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Clinical Guideline

Adapted Guidelines for Malaria Case Management in Sudan

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Abstract

Background: Malaria is a major public health hazard in Sudan. The latest update to the malaria diagnosis and treatment protocol in Sudan was in 2017, after which multiple developments in the global guidelines for malaria case management have taken place. Sudan's Federal Ministry of Health (FMOH) has updated its malaria case management policy to guide healthcare workers in making informed decisions about malaria diagnosis, treatment, and prevention.

Methods: The National Malaria Control Program (NMCP) selected a multidisciplinary Technical Advisory Committee (TAC) balanced to bring together diverse expertise. The committee convened with the NMCP writing team to propose, discuss, and approve updates to the malaria case management protocol. Protocol updates were prioritized based on the guidelines' efficacy, safety, and cost-effectiveness.

Results: The management guidelines for severe malaria were updated so that parenteral artesunate is the first-line treatment, with parenteral quinine reserved as second-line therapy. Other updates include the adoption of oral artemether-lumefantrine (AL) as the first-line treatment for uncomplicated malaria in the first trimester of pregnancy. The 2023 protocol upheld the 2017 treatment guidelines for uncomplicated malaria in other groups, including children, adults, and pregnant women in their second and third trimesters, with AL as the first-line treatment and dihydroartemisinin-piperaquine (DHAP) as the second-line treatment.

Conclusion: Key changes in the 2023 protocol include updates to the treatment guidelines for severe malaria in all patient groups and uncomplicated malaria in the first trimester of pregnancy. Future adjustments to the malaria protocol will take place in accordance with changes in the local context of Sudan as well as global malaria guidelines.

Keywords: Sudan, malaria, protocol, case management, prevention

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Summary of Guidelines

Recommendation 1: Malaria diagnosis

To confirm the diagnosis of malaria, all suspected cases should undergo a parasitological test (microscopy or rapid diagnostic test [RDT]).

Recommendation 2/3: Treatment of uncomplicated malaria

The first-line treatment for uncomplicated malaria is artemether-lumefantrine (AL).

The second-line treatment is dihydroartemisinin-piperaquine (DHAP); it is indicated in the case of treatment failure or when the first-line treatment is contraindicated or unavailable.

Recommendation 4: Treatment of uncomplicated Plasmodium vivax malaria

In addition to AL, patients with *Plasmodium vivax* malaria should be prescribed primaquine (except pregnant and breastfeeding women, and infants aged <6 months).

In people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, primaquine is prescribed in adjusted dosage under close medical supervision.

Recommendation 5: Specific treatment of patients with severe malaria

Parenteral artesunate is the first-line treatment for severe malaria.

Parenteral quinine is the second-line treatment; it should only be used if artesunate is unavailable or contraindicated.

Recommendation 6: Pre-referral treatment of severe malaria at peripheral units

Where complete management of severe malaria is not feasible, but injections are available, adults and children should be given a single intravenous dose of artesunate followed by immediate referral.

If artesunate injections are not available, children under 6 years of age should be given a single rectal dosage (10 mg/kg bw) of artesunate followed by immediate referral. Rectal artesunate should not be used in older children and adults.

Recommendation 7: Treatment of uncomplicated malaria in pregnancy

The first-line treatment for uncomplicated malaria in all trimesters of pregnancy is AL.

The first-line treatment for severe malaria in all trimesters of pregnancy is parenteral artesunate.

Recommendation 8: Intermittent preventive treatment of malaria in pregnancy (IPTp)

Pregnant women in high transmission settings should be prescribed sulfadoxine-pyrimethamine (SP) at regular intervals to minimize disease burden and unfavorable pregnancy and birth outcomes.

SP should be started as early as possible in the second trimester, but no earlier than week 13 of pregnancy.

Recommendation 9: Malaria in children

The antimalarial drugs recommended in these guidelines are safe and effective in children. The only exception is primaquine, which is contraindicated for children under 6 months of age.

