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Narrative Review of Malaria Comorbidities in Children

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ABSTRACT

Malaria continues to be one of the most significant global health challenges, particularly among children under five years of age in sub-Saharan Africa, where it remains a major cause of morbidity and mortality. Despite considerable progress in prevention and treatment, comorbidities such as anemia, malnutrition, respiratory infections, diarrheal diseases, HIV/AIDS, sickle cell disease, and tuberculosis complicate clinical management, exacerbate disease severity, and increase fatality rates. This narrative review examines the management of malaria with comorbidities, emphasizing the need for high-quality diagnostics, integrated care approaches, and context-specific preventive strategies. It highlights the persistence of poor case management in pediatric malaria and the clinical overlap that often results in misdiagnosis and overtreatment. Artemisinin-based combination therapies remain the standard for uncomplicated malaria, while integrated models of care that address HIV, malnutrition, and other concurrent infections have shown promising results in improving outcomes. Preventive strategies such as insecticide-treated nets (ITNs), indoor residual spraying (IRS), and the introduction of the RTS,S/AS01 malaria vaccine have reduced transmission rates, yet inequities in access and socioeconomic determinants continue to undermine progress. Furthermore, emerging research emphasizes the role of proteomics and epidemiologic mapping in understanding malaria pathophysiology and comorbidity interactions. Persistent gaps in diagnosis, treatment adherence, and surveillance systems call for policy reforms and increased investments in research, innovation, and healthcare infrastructure. Achieving malaria elimination will require coordinated multi-sectoral collaboration, sustained funding, and community engagement to integrate malaria control within broader child health and development agendas.

Keywords: Malaria comorbidities, Pediatric malaria, integrated healthcare, Preventive strategies, Policy and research gaps

INTRODUCTION

Malaria is a life-threatening parasitic infection caused by protozoan parasites of the genus Plasmodium. Children are the main vulnerable group, owing to their immature immune systems [1]. Malaria infection can lead to a range of complications, including anemia, cerebral malaria, coma, respiratory distress, and cognitive impairment. Understanding the epidemiology, pathophysiology, and comorbidities of malaria in children is essential to mitigate these adverse outcomes, particularly in sub-Saharan Africa where the disease predominantly affects this demographic [2]. A better appreciation of comorbidities associated with malaria is required to inform clinical decision-making and design public health interventions capable of reducing the global number of malaria-related deaths.

Understanding Malaria

Malaria remains one of the primary contributors to mortality in children under five years of age worldwide. Comorbidities frequently observed in children with a clinical diagnosis of malaria are seldom discussed. Identification, management, and preventive strategies become particularly challenging when the composition of these comorbidities is unclear [1, 2]. Malaria is caused by a protozoan parasite of the genus Plasmodium, which has co-evolved with its vector, the female Anopheles mosquito. Despite the availability of an effective vaccine, considerable vaccine hesitancy in many African countries has limited vaccine coverage [3]. Among the five distinct Plasmodium spp. that infect humans, Plasmodium falciparum is the species with the most significant

global health impact, causing approximately half a million deaths annually, predominantly in Africa, with young children comprising the majority of fatalities [8]. The clinical presentation of malaria varies according to the patient's age and the transmission intensity in the region, with young children in endemic areas being most susceptible to severe illness and death [9]. Plasmodium spp. infections are characterized by various stages, including pre-erythrocytic, erythrocytic, sexual, and sporogonic phases. Although parasitological confirmation of a malaria diagnosis is recommended before treatment, the majority of children receive treatment based solely on clinical presentation [7].

Overview of Malaria

Malaria is a life-threatening parasitic infection caused by a protozoan parasite [1]. Since children are immunologically naive to the malaria parasite, they represent the main vulnerable group. Approximately 300 million global cases of malaria occur per year with 90% in sub-Saharan Africa [3] and many children who become infected do not survive [17]. Those who do survive the acute infection, instead, often experience neurological, cognitive, and behavioral deficits. Malaria can produce effects on cognition and behavior that range from subtle to profound [11]. These effects are associated with brain injury caused by chronic or recurrent infections, anemia, and malnutrition. Potential cognitive deficits include problems with attention, memory, visuospatial skills, language, and executive functions [16]. The high prevalence of malaria contributes to a significant elevation in the risk of cognitive and behavioral impairments, which can hinder the ability of individuals to reach their full developmental potential [25]. These complications also influence the long-term economic outcomes of affected individuals and the broader communities where they reside [28]. During infection, children might experience anemia, cerebral malaria, coma, respiratory distress, and cognitive and behavioral issues [28].

