search conducted in PubMed and Scopus that initially identified 1,105 records, of which 56 studies met the inclusion criteria after screening. Data were synthesized narratively to evaluate pharmacokinetic alterations and treatment outcomes, and bibliometric analysis using VOSviewer was performed to map research trends. The findings indicate that chronic malnutrition significantly alters key pharmacokinetic parameters of antimalarial drugs, including absorption, distribution, metabolism, and elimination.

Keywords: Antimalarial Pharmacokinetic, Treatment Outcomes, Chronic Malnutrition

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INTRODUCTION

Children in low and middle density countries are particularly affected by malaria, which continues to be a significant public health problem worldwide. The World Health Organization states that children under five years of age are most likely to contract malaria, resulting in illness or death. Globally, an estimated 249 million malaria cases and 608,000 deaths were reported in 2022, with the majority occurring in children under five in endemic regions.Despite significant progress in antimalarial treatments, like artemisinin-based combination therapy (ACT), the results of treatment are still not ideal in many areas where malaria is common. This suggests that, in addition to how the parasite responds to the treatment, factors related to the patient, such as their genes, nutrition, and other infections, may also affect how well these treatments work (WHO, 2023).

Malaria is often found in places where chronic malnutrition is common, and these two health problems often occur together in children. According to the World Health Organization, approximately 148 million children under five are stunted and 45 million are wasted globally, with the highest burden in low- and middle-income countries. Being underweight is known to impair the immune system, altering the body's natural balance, and making people more susceptible to disease (Schaible & Kaufmann, 2007). Malnutrition impacts disease progression and the effectiveness of treatment, particularly antimalarial drugs.

Recent research has shown that malnutrition can significantly impact how drugs are processed in the body. This is because malnutrition alters how drugs are absorbed, distributed, metabolized, and eliminated. For example, gastrointestinal problems can complicate the absorption of oral medications, and low albumin levels can alter drug distribution by increasing the unbound fraction. Furthermore, abnormalities in kidney function and liver enzyme activity can affect drug exposure (Ayegua et al., 2022 ; Whalen et al., 2019). Several studies have reported that malnourished children may experience reductions in antimalarial drug exposure, with decreases in plasma concentrations of up to 20–50%, potentially leading to subtherapeutic levels.

Reports indicate that malnourished children exhibit poorer outcomes after antimalarial treatment. These results suggest that parasite eradication takes time, increasing the risk of treatment failure and death (Ali et al., 2023; Goodwin et al., 2024). Variations in study design, dietary assessment techniques, antimalarial protocols, and regional epidemiology can lead to conflicting findings (Nji et al., 2021). The effect of different types of malnutrition on how well treatments work is still not fully understood. This distinction is crucial for understanding the differences between acute and chronic malnutrition, as (Chotsiri et al., 2019) have shown.

Studies show that malnutrition weakens the immune system, affecting both natural and acquired defenses. It also impairs the body's ability to protect itself and alters the way inflammation works. These interrelated factors collectively influence how the disease progresses and how well treatment works (Bartels et al., 2019). Therefore, it is crucial to understand how nutritional status affects the safety and effectiveness of antimalarial treatment. Despite increasing attention, current evidence remains fragmented, with limited integration of pharmacokinetic, pharmacodynamic, and clinical outcome data. Although this problem is gaining more attention, the current evidence is still incomplete. The current understanding doesn't fully combine the pharmacokinetics, pharmacodynamics, and overall effects of drugs. Furthermore, a comprehensive review of the existing literature has not yet been conducted to

consolidate all available evidence and pinpoint critical areas necessitating further investigation (Njunge et al., 2019; Bartels et al., 2019).

Consequently, this scoping review aims to systematically map and synthesize existing evidence on the influence of chronic malnutrition on the efficacy of antimalarial treatments and therapeutic outcomes in pediatric populations. Specifically, this review examines trends in the literature, including the geographic distribution of studies, methodological approaches, and populations studied in relation to malnutrition and antimalarial drug response in children. It further evaluates how chronic malnutrition affects antimalarial pharmacokinetics, including drug absorption, distribution, metabolism, and elimination, and assesses its impact on treatment outcomes such as treatment failure, parasite clearance time, and mortality. In addition, the review explores how different forms of malnutrition such as stunting, wasting, and underweight may differentially influence the efficacy and safety of antimalarial drugs, as well as the biological and physiological mechanisms underlying altered drug responses in malnourished children.

RESEARCH METHOD

Protocol

The present scoping review was undertaken in accordance with the PRISMA Extension for Scoping Reviews guidelines, as delineated by (Tricco et al., 2018). This approach ensured a transparent and systematic process for identifying, selecting, and reporting relevant studies. Furthermore, the review methodology followed established scoping review frameworks, as originally proposed by Arksey & O'Malley. A scoping review design was selected due to the heterogeneous and multidisciplinary nature of the available evidence, as well as the need to systematically map existing literature and identify key research gaps.The study selection process is illustrated in Figure 1 using a PRISMA flow diagram. To complement the narrative synthesis, a bibliometric analysis was conducted using VOSviewer to identify key research themes, keyword relationships, and the overall knowledge structure within the included studies.

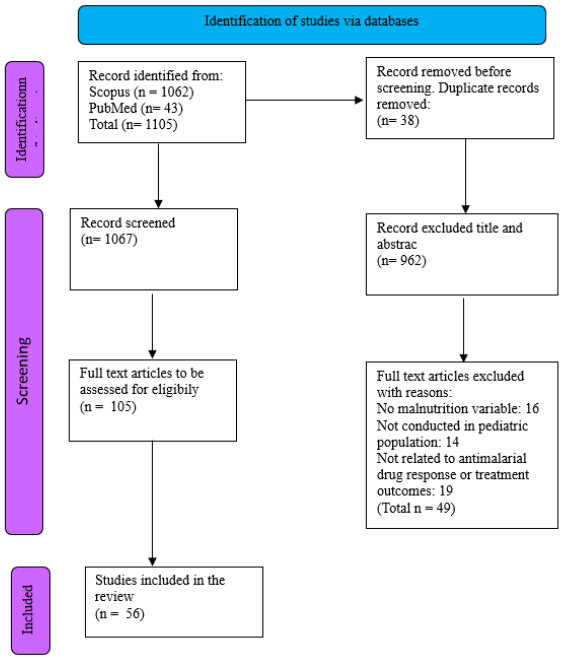

Figure 1. Prisma Flow Diagram Illustrating the Study Selection Process

A total of 1,105 records were identified through database searching (PubMed and Scopus). After duplicate removal and screening of titles and abstracts, full-text articles were assessed for eligibility. Finally, 56 studies were included in the analysis. Some studies reported multiple outcomes and were therefore assigned to more than one domain (Tricco et al., 2018).

Eligibility criteria

This study used a systematic method to thoroughly assess how prolonged malnutrition affects the effectiveness of antimalarial treatments and the resulting health outcomes in children. This study specifically focused on research that examined the relationship between malnutrition and the use of antimalarial drugs. The research included in this review, focusing on children, produced important findings.