Recommendation 10: Malaria prevention

Insecticide-treated nets (ITNs) are the most effective intervention for malaria control. Healthcare workers should counsel all patients on the importance of utilizing ITNs, especially children and pregnant women.

1. Introduction

Malaria is a significant public health hazard in Sudan. It is the leading cause of outpatient attendance, hospital admissions, and inpatient deaths in the country [1]. The protocol of malaria case management in Sudan was last updated in 2017 in response to the findings of a therapeutic efficacy study, in which the efficacy of artesunate + sulphadoxine-pyremethamine (AS + SP) was found to be decreasing, particularly in Gedarif State. In contrast, AL and DHAP were shown to be highly effective [2, 3]. In light of these findings, AL and DHAP were recommended as first- and second-line treatments of uncomplicated malaria, respectively. These guidelines were applicable to all groups, with the exception of women in the first trimester of pregnancy, in which the recommended treatment for uncomplicated malaria was oral quinine. The 2017 protocol had additionally endorsed IV quinine and IV artesunate as interchangeable treatment options for the management of severe malaria [4]. However, the subsequent release of new evidence on the management of severe malaria and uncomplicated malaria in pregnancy have prompted the release of updated malaria case management guidelines in 2023 [5, 6]. This collection of guidelines aims to provide evidence-based instructions about the diagnosis, treatment, and prevention of malaria in Sudan to reduce malaria-related morbidity and mortality.

The primary audience includes healthcare workers such as doctors, nurses, paramedics, pharmacists, and laboratory technicians. Other targeted groups include students in health-related fields, public health professionals, and the general public.

2. Methods

The technical advisory committee (TAC), in close coordination with the National Malaria Control Program (NMCP) writing team, developed the recommendations. The NMCP oversaw the guideline formulation process, which included panel formation, review coordination, and guideline drafting.

2.1. Panel composition

The panel included the TAC and the NMCP writing team. The membership of the TAC and the writing team, as well as the respective affiliations and positions of the members, are described in Appendices. The TAC included professors of community medicine, internal medicine, pediatrics, obstetrics and gynecology, and parasitology, all with experience on the guideline topic; directors of relevant directorates at the Federal Ministry of Health (FMOH); and representatives of the World Health Organization (WHO) and the Global Fund. The writing team primarily consisted of the case management team at the NMCP.

2.2. Prioritization of questions

The panel reviewed the then-official malaria protocol, the Sudan Malaria Treatment Protocol 2017, to prioritize and discuss the questions listed in Table 1.

2.3. Review of evidence and formulation of recommendations

The latest published WHO guideline on malaria control at the time, *WHO Guidelines for Malaria, November 25, 2022*, was selected by the panel as the source guideline for adaptation [5]. Recommendations outlined in the source guideline were individually assessed in terms of evidence quality (based on the GRADE criteria), cost-effectiveness, acceptability and feasibility, and were accordingly adopted, adapted, or not incorporated into this guideline. Decisions regarding adoption, adaptation, or exclusion were reached based on consensus among panel members. In cases where consensus was not reached, the chairman of the TAC made the final decision. As the recommendations of the panel are directly adopted in the

Table 1: Questions prioritized by the guideline panel.

No.	Question
1	What are the diagnostic criteria for uncomplicated and severe malaria?
2	What are the lines of management for uncomplicated malaria?
3	What are the lines of management for severe malaria?
4	What are the special considerations in the diagnosis and management of uncomplicated and severe malaria in pregnant women?
5	What are the special considerations in the diagnosis and management of uncomplicated and severe malaria in children?
6	What role can healthcare providers play in malaria prevention?

national protocol, a legally binding document, all recommendations outlined in this article are classified as "strong," that is, the panel is confident that the benefits of following the recommendation outweigh any potential drawbacks.