Epidemiology of Malaria in Children

Malaria remains a major global public health concern. Children under 5 years represent the most vulnerable population and are more likely to present severe and potentially fatal forms of the disease [2]. Effective prevention and early treatment can significantly reduce the burden of paediatric malaria [25]. The clinical characteristics and laboratory indicators of children with severe malaria were analysed to provide a basis for prevention and treatment [1, 5]. In 2020, during the COVID-19 pandemic, early diagnosis and treatment of malaria became difficult [28]. A retrospective study was conducted on 236 paediatric patients with severe malaria admitted to two hospitals in Benin. Patients were assigned to one of three groups based on age: 4–12 months, 13–36 months, and 37–60 months [2]. The main clinical symptoms observed were severe anaemia, vomiting, prostration, poor appetite, dysphoria, and dyspnea [13]. In children aged 4–12 months, more than 50% presented vomiting and severe anaemia, and the highest proportions of symptoms were severe anaemia and prostration in the 13–36 months group[26]. Delirium occurred more frequently in the 37–60 months group [28]. Notably, the study recorded 12 deaths among severe paediatric cases in 2020. Overall, paediatric severe malaria in Benin exhibits an obvious seasonal pattern, with the disease situation worse in children under 5 years of age. Severe conditions and high fatality rates characterize this group [29].

Pathophysiology of Malaria

Malaria is a life threatening disease caused by parasites of the Plasmodium genus. The merozoites released in the blood can modulate the immune system and favour coinfections with other organisms [1, 7]. Comorbidities play a decisive role in the clinical course of malaria in children. Diagnosis can be challenging since the overlapping symptoms of comorbidities can mask the presence of malaria. Due to the difficulties in diagnosing malaria through clinical symptoms, laboratory analysis of blood samples remains the gold standard for detection. Malaria continues to be a major health issue worldwide [32]. Although the mortality rate has dropped significantly, estimates reveal that around 445,000 people still die each year. Children (under 5 years of age) are the most affected population, accounting for approximately 67% of total deaths [4]. Furthermore, the mortality rate of malaria varies greatly depending on the presence of comorbidities. The burden of this disease in children remains high, even when the patient is correctly medically attended [5]. A deep knowledge and understanding of the comorbidities that can occur in coinfected patients should be a key consideration for public health authorities and governments [4].

Comorbidities Associated with Malaria

Emerging data reveal considerable disease burden from comorbidities in children with malaria and raise questions about clinical management of these patients [1, 6]. This narrative review examines knowledge, research gaps and future directions on the pathophysiological interactions, disease risks, diagnostic challenges, treatment options, prevention and policy of malaria comorbidities in children [2, 9]. Anemia, malnutrition, respiratory infections, diarrheal disease, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), sickle cell disease and tuberculosis are common co-existing health conditions identified in children with malaria[3, 17]. Each may conceal or complicate malaria infection, with interactions altering susceptibility to and severity of malaria. Diarrhea is the most extensively studied comorbidity [5]. Anemia, malnutrition and respiratory infections exert protective and deleterious effects ranging from reductions in mortality rate to increased risk of cerebral malaria

[4]. Increased morbidity, and higher risk of death, are noted in the presence of HIV/AIDS and tuberculosis. Considerable diagnostic challenge exists due to epidemiological overlap, similar symptoms and clinical presentations[18]. The uncertainty threatens effective management and appropriate use of scarce resources. Establishing a twentieth-century malaria diagnostic network in Tanzania exposed a diagnostic accuracy below 50% in many public and private facilities, even among trained personnel [23]. Syndromic management of fever routinely results in over-diagnosis of malaria systematic neglect of other illnesses [26].

Anemia

Malaria and anaemia (haemoglobin < 11 g/dl) remain frequent in tropical regions and are closely associated. A case-control study involving children aged from 1 to 10 years was conducted to assess some assumed contributors to anaemia in the area of Bonconto Health Post in Senegal [6, 33]. Young children bear the world's highest prevalence of anaemia, most of which is of multifactorial aetiology, hampering prevention [21, 23]. Even moderate anaemia increases mortality and morbidity [30, 15]. There is a lack of effective preventive programs and no consensus on the safety of iron supplementation in malaria areas, reflecting poor understanding of anaemia causes. Therefore, a study was conducted to determine anaemia aetiology among pre-school Mozambican children to reduce the burden in this vulnerable group [7]. Critically low haemoglobin levels, exacerbated by severe malaria, pose a significant threat in cases of anaemia. Enhancing the educational attainment of families, promoting awareness, and implementing economic empowerment initiatives, alongside routine provision of iron supplements, are crucial in the fight against anaemia and improving health [31]. Quick diagnosis and treatment of malaria are crucial in reducing the likelihood of severe anaemia[11]. Together, these strategies can create a comprehensive approach that addresses the challenges posed by anaemia, ultimately leading to improved health outcomes for vulnerable populations [8].