These findings needed to cover how the body processes the drugs, how the drugs work, how well the treatment worked, whether the parasites were eliminated, or if the treatment failed. We only included publications from the last twenty years (2004-2026) to ensure the information was current, to highlight changes over time, and to support future research and clinical practice. Studies that didn't consider malnutrition, didn't include children, or weren't relevant to how well antimalarial drugs worked or the results of treatment were excluded. Additionally, any papers with findings that didn't match the goals of this research were also left out.

Type of Sources

Comprehensive searches of electronic databases, including PubMed and Scopus, were conducted to identify pertinent studies. These databases were chosen because of their broad scope in biomedical and pharmacological research. This review incorporated a variety of evidence sources, encompassing original research articles, such as observational studies and clinical trials, that investigated the association between chronic malnutrition and antimalarial drug response or therapeutic outcomes in pediatric populations. To ensure the quality and reliability of the evidence, only peer-reviewed publications were considered.

Search strategy

A comprehensive literature search was conducted in the PubMed and Scopus databases to identify studies examining the effects of chronic malnutrition on the efficacy of antimalarial drugs and subsequent therapeutic outcomes in pediatric populations. The search strategy combined controlled vocabulary (MeSH terms) with relevant free-text keywords related to malnutrition, malaria, pharmacokinetics, pharmacodynamics, drug response, and pediatric populations, using Boolean operators (AND, OR) to enhance search sensitivity and specificity. The Scopus search string was formulated as follows: TITLE-ABS-KEY (malnutrition OR undernutrition) AND (malaria) AND (pharmacokinetics OR pharmacodynamics OR "drug response" OR efficacy) AND (child*). The PubMed search strategy was structured as: (("Malnutrition"[Mesh] OR malnutrition[tiab] OR undernutrition[tiab]) AND ("Malaria"[Mesh] OR malaria[tiab]) AND ("Pharmacokinetics"[Mesh] OR "Pharmacodynamics"[Mesh] OR pharmacokinetics[tiab] OR pharmacodynamics[tiab] OR "drug response"[tiab] OR efficacy[tiab]) AND ("Child"[Mesh] OR child*[tiab] OR pediatric[tiab])).

Selection of sources of evidence

The study selection process followed a two step method. Initially, two reviewers independently examined the titles and abstracts of all retrieved records, employing the Rayyan platform. Following this, the full text articles were assessed for eligibility, adhering to pre established inclusion and exclusion criteria. Studies were deemed eligible if they investigated the association between chronic malnutrition and either the effectiveness of antimalarial medications or therapeutic results within pediatric cohorts. Discrepancies among reviewers were addressed through deliberation, and, when required, a third reviewer was enlisted to ensure uniformity and precision in the study selection procedure.

Data Charting

Following the PRISMA-ScR framework, two reviewers worked together to create a standardized data charting form, which helped to identify the key variables to be extracted. The data that was extracted included details about the studies, the populations involved, the types of malnutrition, the antimalarial drugs used, the pharmacokinetic and pharmacodynamic properties, and the therapeutic results.

Each reviewer independently charted the data, and their findings were then compared to verify accuracy and consistency. Discrepancies were addressed through discussion, and the data charting form was refined iteratively as required. This approach facilitated a transparent, consistent, and thorough extraction of pertinent information across all included studies. The finalized data charting form was uniformly implemented across all included studies.

Data item

Data extraction was conducted using a standardized data-charting form to collect key study variables relevant to the objectives of this review. The extracted data included author(s), year of publication, study location, and study design. In addition, information on population characteristics (e.g., age and sample size), types of malnutrition (e.g., stunting, wasting, underweight), and types of antimalarial drugs was collected.

Further variables included pharmacokinetic and pharmacodynamic parameters, as well as reported therapeutic outcomes such as treatment efficacy, parasite clearance, treatment failure, and mortality. The chosen data points were selected to comprehensively capture the relationship between long-term malnutrition and how well children respond to antimalarial treatment.

Synthesis of Results

The studies were summarized descriptively using a narrative synthesis, which helped analyze and combine the findings. This method allowed for the identification and comparison of key patterns across the studies, focusing on the relationship between long term malnutrition and how children responded to antimalarial drugs.

Thematic analysis was employed to classify the results into key areas, encompassing pharmacokinetic changes, pharmacodynamic effects, and therapeutic results, specifically treatment effectiveness, parasite elimination, and treatment failure. In addition, this review also discusses the differences related to various types of malnutrition, such as stunting, wasting, and underweight.

RESULTS AND DISCUSSION

RESULT

Study Selection and Evidence Mapping

The database searches yielded 1,105 records, comprising 1,062 from Scopus and 43 from PubMed. Following the elimination of duplicates, 1,067 studies remained for title and abstract screening. During this stage, 962 records were excluded based on the predefined eligibility criteria. Consequently, 105 full-text articles were assessed for eligibility. Studies that did not include malnutrition variables, were not conducted in pediatric populations, or did not address antimalarial drug response or treatment outcomes were excluded. Ultimately, 56 studies met the inclusion criteria and were included in this scoping review. The study selection process is illustrated in Figure 1.

To complement the systematic selection process, an evidence mapping approach was conducted to categorize the included studies into major research domains. The distribution of studies across these domains is presented in Table 1 and further visualized in Figure 2.

Table 1. Distribution of Included Studies by Research Domain and Key Findings

No	Research Domain	Number of Studies (n=56)	Key Findings Summary
1	Malnutrition and Malaria Susceptibility	20	Malnutrition, particularly stunting and wasting, was frequently associated with increased susceptibility to malaria and higher morbidity. However, several studies reported inconsistent findings, indicating context-specific interactions.
2	Malaria and Nutritional Outcomes	10	Malaria infection contributed to impaired growth outcomes, including stunting and wasting. Recurrent malaria episodes were associated with reduced linear growth in children.
3	Drug Efficacy and Resistance	8	Malnutrition influenced antimalarial treatment outcomes, increasing the risk of treatment failure and drug resistance. Suboptimal dosing and poor adherence further exacerbated these risks.
4	Pharmacokinetics and Pharmacodynamics (PK/PD)	12	Malnutrition altered drug absorption, distribution, metabolism, and clearance, leading to variability in drug exposure. Nevertheless, some studies reported no significant differences between malnourished and well-nourished children.
5	Nutritional and Malaria Interventions	15	Nutritional supplementation and malaria preventive interventions (e.g., chemoprevention, vitamin A, IPT) reduced malaria incidence, improved nutritional status, and contributed to lower child mortality.

The evidence mapping presented in Table 1 highlights the complex and bidirectional relationship between malnutrition and malaria, particularly in pediatric populations. The largest proportion of studies (n=20) focused on malnutrition and malaria susceptibility, indicating a strong research emphasis on how nutritional deficits especially stunting and wasting may compromise immune function and increase vulnerability to malaria infection. However, inconsistencies across several studies suggest that this relationship is highly context-dependent, influenced by environmental exposure, endemicity levels, and socioeconomic conditions. This variability underscores the need for more context-sensitive and stratified analyses in future research.