3. Recommendations

3.1. Recommendation 1: Malaria diagnosis

The committee recommends confirming suspected malaria cases using quality-assured microscopy or RDTs, with no room for clinical diagnosis (strong recommendation based on high-certainty evidence).

3.1.1. Overview of the evidence

Quality-assured microscopy remains the gold standard diagnostic tool for malaria [7–9]. It is highly sensitive and specific, allows for the quantification of parasite density, and offers valuable insight into treatment response. However, the method is highly operator-dependent, and the relatively high cost of microscopy training and laboratory equipment poses challenges to the modality's use in resource-limited settings [5]. RDTs offer an alternative diagnostic method with high sensitivity and specificity. A meta-analytic review found that histidine-rich protein 2 (HRP-2) RDTs had an average sensitivity of 95.0% and an average specificity of 95.2% for diagnosing *P. falciparum* [10]. Since RDTs have fewer training requirements, they can be utilized by less skilled personnel, such as community workers [11]. It should be noted, however, that HRP2 tends to persist even after effective treatment, rendering HRP2-based RDTs unsuitable for the detecting treatment failure [10].

3.1.2. Decision criteria and other considerations

The certainty of the evidence was graded as high. Other key factors supporting the recommendation to use quality-assured microscopy or RDTs for confirming malaria diagnosis include their established roles as the preferred diagnostic tools outlined in the 2017 national malaria protocol.

3.1.3. Conclusions and research priorities

The panel determined that there is strong evidence of a net health benefit from the use of light microscopy and RDTs for diagnosing malaria in Sudan. Future research on malaria diagnosis in Sudan should focus on areas of concern, including the competence of lab personnel in malaria diagnosis via microscopy and the level of trust in RDTs as a diagnostic tool among healthcare workers. Furthermore, the adequacy of laboratory supplies and their proper storage should be continuously monitored.

3.2. Recommendation 2: Treatment of uncomplicated malaria

In patients with uncomplicated malaria, the committee recommends using AL as the first-line treatment (Table 1; strong recommendation based on high certainty evidence).

3.2.1. Overview of the evidence

Numerous systematic reviews have examined the efficacy of AL in various clinical settings, including one addressing the drug's efficacy in the context of Sudan [12–14]. Other relevant outcomes, such as adverse effects, have been additionally considered in these reviews. A Cochrane review concluded that AL achieved PCR-adjusted failure rates of <10% at most study sites, in line with WHO recommendations [12]. Another systematic review evaluating the efficacy and safety of artemisinin-based combination therapy (ACTs) in Sudan reported a 98% success rate for malaria treatment with AL. This review also noted that adverse drug reactions, including nausea, abdominal pain, diarrhea, dizziness, and rash, have occurred in 4.65% of patients; all were mild and resolved spontaneously [14].

3.2.2. Decision criteria and other considerations

The certainty of the evidence was graded as high. Other key factors supporting the recommendation of AL as the first-line treatment in the 2023 guidelines include its pre-existing status as the first-line treatment of uncomplicated malaria in Sudan as per the 2017 national malaria protocol, and the efficiency conferred by continuing with the same treatment given that no verifiable concerns about drug resistance have emerged.

3.2.3. Conclusions and research priorities

The panel determined that there is strong evidence of a net health benefit from the continued use of AL as the first-line therapy for uncomplicated malaria in Sudan. The available evidence indicates that AL has a high success rate in treating uncomplicated malaria with low rates of adverse drug reactions. While the evidence to support the use of AL is strong, there is a need for continued monitoring of drug efficacy to promptly detect any emergence of resistance.

3.3. Recommendation 3: Second-line treatment for uncomplicated malaria

In patients with uncomplicated malaria, the committee recommends DHAP as a second-line treatment. It is indicated in the case of treatment failure or when the first-line treatment is contraindicated or unavailable (Table 2; strong recommendation based on high certainty evidence).

Table 2: Dosage schedule for artemether–lumefantrine (AL).