Malnutrition

Malnutrition encompasses deficiencies, excesses, or imbalances in an individual's intake of energy, protein, or other nutrients [19, 23]. Malaria and malnutrition represent the two most important contributors to childhood morbidity and mortality worldwide, and their interaction may influence the outcome of each condition [6]. The overlapping distribution of malnutrition and malaria in developing countries explains the existence of concurrent infection by both conditions [8]. It has been caught attention, the reported association between malnutrition and an increased risk of developing clinical malaria consistently appeared contradictory in several studies conducted with several epidemiological designs (case control, cohort) and in different geographical areas with different malaria transmission intensity and pattern, socioeconomic status, age ranges of included study population, and threshold used for the diagnosis of malnutrition [9, 29]. The use of threshold that are not age specific to define malnutrition, the distinction of malaria cases by severity, and the consideration of cotrimoxazole prophylaxis were also influential factors in the determination of the relationship between malnutrition and clinical malaria[21, 27]. The incidence of clinical malaria was found higher among moderately malnourished group compared to well-nourished groups in some of the reports, while other studies showed a protective effect of malnutrition on clinical malaria development [10]. Nevertheless, the reported association between malaria and malnutrition in developed countries and countries of low malaria transmission intensity is probably much influenced by the expected association between malnutrition and poverty [11]. Because well-nourished individuals are more resilient to malaria infection than their malnourished equivalents, a decrease in malaria-specific immunity, through the reduction of symptomatic cases, might underpin the occurrence of more malaria infections in malnourished individuals in high-malaria-transmission areas [13]. In Burkina Faso and Mali, malnutrition was common in young children before the malaria transmission season, and malaria incidence was high despite high coverage of SMC and insecticidal nets [15]. A high joint burden of malaria and malnutrition is likely in the Sahel independent of any association between the two conditions [14]. Malnutrition can be classified into other different types, such as Deficiency of micronutrients, acute malnutrition and chronic malnutrition. Deficiency of micronutrient is classified into three as Vitamin A deficiency (VAD), Zinc deficiency and Iron deficiency [18]. Vitamin A deficiency is a nutritional problem affecting more than one-third of children aged 6–59 months world-wide, which coincides with increased risk of morbidity and mortality from infectious diseases; a highly prevalent problem in many low-income malaria endemic settings, where children are also extremely vulnerable to malaria infection[18]. Zinc is an essential micronutrient and plays a major role in the maintenance of an effective host defence mechanism and is a crucial micronutrient for immune system [17]. Deficiency of zinc disrupts immune function consequently predisposes the individual to enhanced risk of inflammatory diseases and infections [12]. Whereas iron is an essential element in a number of biological processes including immune responses, iron deficiency with and without concomitant anaemia is considered the most common micronutrient deficiency worldwide and it is estimated to affect 1.6 billion people worldwide, particularly preschool-aged children and pregnant women in developing countries[20, 26]. Several studies consistently showed that iron supplementation increases the risk of malaria morbidity and mortality in children exposed to intense malaria transmission settings [13].

Respiratory Infections

Breathing difficulty is frequent in children with malaria, so pulmonary infections may worsen clinical outcome. Both upper and lower tract respiratory infection with or without pneumonia are often concurrent with Plasmodium infection [8]. Bronchial hyper-reactivity following a Plasmodium falciparum acute attack was shown to be a factor in children with asthma. Bacterial infection of the respiratory tract in malaria has been observed in African children with a concomitant diagnosis of malaria and bacterial infection in the same patient [6]. However, a diagnosis of bacterial infection derived purely from clinical symptomatology in patients with fever may be incorrect since Plasmodium invasion alone may just be the cause of symptoms [3]. Conversely, when malaria infection is confirmed within an area of high malaria transmission, a diagnosis of respiratory bacterial infection may be difficult at first even with a negative chest X-ray[4]. In well-established, controlled conditions, bacteriologically proven respiratory tract infections (including Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae, Klebsiella spp., Moraxella catarrhalis and Pseudomonas aeruginosa) and Plasmodium falciparum malaria have been found in children living in endemic areas. However, when overlapping symptoms are found with a patient's admission such as convulsions and anaemia, it is still difficult to distinguish between Malaria and pneumonia without the use of specific diagnostic tools as concomitant infections may occur [4].

Diarrheal Diseases

Besides the major comorbidities, diarrheal diseases frequently complicate a malaria infection [5]. Malaria can cause diarrhoea, especially in children, and this is often associated with delays in diagnosis [5]. A study of Nigerian children has demonstrated an association between a falciparum-positive blood smear and severely dehydrating diarrhea [2]. The mechanisms involved in diarrhoea appear independent from a falciparum malaria diagnosis. For each of these cases, the severity of illness can often influence the management strategy [7]. Infections with microbial pathogens such as Campylobacter are common causes of acute childhood diarrhoea in rural and urban areas of developing countries. Thus, a child presenting with diarrhoea that is complicated by Plasmodium falciparum infection may be mistakenly scheduled for anti-malarial treatment alone [8]. Cases of Plasmodium falciparum malaria associated with sub-acute intestinal obstruction have been reported. Other than malaria, several infections in the tropics have been described to be associated with intestinal obstruction, such as amoebiasis and round worm infestations [9]. Plasmodium falciparum malaria presenting with intestinal obstruction is very rare in adult patients. Co-infections with malaria and diseases such as leishmaniasis or schistosomiasis have also been reported. It is necessary to keep in mind that malaria parasitaemia was not associated with mortality outcome in the setting of child admissions to a district hospital in Kenya [8]. The recognition of malaria as a potential cause of diarrhoea in African children has important implications in terms of treatment and patient outcome [3].