A smaller but substantial body of evidence (n=10) examined the impact of malaria on nutritional outcomes. These studies consistently demonstrated that recurrent malaria episodes contribute to growth faltering, particularly reduced linear growth. This finding reinforces the concept of a malnutrition–infection cycle, in which infection exacerbates nutritional deficiencies, thereby increasing susceptibility to subsequent infections. The domains of drug efficacy and resistance (n=8) and pharmacokinetics/pharmacodynamics (n=12) provide important clinical insights. Evidence suggests that malnutrition can influence antimalarial treatment outcomes both directlythrough altered drug metabolism and indirectly through its association with disease severity. Variability in drug exposure among malnourished children raises concerns regarding suboptimal dosing, which may contribute to treatment failure and the emergence of drug resistance. However, some studies reported no significant pharmacokinetic differences, indicating that the effects of malnutrition may vary depending on the type of drug, severity of malnutrition, and individual patient characteristics, including genetic factors.

Finally, studies categorized under nutritional and malaria interventions (n=15) provide encouraging evidence that integrated strategies can yield substantial health benefits. Interventions such as chemoprevention, vitamin supplementation, and nutritional support were shown to reduce malaria incidence, improve nutritional status, and decrease child mortality. These findings highlight the importance of adopting a holistic and multisectoral approach in addressing malaria in resource-limited settings, particularly among vulnerable pediatric populations.

Overall, the distribution of evidence across these domains reflects a growing recognition of the interconnected nature of malnutrition and malaria. Nevertheless, important gaps remain, particularly in longitudinal and mechanistic studies that can better elucidate causal pathways and inform optimized treatment strategies. Future research should prioritize integrated intervention models and precision dosing approaches tailored to the nutritional status of pediatric patients.

To complement this synthesis and provide a clearer visual comparison of the distribution of studies across domains, the findings are further illustrated in Figure 2. Future research should prioritize integrated intervention models and precision dosing approaches tailored to the nutritional status of pediatric patients. To further illustrate the relative distribution of evidence across these domains, the findings are presented graphically in Figure 2.

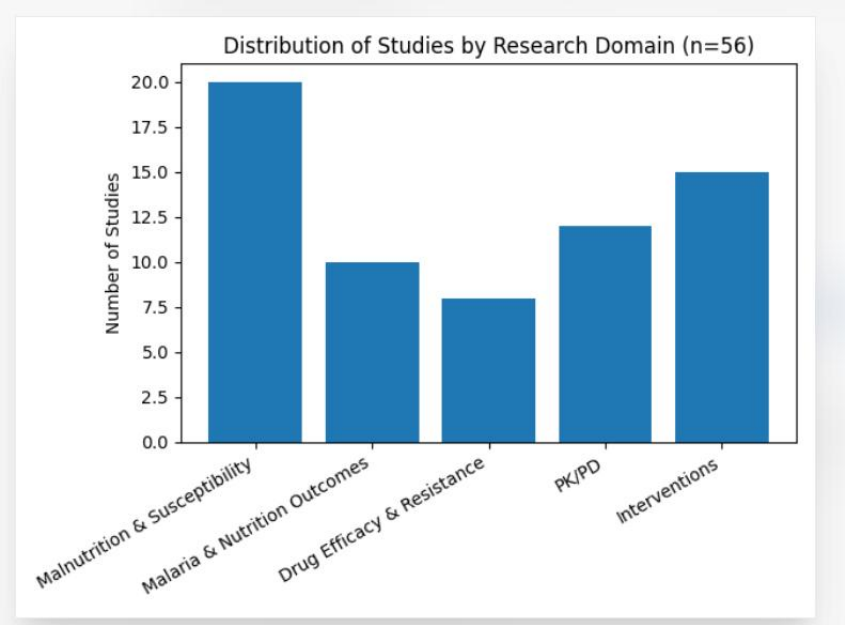

Figure 2. Distribution of Studies Across Research Domains

Figure 2 illustrates the distribution of the 56 included studies across five major research domains. The largest proportion of studies is concentrated in the domain of malnutrition and malaria susceptibility (n=20), indicating that this area has received the most research attention. This is followed by studies on nutritional and malaria interventions (n=15) and pharmacokinetics and pharmacodynamics (PK/PD) (n=12), reflecting a growing focus on treatment optimization and integrated intervention strategies.

In comparison, fewer studies addressed malaria and nutritional outcomes (n=10) and drug efficacy and resistance (n=8), suggesting relatively limited exploration in these areas. Despite the smaller number of studies, these domains provide critical insights into the impact of malaria on child growth and the effectiveness of antimalarial therapies.

Overall, the figure highlights an uneven distribution of research efforts, with a stronger emphasis on disease susceptibility and intervention strategies, while areas such as treatment response and long-term nutritional consequences remain comparatively underexplored. This imbalance underscores the need for more comprehensive and balanced research to better understand the multifaceted relationship between malnutrition and malaria

Evidence Synthesis, Research Trends, and Thematic Insights

Research Landscape and Thematic Structure

The reviewed studies demonstrated an escalating interest in the impact of long-term malnutrition on the effectiveness of antimalarial drugs and treatment outcomes within pediatric populations. This heightened research focus mirrors a wider acknowledgment of the influence of nutritional status on drug absorption, pharmacokinetics, and therapeutic efficacy in malaria-endemic regions (Bassat et al., 2008).

The studies included in this review used various methods. The majority of the research consisted of observational studies or clinical trials. The primary focus of these investigations was the assessment of therapeutic efficacy and treatment outcomes in pediatric populations experiencing malnutrition. These methodologies are consistent with prior research endeavors that explored host-related determinants influencing the efficacy of antimalarial interventions (Gogtay et al., 2021)

A keyword co-occurrence network analysis, employing VOSviewer, was performed to ascertain the principal research themes within the selected studies. This analysis subsequently identified three discrete clusters, each representing the prevailing areas of investigation (Van Eck & Waltman, 2010; Donthu et al., 2021).

The first cluster (red), predominantly comprises terms associated with epidemiological and clinical burden, such as prevalence, morbidity, anaemia, undernutrition, and clinical malaria; this suggests a significant emphasis on disease burden and nutritional status. These observations are congruent with earlier studies that have underscored the substantial burden of malnutrition and the co-occurrence of malaria in endemic areas (Ali et al., 2023)

Conversely, the second cluster, represented in green, pertains to pharmacological and treatment-related dimensions, featuring key terms like pharmacokinetic, drug, concentration, dose, and chloroquine, thereby reflecting investigations into drug exposure and therapeutic management within pediatric populations. This observation is consistent with pharmacokinetic investigations that reveal differences in antimalarial drug exposure, which are contingent upon the physiological state of the host (Olanrewaju & Johnson, 2001).

The third cluster, represented in blue, encompasses terms related to methodology and associations, including incidence, malaria infection, association, and confidence interval. This observation underscores the significance of statistical associations and methodological frameworks, elements commonly utilized in clinical and epidemiological investigations.

Moreover, the observed relationships between different groups suggest that, despite a strong representation of both epidemiological and pharmacological viewpoints, their combination is somewhat limited. In particular, the direct connections between nutritional status and pharmacokinetic results are relatively few. This difference highlights a broader problem in current research: the tendency to study mechanistic and clinical aspects separately (Mercer & M, 2011). The thematic relationships between keywords are visually presented in Figure 2.