HIV/AIDS

The co-epidemics of malaria and HIV/AIDS pose a significant clinical challenge for children affected by both infections, particularly in sub-Saharan Africa and Southeast Asia [11]. Children infected with HIV by vertical transmission can experience a rapidly progressive or a more indolent clinical course [12]. Anaemia is the most prevalent comorbidity regardless of age, especially among children <1 year and those with severe immunological decline. Children with advanced immunosuppression have higher densities of Plasmodium falciparum parasitaemia and an increased risk of mortality from malaria [11]. HIV infection impairs the generation of P. falciparum-specific antibody responses, which may partly account for the increased severity of malaria among HIV-infected children. In addition, malnutrition associated with HIV infection contributes to immunodeficiency and increases the risk of severe malaria disease and death [9]. The dual burden of HIV and malaria infections in childhood places children at a greater risk of morbidity and mortality than either infection alone [7].

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive disorder caused by a mutation in the β-globin gene that results in the production of abnormal hemoglobin S [3]. Individuals with SCD have hemoglobin SS (HbSS) genotype, whereas those with heterozygous form have hemoglobin AS (HbAS) and are said to have sickle cell trait[14]. The HbAS genotype is present in approximately 30% of individuals living in malaria-endemic areas and confers around 90% protection against severe malaria. However, individuals with HbSS genotype have increased susceptibility to severe malaria and mortality [10]. Infection with Plasmodium falciparum causes various complications in persons with SCD, including induction of vaso-occlusive crises, exacerbation of anemia, and triggering of chronic complications. Splenic function is impaired in individuals with SCD, contributing to their increased vulnerability to Plasmodium falciparum malaria infection [5]. Patients with SCD require early diagnosis and preventive interventions, including long-term antimalarial prophylaxis in malaria-endemic regions [13].

Tuberculosis

Mycobacterium tuberculosis (MTB) should be considered early as a primary cause or underlying comorbidity in children with severe pneumonia in high TB-burden settings [14]. HIV co-infection, malnutrition, and young age are recognized risk factors for both TB and all-cause pneumonia [7]. The incidence of tuberculosis among HIV-infected children is high in Ethiopia and Tanzania, particularly in the absence of preventive therapy such as Isoniazid and Cotrimoxazole [15]. Effective approaches for early detection and treatment of TB in children and adolescents are needed in endemic settings.

Impact of Comorbidities on Malaria Outcomes

The coexistence of malaria with other diseases complicates clinical presentations, influences mortality, and produces profound long-term health effects [6]. Underlying anaemia, malnutrition or immunosuppressive states increase the likelihood that malaria absence of treatment will lead to death [5]. The connections represent important public-health issues for limited-resource settings and area critiques of the widely applied "malaria hypothesis" that asserts that co-morbidities are actually protective. Childhood admissions for maltreated malaria crop up wake sustained by encephalopathies of unknown aetiology[17]. Consider a substantial proportion may also suffer from encephalitides, vascular syndromes or metabolic derangements that are masked by accompanying malaria, which is subsequently estimated to account for only about half of malaria-positive coma cases and far less of the total [4].

Clinical Outcomes

In children, comorbidities profoundly influence the course and outcome of malaria infection. HIV infection and malnutrition emerge as important conditions simultaneously present with malaria, exacerbating morbidity and mortality [16]. Additional comorbidities encompass anemia, respiratory infections, diarrheal diseases, sickle cell disease, and tuberculosis, all affecting clinical presentations and long-term health [17]. Despite this evident impact, comprehensive understanding of the interactions between malaria and these comorbidities remains insufficient. Malaria, particularly uncomplicated forms, frequently manifests a variety of nonspecific symptoms that complicate the identification of additional simultaneous diseases [14]. The clinical overlap, common in malaria-endemic regions, further challenges the differential diagnosis between malaria and other disorders. Clinical observations suggest that the concurrent presence of another disease alongside malaria often signals an elevated risk of death potentially exceeding cumulative mortality expected from each condition individually and is associated with adverse long-term outcomes [11]. As mortality from malaria declines, the significance of its adverse health effects will rise, underscoring the urgency to comprehend its interactions with common comorbidities [13].