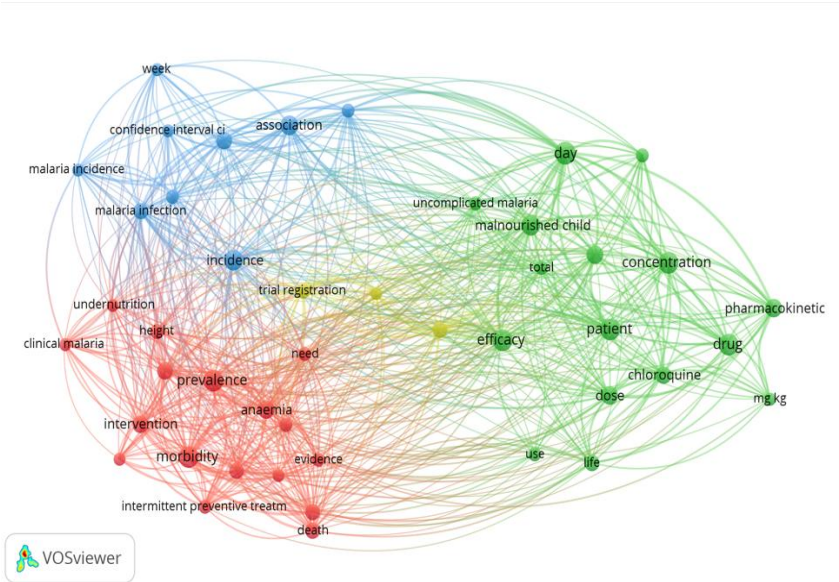

Figure 3. Visually Presents the Thematic Relationships Among The Keywords

The keyword co-occurrence network, shown in Figure 2, provides a visual representation of the intellectual structure of the studies examined. In this network, the size of each node

reflects the frequency of the corresponding keyword, while the distance and line thickness between nodes indicate the strength of their co-occurrence associations.

Clustering analysis shows that research in this area is organized into distinct, but related, fields. The main areas of focus include studying the frequency of diseases, research on malaria treatments, and important methodological considerations. Moreover, the frequent use of terms related to how malaria spreads and its clinical effects highlights the significant attention given to the disease's transmission, the resulting health problems, and nutritional status in areas where the disease is common.

Conversely, the classification of drugs reflects a growing body of research on how children are exposed to medications, how they are dosed, and how their bodies process drugs differently. This approach, which uses statistical and relationship focused methods, reflects the increasing use of analytical techniques to study the connections between malnutrition and malaria related results (Beeson et al., 2015).

Despite these separate groupings, the lack of direct connections between nutritional status and pharmacokinetic terms suggests that research in this area is not fully integrated. These findings align with previous studies that have shown how fragmented research areas often reflect limited collaboration between different fields, particularly when addressing complex global health issues (Van Eck & Waltman, 2010;Donthu et al., 2021).

Consequently, the findings from this network analysis underscore the need for a more comprehensive investigation that simultaneously considers nutritional, pharmacological, and clinical dimensions.The conclusion of this review is substantiated by a comprehensive bibliometric analysis. This analysis indicates that, despite the abundance of research in a particular field, there remains a substantial need for the application of mixed methods.The review's conclusions are supported by a thorough bibliometric analysis.

This analysis shows that, despite a lot of research in certain areas, there's a significant need for using combined methods.These methods would help us better understand the complex relationship between chronic malnutrition and the effectiveness of antimalarial treatments in children.Moreover, a density visualization was created, which, along with the network visualization, helped identify the most important research areas in the existing literature, as shown in Figure 3.

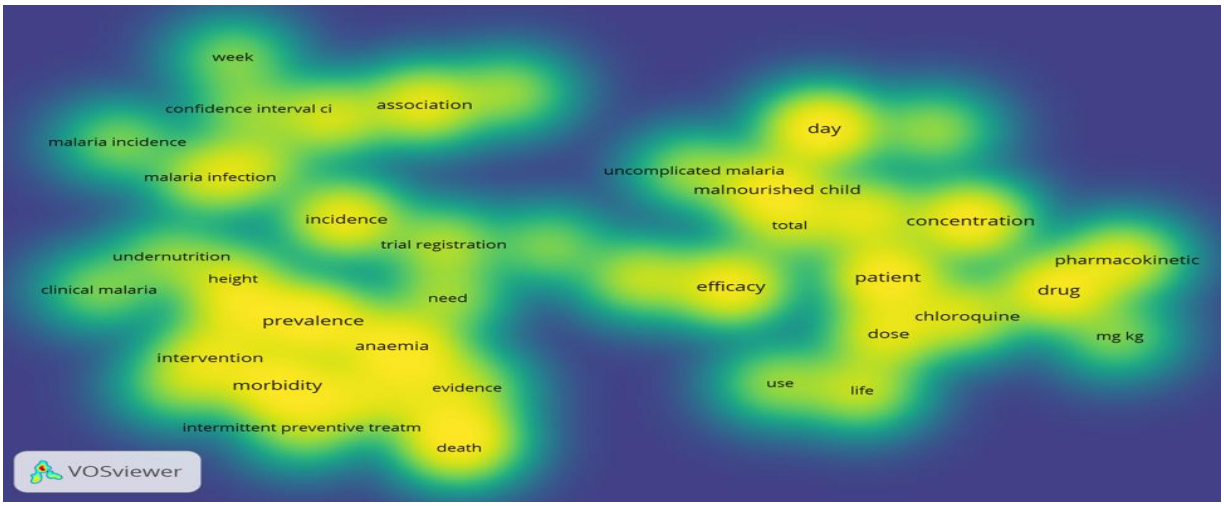

Figure 4. Density Visualization Of Keyword Co-Occurrence Generated Using Vosviewer

The density visualization highlights the concentration of research activity within specific thematic areas.Keywords displayed in brighter colors (yellow) indicate higher frequency and stronger representation in the literature, whereas darker regions represent less frequently studied topics. The data presented in the map indicates that the predominant focus of research centers on the epidemiological dimensions of diseases, encompassing their prevalence and associated morbidities, alongside pharmacological considerations, which include drug properties, pharmacokinetics, and concentration levels.

Conversely, the extant literature appears to contain a relative scarcity of studies explicitly examining the relationship between malnutrition and alterations in drug metabolism and efficacy, thereby implying a deficiency in research that integrates these two domains.This observation aligns with the network analysis results, which suggest that, despite the established nature of individual domains, interdisciplinary investigations encompassing nutrition, pharmacology, and clinical outcomes are still relatively few (Carmona Fonseca et al., 2008;Trocha et al., 2010).

Pharmacokinetics Alterations in Malnourished Children

Consistent with the pharmacological cluster identified in the bibliometric analysis (Figure 2), several studies have investigated the impact of chronic malnutrition on the pharmacokinetics of antimalarial drugs in pediatric populations. The limited integration between nutritional and pharmacokinetic domains observed in the network analysis highlights the need for a more focused evaluation of drug-related mechanisms (Checchi et al., 2006).