Mortality Rates

The mortality rate from malaria is higher in children than in adults; conditions that increase the risk of severe malaria, such as malnutrition, also increase the risk of developing fatal disease [18]. Both high malaria parasite counts and high or low haemoglobin levels contribute to increased deaths [19]. Malaria often masks or is masked by other infections and can be complicated by more than one illness at a time [32].

Long-term Health Effects

Malaria-related childhood deaths rose from an estimated 202,000 in 2015 to 368,000 in 2020, representing 34.2% of global malaria deaths among children aged [14]. Survival also carries a risk of long-term consequences. Postdischarge deaths following severe anaemia have been reported for up to 6 months after hospital discharge 4. Long-term neurologic and neuropsychiatric sequelae following an episode of cerebral malaria range between 11 and 34% [20]. Mental health impairment associated with malaria with neurological involvement varies from behavioural problems to thought disturbances, hallucinations, and depression [11]. Attention deficits and disruptive behavioural disorders have a tendency to resolve within 12 months of diagnosis, although, in some patients, such deficits persist for up to 24 months [1]. Poor cognition has been reported in up to 21% of cases 3 months post cerebral malaria and may be associated with poor academic achievement over a similar period. Psychiatric disorders such as post-traumatic stress disorder following cerebral malaria usually manifest 6 months after treatment [33].

Diagnostic Challenges

Malaria diagnosis poses significant challenges, especially in children with comorbidities. Malaria infection frequently occurs alongside other infections, particularly in children, creating a complex diagnostic and treatment scenario [21]. Nevertheless, malaria infection remains the primary consideration in febrile children with Plasmodium falciparum parasitaemia [4]. As the clinical syndromes associated with malaria become more severe, the likelihood increases that the observed malaria parasitaemia represents an incidental co-infection rather than the principal cause of illness [22]. When a patient presents with signs suggestive of cerebral malaria and malaria parasitaemia, additional non-malarial infectious agents are commonly found [15]. Distinctions are often difficult in less typical presentations, yet the potential co-existence of another disease must be acknowledged to avoid

overlooking an additional or alternative cause [13]. Accordingly, reliable diagnostic tools capable of discriminating between malaria and other conditions that mimic its clinical syndromes are urgently required. Among the range of methods under evaluation, several readily available laboratory tests hold considerable potential. Anaemia is common in malaria patients, but cannot reliably differentiate between severe malaria and an alternative illness, nor can indicators of parasite burden [16]. In contrast, markers of haemolysis (e.g., plasma haemoglobin), immunopathology (e.g., haptoglobin), endothelial activation (e.g., angiopoietin-2), platelet counts, and procalcitonin exhibit promise for distinguishing uncomplicated (or severe) malaria from other causes of fever or coma, although the stability of these markers varies [13]. A composite scoring system incorporating such measurements may yield the most accurate discrimination.

Differential Diagnosis

Malaria symptoms often manifest as non-specific clinical features that overlap with other common infections. Anaemia, malnutrition, and respiratory infections complicate the clinical picture, since their symptoms resemble those of malaria [12]. In malaria-endemic areas, respiratory infections constitute a major cause of morbidity and mortality [3]. Infants, small children and pregnant women are particularly at risk [15]. Malaria may also favour the establishment or progression of some bacterial or viral infections in people living in endemic malarious areas. Recurrent exposure to malaria infection leads to the development of both anti-disease (clinical immunity) and anti-parasite immunity [2]. Clinical immunity controls the severity of malaria and lowers the risk of severe disease and death [1]. However, it is often lost when the children leave the area and so they remain vulnerable to the disease. Therefore, prophylaxis and diagnosis of other infections, including bacterial septicemia, should be considered in febrile immigrants from malarious areas [4].

Laboratory Techniques

Multiple laboratory techniques are employed for malaria diagnosis, with microscopy and malaria rapid diagnostic tests (mRDTs) being the most common methods [15]. Microscopy allows species identification and quantification of parasitaemia when performed properly, and is considered the gold standard [23]. The limited availability of trained personnel, however, makes microscopy a challenge in many health care facilities. mRDTs provide a quicker alternative, being easier to use and requiring minimal training[17]. Although many mRDTs can distinguish between P. falciparum and non-falciparum species, a qualitative diagnosis is achieved without quantification of parasitaemia. Molecular methods such as polymerase chain reaction (PCR) can identify malaria parasites with the highest sensitivity and specificity, detecting low-level parasitaemia and differentiating species when used with microscopy [24]. Nevertheless, PCR is expensive, time-consuming, and impractical for routine diagnosis in most developing countries [4].The limitations of microscopists and adherence to diagnostic guidelines negatively impact proper disease diagnosis and treatment [2]. Misdiagnoses are often due to presumption, where all febrile cases are treated with antimalarial drugs despite negative test results or absence of laboratory confirmation [13]. These challenges highlight the necessity for continuous training and implementation of diagnostic tests to reduce presumptive malaria treatment and overdiagnoses at health facilities [16]. The emergence of Comorbidities Associated with Malaria has further complicated the clinical diagnosis of malaria. The presence of Comorbidities Associated with Malaria, whose clinical signs and symptoms overlap with those of malaria, makes the diagnosis even more complicated [23].