Evidence from the included studies indicates that chronic malnutrition significantly alters key pharmacokinetic parameters, including drug absorption, distribution, metabolism, and elimination (Hughes et al., 2021; Mercer & M, 2011). Malnourished children particularly those with wasting or underweight conditions frequently exhibit reduced drug exposure, as reflected by lower plasma concentrations and altered bioavailability. These changes have been linked to decreased drug exposure in several investigations; specifically, reductions in plasma concentrations and the area under the curve (AUC) were observed, with malnourished children exhibiting decreases of roughly 20% to 50% relative to their adequately nourished peers (Kadam et al., 2016; Gogtay et al., 2021). These observed alterations are largely due to physiological factors, such as lowered plasma protein levels, hepatic impairment, and shifts in body composition (Denoeud-Ndam et al., 2015).

Moreover, several studies on how drugs move through the body have shown that undernutrition can significantly hinder how drugs are absorbed. Gastrointestinal problems, characterized by changes in how the intestines absorb substances and how food is digested are a contributing factor (Kadam et al., 2016;Gogtay et al., 2021). As a result, these changes can hinder the absorption of antimalarial drugs taken by mouth, leading to less of the drug entering the bloodstream.

Moreover, changes in body composition caused by malnutrition, such as a decrease in lean body mass and shifts in fat distribution, could affect how antimalarial drugs are distributed in the body, particularly those that are fat soluble (Mercer & M, 2011). Lower levels of proteins in the blood, especially albumin, can also affect how drugs bind to proteins, increasing differences in the amount of free drug and potentially changing how well the drugs work.

In addition, liver function is affected in malnourished children, as studies show changes in enzyme activity and reduced metabolic ability, which can impact how quickly drugs are cleared from the body and contribute to differences in drug exposure between individuals.

These findings are consistent with broader studies that highlight the importance of individual factors in how antimalarial drugs are processed (Hughes et al., 2021).

Clinical pharmacokinetic studies in malaria endemic settings further support these findings. For example, altered drug exposure and variability in treatment response have been observed in children receiving artemisinin-based combination therapies and other antimalarials (Denoeud-Ndam et al., 2015; Ali et al., 2023; Mukaka et al., 2023). In addition, variations in drug efficacy and treatment response have been linked to both nutritional status and genetic factors influencing drug metabolism (Carmona-Fonseca et al., 2009).

Furthermore, inadequate drug exposure associated with malnutrition may contribute to reduced therapeutic efficacy and increased risk of treatment failure, particularly in areas with existing drug resistance (Olanrewaju & Johnson, 2001; Beeson et al., 2015). Preventive and adjunctive strategies, including nutritional interventions and micronutrient supplementation, have also been shown to influence malaria related outcomes (Rupérez et al., 2016).

Collectively, these pharmacokinetic alterations highlight the critical role of nutritional status in determining drug disposition and therapeutic effectiveness. The interplay between altered pharmacokinetics, host physiology, and treatment response underscores the need for optimized dosing strategies and integrated clinical approaches in malnourished pediatric populations (Seaton et al., 2007;Tona Lutete et al., 2021). These reductions in drug exposure may have important clinical implications, as subtherapeutic drug levels are likely to compromise parasite clearance, thereby contributing to reduced treatment efficacy and adverse therapeutic outcomes in malnourished children.

Therapeutic Outcomes and Treatment Efficacy

Building on these pharmacokinetic findings, the following section examines how these alterations translate into therapeutic outcomes in pediatric populations. Although therapeutic outcomes were not represented as a distinct cluster in the bibliometric network (Figure 2), they are still important endpoints closely related to pharmacokinetic changes and the severity of the disease.The studies reviewed suggest that children with malaria who are also malnourished show a significantly reduced response to treatment.

Children who are malnourished often have slower parasite clearance, which could increase the chance of treatment failing compared to children who are well-nourished.In addition, they appear more susceptible to recurrent infections and, in severe cases, higher mortality. The study showed that treatment worked less well and that the disease was more likely to come back. These findings suggest that the interaction between a weakened immune system and changes in how drugs are used is crucial for how effective a treatment (Oldenburg et al., 2018).

Specifically, the analysis of how the body processes drugs shows that less drug exposure could directly hinder the elimination of the parasite, leading to a less effective treatment.Conversely, the influence of malnutrition on therapeutic results is not uniform across the existing literature.Although numerous studies have documented reduced efficacy and extended parasite clearance, others have found no statistically significant disparities when standard dosing protocols are utilized (Maketa et al., 2015).

This variability may stem from differences in study methodologies, the severity of malnutrition, the specific antimalarial regimens employed, and the inherent variability in pharmacokinetic responses observed within diverse populations.Despite this variety, a common pattern indicates that a lower nutritional status negatively affects clinical recovery, especially in

cases of significant undernutrition.Factors likely contributing to this include a delayed immune response, concurrent anemia, and diminished drug exposure (Rogerson et al., 2010).

These findings collectively underscore the need for more thorough investigations that simultaneously evaluate pharmacokinetic parameters and clinical outcomes.This methodological approach is essential for improving our understanding of how effective treatments are for malnourished children.

Interaction between Malnutrition and Drug Efficacy

The interplay between chronic malnutrition and the effectiveness of antimalarial medications is intricate, encompassing both pharmacokinetic processes and immune function. Physiological alterations induced by malnutrition, including diminished plasma protein concentrations, shifts in body composition, and decreased hepatic enzyme activity, can substantially influence a drug's absorption, distribution, metabolism, and excretion.These alterations could potentially decrease drug exposure, leading to subtherapeutic plasma concentrations and, consequently, a diminished pharmacological effect.Clinical pharmacokinetic data corroborates this mechanism; for instance, Chotsiri et al (2019), researchers found that children with severe acute malnutrition had significantly lower exposure to lumefantrine when treated with artemether–lumefantrine.This suggests that the drug concentrations in t his group might not be enough.Therefore, the differences seen in how children respond to drugs and how drugs are distributed in their bodies highlight the need for personalized dosing, especially for those most at risk (Wallender et al., 2021).

Moreover, the effects of long term malnutrition on the immune system are significant, going beyond how drugs are processed. A compromised immune response and diminished capacity to combat parasitic infections are also implicated. Epidemiological data suggest that children experiencing severe acute malnutrition face an elevated risk of malaria infection, increased morbidity, and unfavorable clinical consequences, thereby underscoring the reciprocal association between nutritional status and the burden of malaria (Oldenburg et al., 2018; Mmbando et al., 2022). Furthermore, nutritional status has been shown to influence both susceptibility to infection and recovery dynamics, as well as growth outcomes in malaria-endemic settings (Ntab et al., 2007).

Consequently, nutritional status has been shown to influence susceptibility to infection and the trajectory of recovery, as well as growth outcomes in areas where malaria is endemic. The interaction between altered drug metabolism and an impaired immune system could significantly increase the chance of parasites taking longer to be eliminated, treatment failures, and the potential for drug resistance to develop.This is especially pertinent in areas already grappling with antimalarial resistance, where suboptimal drug concentrations could further diminish treatment effectiveness. This observation highlights the significant impact of a child's nutritional status on how well antimalarial treatments work (Ntab et al., 2007).