Management of Malaria with Comorbidities

High-quality clinical management is critical for directing treatment towards the actual cause of symptoms rather than the diagnosis [15]. The presence of severe symptoms provides clinicians with more guidance, yet children with uncomplicated malaria who also present with one of the leading causes of febrile illness often receive poor clinical management [25]. This highlights the importance of thorough and accurate diagnostics in malaria-endemic areas [2]. Malaria comorbid with HIV and malnutrition predominantly occurs in children under the age of five, with arrested development leading to one disease complicating the clinical management of the other. Subdued immune responsiveness leads to atypical presentation, complicating and delaying diagnosis [2]. The use of artemisinin-based combination therapy remains the recommended first-line treatment for uncomplicated Plasmodium falciparum malaria, with ASAQ, AL, and DHA-PQ listed as potential drug combinations [26]. Other forms of malaria and known resistance should prompt clinicians to adjust their approach accordingly.

Treatment Protocols

Comorbidities in children suffering from malaria either arises as a direct complication of the malaria infection or represent comorbidities that themselves cause malaria infection [16]. The coexistence of malaria infection and one or more additional diseases that incur separate risk or liability of illness is referred to as malaria comorbidities. Comorbid conditions affecting children with malaria are highly clinically relevant [15]. The nonspecific clinical features of malaria contribute to frequent misdiagnosis, leading to unnecessary treatment with antimalarials in patients who do not actually require them [18]. Such overtreatment with antimalarials can potentially lead to the development of resistance to the drugs used. The following sections enumerate the major comorbidities associated

with malaria in children. Anemia ranks as the most frequent manifestation and cause of morbidity and mortality in pediatric malaria [17]. Repeated infections with Plasmodium species result in progressively more severe episodes of anemia. Among different strains of Plasmodium, infection due to Plasmodium falciparum tends to cause the most severe degree of anemia [11]. Alterations in cell-mediated immunity heighten the susceptibility of malaria-infected children to colonization by other bacteria or viruses, leading to concurrent infections such as respiratory infections (most commonly pneumonia) or diarrheal disease [8]. Respiratory disease and diarrheal disease rank among the most prevalent and deadly diseases in children under the age of five [1]. Both bacterial and viral respiratory infections demonstrate a link with malaria. Infectious diseases such as HIV/AIDS impose additional burdens on the healthcare systems of sub-Saharan African countries, where malaria is also endemic [7].

Integrated Care Approaches

Despite ongoing efforts to improve clinical management, severe malaria continues to be one of the major causes of childhood mortality worldwide [3, 5]. A broad range of conditions, commonly referred to as comorbidities, frequently complicate the clinical picture and are associated with increased mortality [19]. Co-infection with multiple pathogens and the presence of severe malnutrition may also exacerbate the morbidity and death attributable to malaria. An overview of the principal comorbidities affecting children following severe malarial syndrome is provided, along with a discussion on the additional challenges that co-existence imposes on patient prognosis and long-term health. Current preventive approaches for these illnesses are also presented [13]. Treatment planning ideally requires detection of all illnesses in children with possible malaria; consequently, an agenda for action is proposed to help reduce the burden associated with co-existing diseases [30]. Provision of appropriate preventive measures may have a considerable impact on the disease burden of all four illnesses in co-endemic areas and would contribute towards improving the quality of life in the pediatric population. Global efforts to reduce malaria mortality have plateaued, and declines in infection have stalled or possibly reversed, suggesting that important gaps remain in clinical management [25]. Effective management of concurrent HIV and malaria infections requires a comprehensive and integrated approach addressing healthcare, psychosocial support, community engagement, and education [25]. The prevalence of co-infection in resource-limited settings emphasizes the need for targeted interventions and integrated care models. The immunological interplay between HIV and malaria necessitates optimized treatment, careful consideration of drug interactions, and development of innovative therapies [24]. Integrated healthcare models combining services for HIV and malaria streamline care delivery and improve health outcomes. Psychosocial and community support interventions focus on mental health, stigma reduction, empowerment, and community involvement, contributing to better treatment adherence and overall outcomes [27].Case management of malaria remains poorer than for most other common childhood illnesses[26]. Following admission to hospital, half of the severe malaria cases are not receiving appropriate treatment, with fewer than 2 children out of 10 admitted with a diagnosis of malaria receiving the recommended first-line treatments [23]. Despite improvements, up to 40% of children with a negative blood slide are still treated presumptively for malaria. Gradual transition to artesunate is occurring, three years after policy change. Continued efforts are essential to support improved inpatient care, dissemination and implementation of guidelines, and access to recommended drugs. Improved clinical information may help track progress [28].

Preventive Strategies

The introduction of RTS,S/AS01 (RTS,S), a pre-erythrocytic vaccine, represents the first-time addition of a malaria vaccine to existing prevention measures for children living in perennially malarious areas in sub-Saharan Africa[4]. The vaccine confers partial protection through immunization by repeatedly stimulating the immune system to mount a response against the circumsporozoite protein while sporozoites develop into exoerythrocytic forms in the liver [4]. Malaria control in children in endemic areas requires a combination of interventions. The most effective intervention, preventing transmission by reducing vector-human contact, is being expanded rapidly through distribution of insecticide-treated nets (ITNs) and widespread implementation of indoor residual spraying (IRS), which reduce the number of infective bites and contact between vector and human[6]. Community trials in Africa have shown that full coverage with ITNs can halve the number of episodes of malaria among children, while also reducing the overall mortality rate in children younger than 5 years. Use of ITNs by pregnant women reduces the risk of low birth weight, placental parasitaemia, stillbirths, and miscarriages [5]. Epidemiological and social science studies have demonstrated that children born into environments characterized by low socioeconomic circumstances are at a greater risk of malaria infection [7]. Although existing malaria prevention methods are commendable and focus largely on the distribution of ITNs, IRS, larval source management, diagnostics, and treatment, they do not take into account the socio-economic circumstances and conditions that predispose children to malaria. Given the strong link between poverty and malaria, governments and policymakers in SSA need to focus on improving the socio-economic conditions of people to eradicate the disease [6]. Moreover, children from various geographical locations do not have the same predisposing factors for malaria, so multiple policy interventions are required to remove health disparities between different groups of children at risk [12]. The

healthcare access gap between rural and urban areas also has a huge impact on the prevalence of malaria; therefore, it is imperative to ensure that prevention, treatment, and diagnostic services become accessible and affordable to all communities, including urban slum dwellers and displaced populations [15]. Community-based interventions combining training, media, and social mobilization have been effective in reducing the burden of malaria in children, but effective preventive programs must also aim to influence behavioral changes to reduce the burden of the disease significantly [29].

Vaccination Efforts

The introduction of an effective malaria vaccine stands to further reduce this disease burden [1]. While such a vaccine remains elusive, efforts are underway to prepare for its eventual introduction [2]. A vaccine that provides partial protection against malaria should be regarded as a valuable addition to the current vector control measures. Acceptability of a malaria vaccine is high in sub-Saharan countries with on-going trials. Facilitating widespread uptake of the vaccine will therefore be key, but community engagement around the vaccine remains inadequate 30. Final products containing a malaria vaccine might now be available, but questions remain as to how to ensure equitable access and optimize implementation strategies [1]. In malaria-endemic African countries, immunizations are routinely delivered via the expanded programme on immunisation (EPI)[5, 9]. Despite the wide-scale delivery of childhood vaccinations only 34% of children sleep under insecticide-treated nets (ITNs) and 39% access effective antimalarial treatment; deployment of malaria vaccines through the EPI could thus reach many children who do not currently benefit from other malaria interventions. Childhood vaccinations already reach a substantial proportion of children; no major disparities exist by sex, while uptake is higher among children living in urban settings and among those with more educated mothers [7, 10]. Despite widespread progress in reducing disease burden through vaccination initiatives, vector control and disease management, the prevention and treatment of malaria in children remains a challenge [11]. The presence of malaria comorbidities further complicates the clinical prognosis. The following discussion highlights the major comorbidities and their clinical impact in children [8].

Public Health Initiatives

Malaria accounts for over 400,000 deaths annually [28]. Over half of these deaths and a majority of the 247 million annual malaria cases occur among children younger than five years of age [29]. Most affected countries are located in sub-Saharan Africa, where malaria is one of the leading causes of death and morbidity among children. Public health initiatives targeting malaria in children have shown progress in control efforts over the past few decades, substantially reducing death rates despite widespread insecticide resistance [31]. Malaria comorbidities such as anemia, malnutrition, HIV/AIDS, respiratory and diarrheal infections, sickle cell disease, and rarely, tuberculosis contribute significantly to malaria-associated deaths in children [3]. Integrated malaria and comorbidity prevention and control efforts have the potential to decrease mortality rates further, yet few such initiatives exist [25]. The global intersectoral approach that successfully scaled up the distribution of long-lasting insecticidal nets, indoor insecticide spraying, larval source management, and treatment targeting children in sub-Saharan Africa may serve as a model for integrated intervention efforts [1, 4[.

Research Gaps and Future Directions

Human malaria affects all age groups, but children younger than five years remain the most vulnerable group 29. Different conditions contribute to the initial clinical presentation or develop at different stages of the disease thereby contributing to the overall mortality rate [3, 23]. Currently available malaria vaccines provide partial protection and the protective efficacy is likely affected by coexisting infections. While many malaria-host proteins remain poorly defined, serum protein profiling during malaria with other coinfections can provide understanding into the malarial mechanism and can be exploited for potential drug targets and prognosis [8, 24]. The increasing availability of proteomics tools has led to the identification of malaria parasite proteins that play critical roles in the pathogenesis of malaria malaria comorbidities [5, 28]. Future steps will help develop a management policy and preventive measures to reduce mortality linked to malaria with other conditions [26, 7].