In addition, the bibliometric analysis showed a notable difference between research on how drugs move through the body and research on the spread of disease. This suggests that studies combining biological processes with clinical results are relatively uncommon. These observations highlight the need for comprehensive approaches that integrate drug developments with nutritional strategies, including the creation of personalized dosing plans for children with malnutrition.

DISCUSSION

This scoping review offers a thorough evaluation of existing research on how chronic malnutrition affects the effectiveness of antimalarial drugs and the resulting health outcomes in children. The overall findings underscore a multifaceted relationship involving nutritional status, pharmacokinetic modifications, and clinical effectiveness, while simultaneously exposing significant deficiencies in the integration of these areas.

Integration of Epidemiological, Pharmacological, and Clinical Evidence

The bibliometric analysis, employing VOSviewer, revealed three primary research domains: epidemiological burden, pharmacological investigations, and clinical outcomes. Although each of these domains is individually significant, they remain only partially interconnected, thereby reflecting a fragmented research environment. In this environment, malnutrition, malaria, and treatment response are frequently studied in isolation, rather than through integrated frameworks (Van Eck & Waltman, 2010;Donthu et al., 2021).

From an epidemiological standpoint, considerable evidence underscores a robust and reciprocal association between malaria and malnutrition. Malnutrition has been linked to an elevated vulnerability to malaria infection, increased morbidity, and detrimental clinical outcomes in pediatric populations (Ehrhardt et al., 2006;Oldenburg et al., 2018 ; de Wit et al., 2021). Conversely, recurrent malaria infections can worsen growth impairments, stunting, and the decline of nutritional status, thus reinforcing a cyclical connection between infection and undernutrition (Monteiro et al., 2016; Gari et al., 2018; Wilson et al., 2018). This reciprocal relationship underscores the importance of acknowledging nutritional status as both a determinant of and a consequence of malaria in endemic areas.

From a pharmacological perspective, malnutrition clearly affects how drugs are processed in the body through several physiological processes. Changes in how drugs bind to proteins in the blood, how the liver metabolizes drugs, and alterations in body composition can all affect how drugs are absorbed, spread through the body, broken down, and removed. Therefore, this can lead to differences in how much of a drug is available in the body and how well it works (Trocha et al., 2010). Empirical studies of how drugs move through the body further support these mechanisms. Chotsiri et al (2019) found that children with malnutrition had lower levels of important antimalarial drugs in their bodies, such as lumefantrine, chloroquine, and quinine. These reductions in drug exposure may undermine treatment effectiveness, especially within populations already vulnerable to severe disease.

Clinically, treatment outcomes in pediatric malaria are determined by a confluence of host immunity, nutritional status, and drug efficacy. Consequently, children experiencing malnutrition often show reduced effectiveness of treatments. The protracted duration required for parasite eradication, the heightened probability of treatment failure, and the elevated incidence of illness collectively reinforce this perspective (Danquah et al., 2009;Verret et al., 2011). Furthermore, the development of complications such as anemia and immune system dysfunction, coupled with the overall severity of acute malnutrition, exacerbates adverse outcomes and contributes to increased mortality rates (Mockenhaupt et al., 2004;Ahmed et al., 2011). Furthermore, insufficient drug exposure, which can occur due to malnutrition, may increase the risk of treatment failure and contribute to the development or persistence of antimalarial drug resistance (Plowe, 2005).

Despite these established connections, few studies have used combined methods to assess nutritional status, how drugs are processed in the body, and the resulting clinical outcomes.

Contemporary investigations primarily focus on isolated areas, including epidemiological associations or the efficacy of pharmaceuticals, thereby overlooking the complex interactions between host physiology and the response to drugs. This limitation is particularly noteworthy given that pharmacokinetic variability and immune system dysfunction may interact to influence the effectiveness of treatments (Rogerson et al., 2010; Hughes et al., 2021).

Moreover, intervention studies indicate that enhancing nutritional status might improve clinical outcomes and potentially optimize treatment response. Nutritional supplements and preventive strategies, such as intermittent preventive treatment and food-based programs, have shown benefits in reducing illness and improving growth in children living in areas where malaria is common (Ntab et al., 2007; van der Kam et al., 2016; Tona Lutete et al., 2021). Conversely, the degree to which these interventions directly influence pharmacokinetic responses and antimalarial effectiveness has not been thoroughly investigated.

These observations, taken together, highlight the necessity for more comprehensive, multidisciplinary research that integrates epidemiology, pharmacology, and clinical medicine. Such methodologies are crucial for a more profound comprehension of the intricate factors influencing antimalarial treatment outcomes and for guiding the formulation of refined dosing regimens and combined nutritional-pharmacological interventions tailored for at-risk pediatric populations.

Pharmacokinetic Alterations in Malnourished Children

The findings consistently indicate that chronic malnutrition significantly affects the pharmacokinetics of antimalarial drugs. Alterations in drug absorption, distribution, metabolism, and elimination were observed, particularly among children with wasting or underweight conditions.

Malnutrition induced physiological changes, including reduced plasma protein levels, impaired hepatic enzyme activity, and altered body composition, can substantially influence drug disposition and lead to increased variability in pharmacokinetic profiles (Trocha et al., 2010); Boullata, 2021). These alterations may ultimately result in subtherapeutic plasma concentrations, thereby compromising treatment efficacy.

Empirical pharmacokinetic studies further support these observations. Reduced drug exposure has been consistently reported in malnourished pediatric populations, including significantly lower lumefantrine concentrations in children with severe acute malnutrition treated with artemether–lumefantrine (Chotsiri et al., 2019). Similarly, altered pharmacokinetic profiles have been observed for other antimalarial agents, such as chloroquine, primaquine, and quinine, reflecting the influence of nutritional status on drug metabolism and clearance (Kadam et al., 2016;Gogtay et al., 2021).

In addition to host related physiological changes, disease severity and treatment conditions may further contribute to pharmacokinetic variability. Factors such as acute infection, anemia, and differences in drug administration or adherence have been shown to influence drug absorption and bioavailability (Checchi et al., 2006; Hughes et al., 2021).

Similar observations have been reported in broader antimalarial pharmacokinetic research, where variability in drug exposure is influenced by both host-related factors and disease-specific conditions (Mercer & M, 2011). Collectively, these findings reinforce the importance of considering nutritional status as a key determinant of pharmacokinetic variability in pediatric malaria treatment. These pharmacokinetic alterations may have important clinical

implications, as reduced drug exposure is likely to compromise parasite clearance and contribute to suboptimal therapeutic outcomes in malnourished children.

Implications for Therapeutic Outcomes

The relationship between malnutrition and therapeutic outcomes in pediatric malaria remains heterogeneous across studies (Oldenburg et al., 2018; Mmbando et al., 2022). While several studies report reduced treatment efficacy, delayed parasite clearance, and an increased risk of treatment failure in malnourished children, others do not observe statistically significant differences when standard dosing regimens are applied (Ntab et al., 2007;Maketa et al., 2015).

This variability likely reflects differences in study design, antimalarial regimens, transmission intensity, and the severity and type of malnutrition. In addition, variations in pharmacokinetic responses and baseline immunity across populations may further contribute to inconsistent findings (Wallender et al., 2021).

Nevertheless, there is strong biological plausibility supporting a negative impact of chronic malnutrition on treatment outcomes. Malnutrition is associated with impaired immune function, including reduced cell-mediated immunity and diminished capacity to control parasitemia, which may lead to delayed parasite clearance and slower clinical recovery (Rogerson et al., 2010).

Importantly, pharmacokinetic alterations observed in malnourished children may further exacerbate these effects. Reduced drug exposure and subtherapeutic plasma concentrations, as discussed in the previous section, are likely to compromise parasite clearance and increase the risk of incomplete treatment response (Chotsiri et al., 2019;Gogtay et al., 2021). This may contribute not only to higher rates of recrudescence but also to prolonged infection duration.

In high-transmission or drug-resistant settings, these combined effects may further increase the risk of treatment failure and facilitate the selection of resistant parasite strains, particularly when suboptimal drug levels are sustained (Plowe, 2005).

Overall, despite variability in reported outcomes, a consistent trend suggests that compromised nutritional status negatively influences clinical recovery, particularly in cases of severe undernutrition (Oldenburg et al., 2018). This effect is likely driven by the combined impact of impaired host immunity, altered pharmacokinetics, and increased disease severity.

These findings underscore the importance of considering nutritional status in treatment strategies and highlight the need for integrated interventions that address both pharmacological and nutritional determinants of therapeutic response in pediatric malaria.

Mechanistic Pathways Linking Malnutrition and Drug Response

The interaction between malnutrition and antimalarial drug efficacy is mediated through multiple interconnected mechanistic pathways involving both pharmacokinetic and immunological processes. From a pharmacokinetic perspective, malnutrition induces a range of physiological alterations that can significantly influence drug disposition. Gastrointestinal dysfunction, including mucosal atrophy and reduced bile secretion, may impair drug absorption and oral bioavailability. In addition, reduced plasma protein levels, particularly hypoalbuminemia, can alter drug distribution by increasing the unbound fraction of drugs, potentially affecting both efficacy and toxicity (Boullata, 2021).Changes in body composition, such as reduced fat mass and muscle wasting, may further influence the volume of distribution of lipophilic and hydrophilic antimalarial drugs (Mercer & M, 2011; Hughes et al., 2021).

Hepatic metabolism is also frequently compromised in malnourished children due to reduced liver enzyme activity, including alterations in cytochrome P450 function. This may

lead to unpredictable drug clearance and prolonged or insufficient drug exposure, depending on the metabolic pathway invol. Similarly, renal function alterations may affect drug elimination, further contributing to pharmacokinetic variability (Seaton et al., 2007).

Beyond pharmacokinetics, malnutrition-induced immune dysfunction plays a critical role in modulating treatment response. Chronic malnutrition is associated with impaired cell-mediated immunity, reduced T-cell function, and diminished antibody responses, all of which are essential for effective parasite clearance (Rogerson et al., 2010).This weakened immune response may limit the host's ability to complement pharmacological action, thereby reducing overall treatment effectiveness.

Importantly, these pharmacokinetic and immunological mechanisms do not operate in isolation but rather interact synergistically. Suboptimal drug exposure combined with impaired immune-mediated parasite clearance may amplify the risk of delayed parasite clearance, treatment failure, and recrudescence. Over time, sustained subtherapeutic drug levels may also contribute to the selection and spread of drug-resistant parasite strains (Plowe, 2005).

Notably, the limited overlap between pharmacokinetic and epidemiological clusters identified in the bibliometric analysis underscores a lack of integrative mechanistic studies. This gap highlights the need for multidisciplinary research that simultaneously evaluates drug exposure, nutritional status, immune function, and clinical outcomes in order to better understand the complex determinants of antimalarial treatment response in malnourished pediatric populations.

Research Gaps and Future Directions

This review identifies several critical gaps in the current literature. First, there is a lack of well designed studies that simultaneously assess nutritional status, pharmacokinetic parameters, and therapeutic outcomes within the same population. Most existing studies examine these domains in isolation, limiting the ability to establish causal relationships between malnutrition, drug exposure, and treatment response (Denoeud-Ndam et al., 2015; Hughes et al., 2021).

Second, standardized definitions and classifications of malnutrition are inconsistently applied across studies, reducing comparability and limiting the generalizability of findings. The frequent lack of differentiation between stunting, wasting, and underweight is particularly problematic, as these conditions are associated with distinct physiological and metabolic alterations that may differentially affect drug pharmacokinetics (Bhutta et al., 2013).

In addition, pediatric populations especially children with severe acute malnutrition remain underrepresented in pharmacokinetic and pharmacodynamic research. Ethical, logistical, and methodological challenges have contributed to this gap, resulting in limited evidence to guide treatment in one of the most vulnerable patient groups (Hughes et al., 2021).

Furthermore, there is insufficient evidence to inform optimal dosing strategies for antimalarial drugs in malnourished children. Current treatment guidelines largely rely on standard weight-based dosing regimens, which may not adequately account for altered pharmacokinetics, including reduced drug exposure and increased variability observed in malnourished populations (Zaloumis et al., 2014; Chotsiri et al., 2019).

Future research should prioritize integrated and multidisciplinary study designs that combine pharmacokinetic modeling, detailed nutritional assessment, immunological profiling, and clinical outcomes. The application of population pharmacokinetic approaches and physiologically based pharmacokinetic modeling may provide valuable insights into dose optimization in malnourished pediatric populations (Hughes et al., 2021).

In addition, the use of therapeutic drug monitoring could support individualized dosing strategies, particularly in high-risk groups with severe malnutrition or treatment failure. Finally, the role of combined nutritional and pharmacological interventions including nutritional rehabilitation alongside optimized antimalarial therapy warrants further investigation to improve both drug response and overall clinical outcomes (Ali et al., 2023; Bhutta et al., 2013). Addressing these gaps will be essential for developing evidence-based, context specific treatment strategies and improving malaria outcomes in malnourished children.

Strengths and Limitations

This scoping review provides a comprehensive and multidimensional synthesis of the available evidence by integrating systematic screening with bibliometric mapping. This combined approach allows not only the identification of key findings but also the visualization of research trends, knowledge gaps, and the degree of integration between pharmacokinetic, nutritional, and clinical research domains. As such, this review offers a broader conceptual understanding of how malnutrition influences antimalarial drug response in pediatric populations.

However, several limitations should be acknowledged. First, the inclusion of heterogeneous study designs, variations in population characteristics, and inconsistencies in outcome definitions may limit the comparability and generalizability of the findings. Differences in malaria transmission settings, antimalarial regimens, and severity of malnutrition further contribute to this variability.

Second, the reliance on published literature introduces the potential for publication bias, as studies with significant or positive findings are more likely to be reported. In addition, language restrictions and database selection may have resulted in the exclusion of relevant studies, particularly from low-resource settings where malnutrition and malaria are most prevalent.

Third, the lack of standardized classification and reporting of malnutrition across studies limits the ability to distinguish the specific effects of different forms of undernutrition, such as wasting, stunting, and underweight, on pharmacokinetic and therapeutic outcomes.