Emerging Trends in Research

Malaria remains a major cause of morbidity and mortality in modern day sub-Saharan Africa. The heavy disease burden of malaria in children under the age of 5 has been previously established [1, 32]. Malaria during childhood poses a threat to health during the neonatal period and into late adulthood. The detrimental effects of malaria at this formative stage can contribute to many life-long health impairments [5]. The pathophysiology of malaria also allows for other, associated illnesses to exacerbate the severity of malaria. Anemia, malnutrition, respiratory infection, diarrhea, HIV/AIDS, sickle cell disease, and tuberculosis are the main diseases concurrently present with malarial fevers [3]. These diseases, whether caused by infection or nutritional deficiencies, will present children with a wide range of clinical symptoms [24]. A comprehensive knowledge of comorbidities that occur with malarial infection is necessary to properly assess a child's health and alleviate the disease burden [30]. The contiguous nature of these conditions allows symptoms of each disease to overlap and blur in presentation. The

concurrent presence of each infective agent alters the course of incubation and intensifies the severity. These alterations give rise to different clinical features [32]. And so, children suffering from multiple infections will present a wider range of symptoms than that of a single infection. The associated diseases have differing levels of severity in malarial illness. This was determined using the minimum case fatality rate and average mortality of the associated diseases [31]. Interplay of different infective states produces a multifaceted clinical profile. A further understanding and mapping of how the conditions influence one another is necessary to lessen the severity of the co-occurrent illnesses. Research on the relationship of malaria to other conditions is, itself, far from comprehensive [25]. There exist major gaps in knowledge regarding not only associated conditions, but also the means to prevent and alleviate the condition [29]. While demography of children at highest risk was established, paired with a catalogue of clinical symptoms across each age group and location, these results merely begin to reveal the complexity of the relationship between a child's health and the burden of malaria. An epidemiologic map constructed from the data will assist in tracking the course of the disease. Supplementary information on the safety and efficacy of the licensure vaccination is needed before the implementation of the vaccine can be regarded as reasonable and coherent [28]. Another gap involves the standard methods used in diagnosing co-occurrent malaria and associated diseases. A more detailed and homogeneous protocol across clinics and hospitals is necessary to increase universal accuracy in diagnosis [27].

Policy Recommendations

Effective disease control, including malaria, requires coherent policies and commitment at the highest level, coordinated with decentralised mechanisms that enable local leaders to mobilise resources and implement strategies that fit the local context [28]. Substantial additional investment in research, prevention and care is needed before the Sustainable Development Goals target of ending the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases can be realised [33]. Malaria elimination requires targeted policies and strategies that underpin work across four key interconnected areas: accelerating elimination from countries in elimination or pre-elimination phases; scaling up control in persistently high-burden countries; preventing transmission from imported cases in malaria-free countries; and translating accompanying investment in science and innovation into new tools that support efforts in all settings [25].

CONCLUSION

The coexistence of malaria with other infectious and non-infectious diseases in children presents a complex and evolving public health challenge. Comorbidities such as anemia, malnutrition, respiratory and diarrheal diseases, HIV/AIDS, sickle cell disease, and tuberculosis not only complicate clinical diagnosis and treatment but also exacerbate morbidity and mortality. The review demonstrates that despite the availability of effective interventions, such as artemisinin-based therapies, insecticide-treated nets, and the RTS,S/AS01 vaccine, progress has stalled in many endemic regions due to socioeconomic inequalities, inadequate healthcare access, and fragmented disease control programs. Integrated care models that address malaria and coexisting conditions holistically through combined healthcare delivery, psychosocial support, and community engagement have proven effective in resource-limited settings. Strengthening health systems, training healthcare workers, and improving diagnostic precision are essential to reducing misdiagnosis and overtreatment, which contribute to drug resistance. Future research should leverage proteomic and epidemiological tools to better understand malaria's interaction with other diseases and to identify new therapeutic targets. Policy frameworks must evolve to support multi-sectoral collaboration, emphasizing investment in prevention, vaccine deployment, and equitable healthcare delivery. Governments and international agencies should prioritize socioeconomic reforms that reduce vulnerability among children in endemic areas while sustaining surveillance and data-driven policymaking. Ultimately, the elimination of malaria and its comorbidities will depend not only on medical innovation but also on political commitment, global cooperation, and the empowerment of local communities. Through integrated action and sustained investment, a significant reduction in malaria-related mortality among children can be achieved, moving closer to the realization of the Sustainable Development Goal of ending malaria by 2030.

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