Furthermore, most included studies were observational in nature, which restricts causal inference and limits the ability to establish definitive relationships between nutritional status, drug exposure, and clinical outcomes. The limited availability of integrated studies combining pharmacokinetic, immunological, and clinical endpoints further constrains mechanistic interpretation.

Despite these limitations, this review provides important insights into an underexplored yet clinically significant area. By highlighting consistent patterns in pharmacokinetic alterations and their potential clinical implications, this study underscores the need for more integrative, methodologically robust, and context specific research to inform optimized treatment strategies for malnourished children with malaria.

Conceptual Interpretation of Malnutrition Drug Response Interaction

The complex interaction between chronic malnutrition and antimalarial drug response is summarized in the conceptual framework presented in Figure 4. This framework was developed based on the synthesis of evidence identified in this review, integrating pharmacokinetic alterations, immune dysfunction, and clinical outcomes into a unified perspective.

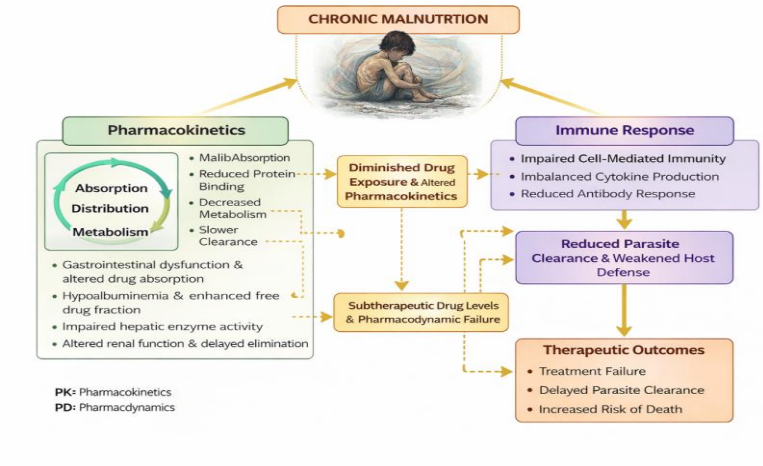

Figure 5. Conceptual Framework Illustrating the Interaction Between Chronic Malnutrition, Pharmacokinetic Alterations, Immune Dysfunction, and Therapeutic Outcomes in Pediatric Malaria

The framework is further supported by the bibliometric findings presented in Figures 2 and 3. Keyword co-occurrence and density analyses indicate that existing research is predominantly concentrated within epidemiological and pharmacological domains, with limited integration across nutritional status, pharmacokinetics, and therapeutic outcomes. This fragmentation is reflected in the conceptual model, which highlights interconnected pathways that are often investigated in isolation. The limited co-occurrence of nutrition-related and pharmacokinetic terms underscores a critical gap in the literature and supports the need for a more integrative approach, as illustrated in Figure 4.

The proposed framework emphasizes the multidimensional relationship between nutritional status and treatment response. Chronic malnutrition can alter key pharmacokinetic processes including drug absorption, distribution, metabolism, and elimination resulting in reduced drug exposure and increased variability in plasma concentrations. Concurrently, malnutrition-induced immune dysfunction further compromises the host's ability to effectively clear parasitemia. The combined effects of these alterations contribute to suboptimal therapeutic outcomes, including delayed parasite clearance, increased risk of treatment failure, and potential recrudescence.

From a mechanistic perspective, chronic malnutrition is associated with systemic physiological and metabolic disturbances that directly influence drug disposition. Impaired gastrointestinal function may reduce oral drug absorption, while decreased plasma protein levels, particularly albumin, can alter drug distribution and bioavailability (Oshikoya & Senbanjo, 2009; Mhango et al., 2023). In addition, compromised hepatic enzyme activity and renal function may impair drug metabolism and clearance, leading to subtherapeutic or unpredictable drug concentrations (Zaloumis et al., 2014).

At the same time, malnutrition contributes to significant immune dysfunction. Chronic undernutrition has been linked to impaired cell-mediated immunity, altered cytokine responses, and reduced capacity to control parasitic infections, all of which are critical for effective malaria clearance (Schaible & Kaufmann, 2007; Katona & Katona-Apte, 2008). This immunological impairment may explain the delayed parasite clearance, increased susceptibility to reinfection, and poorer clinical outcomes observed in malnourished children.

Importantly, the interaction between altered pharmacokinetics and impaired immunity is synergistic rather than independent. Reduced drug exposure, when combined with weakened host defense mechanisms, may substantially increase the risk of treatment failure and diminish overall therapeutic effectiveness. In some contexts, prolonged exposure to subtherapeutic drug levels may also contribute to the emergence and selection of drug-resistant parasite strains (Chotsiri et al., 2019; Gogtay et al., 2021).

This conceptual interpretation reinforces the central finding of the present review: chronic malnutrition should be considered a critical determinant of drug response and clinical outcomes, rather than merely a background condition. Integrating nutritional assessment into pharmacological and clinical management strategies is therefore essential for optimizing treatment effectiveness.

Overall, the framework serves as a visual and conceptual synthesis of the evidence, bridging mechanistic understanding with clinical implications. It highlights the need for a holistic approach to malaria management in pediatric populations, where therapeutic success depends not only on drug efficacy but also on the underlying nutritional and physiological context.

CONCLUSION

This scoping review provides a comprehensive synthesis of current evidence on the impact of chronic malnutrition on antimalarial drug response in pediatric populations, integrating epidemiological patterns, pharmacokinetic alterations, therapeutic outcomes, and underlying biological mechanisms.

The findings demonstrate that chronic malnutrition significantly affects key pharmacokinetic processes including drug absorption, distribution, metabolism, and elimination resulting in altered and often reduced drug exposure. These pharmacokinetic changes, compounded by malnutrition associated immune dysfunction, contribute to suboptimal therapeutic outcomes, including delayed parasite clearance, increased risk of treatment failure, and potential increases in morbidity and mortality.

Bibliometric analysis further highlights a growing but fragmented research landscape, with limited integration between nutritional status, pharmacokinetics, and clinical outcomes. This gap underscores the need for more interdisciplinary and mechanistically informed research approaches.

Importantly, this review identifies critical limitations in the existing evidence base, including the lack of differentiation between forms of malnutrition and the predominance of observational study designs, which constrain causal inference.

Overall, chronic malnutrition should be recognized as a key determinant of antimalarial drug response rather than a contextual background factor. Future research should prioritize integrative study designs that concurrently evaluate nutritional status, pharmacokinetics, immune function, and clinical outcomes. Such approaches are essential to inform optimized, context-specific treatment strategies and to improve malaria outcomes in vulnerable pediatric populations.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) exclusively for language editing, translation, and improving the clarity and readability of the text. Scopus AI and PubMed were used to support the literature search and identification of relevant studies, while Rayyan was utilized to facilitate the screening, selection, and organization of the included literature.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.
Author 2: Conceptualization; Data curation; In-vestigation.
Author 3: Data curation; Investigation.
Author 4: Formal analysis; Methodology; Writing - original draft.
Author 5: Supervision; Validation.
Author 6: Other contribution; Resources; Visuali-zation; Writing - original draft.

DECLARATION OF COMPETING INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript..

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