Weight (Kg)	**Day 1**		**Day 2**		**Day 3**		Total number of tablets	
	Initially	8 hr after the 1st dose	24 hr after the 1st dose	12 hr after the 3rd dose	12 hr after the 4th dose	12 hr after the 5th dose		Tablet strength
<5	Seek consultant advice							
5–14	1	1	1	1	1	1	6	AL "20/120" dispersible
15–24	2	2	2	2	2	2	12	
25–34	3	3	3	3	3	3	18	AL "20/120" standard tablets
Children > 34 kg and adults	1	1	1	1	1	1	6	AL "80/480" standard tablets

Table 3: Dosage schedule for dihydroartemisinin + piperaquine (DHAP).

DHAP tablet strength	Body weight (Kg)	Day 1	Day 2	Day 3	Total no of tablets
	<5	Seek consultant advice			
20/160 Tablet	5 to <8	1	1	1	3
	8 to <11	1.5	1.5	1.5	4.5
40/320 Tablet	11 to <17	1	1	1	3
	17 to <25	1.5	1.5	1.5	4.5
	25 to <36	2	2	2	6
	36 to <60	3	3	3	9
	60 to <80	4	4	4	12
	>80	5	5	5	15

Table 4: Preparation of artesunate for administration.

Calculate and prepare the artesunate for administration:			
Weigh the patient (in Kg)			
Calculate the needed number of artesunate vials (30, 60, or 120 mg) for each patient guided by the following estimate:			
Weight in Kg	**Vials of artesunate powder**		
4–10	One vial of 30 mg		
11–25	One vial of 60 mg		
26–50	One vial of 120 mg		
>50	Two vials of 120 mg		
The solution should be prepared freshly for each administration as follows:			
Add the attached 5% sodium bicarbonate solution to artesunate powder Shake the vial gently for 2–3 mins for better dissolution Add the attached 5% normal saline (not distilled water) to make the concentration of artesunate 10 mg/ ml for intravenous administration Regardless of strength (30, 60, or 120 mg), the final concentration of artesunate after mixing will be 10 mg/kg. The total volume, however, will differ as follows:			
Artesunate injection preparation			
Mode of administration	**Intravenous**		
Strength	30 mg	60 mg	120 mg
Total volume (ml)	3	6	12
Artesunate concentration	10 mg/ml		
Calculate the required dose in ml for each patient using the following table:			
Dosage schedule for IV artesunate			
Weight in kg	Dose to be administered immediately (0), after 12 hr, 24 hr, and then once a day until the patient can take orally		

Table 4: Continued.

		Dose in mg	Dose in ml
<4		10	1
4–6		20	2
7–10		30	3
11–13		40	4
14–16		50	5
17–25		60	6
26–29		70	7
30–33		80	8
34–37		90	9
38–41		100	10
42–45		110	11
46–50		120	12
51–54		130	13
55–58		140	14
59–62		150	15
63–66		160	16
67–70		170	17
71–75		180	18
76–79		190	19
80–83		200	20
84–87		210	21
88–91		220	22
92–95		230	23
≥96		240	24
Administer intravenously as a slow bolus over 1–2 mins			
Note: Artesunate may be administered intramuscularly if intravenous administration is not possible.			
To prepare artesunate for IM administration, the same aforementioned preparatory steps should be followed. However, the concentration should be 20 mg/kg. To make the concentration 20 mg/kg, the amount of 5% normal saline added should be modified as follows: 1 ml for 30 mg vials, 2 ml for 60 mg vials, and 4 ml for 120 mg vials. The dosage in ml will be half that of the dose provided in the “dosage schedule for IV artesunate” table. The IM preparation should be injected slowly into the anterior thigh. If the dose is >2 ml for babies or >5 ml for adults, split the dose between the two thighs.			

Table 5: Dilution schedule and drop rate for intravenous quinine administration.

Weight (Kg)	Quininedose (mg)	Volume ofundilutedquininesolution(300 mg/ml)	Amount offluid to beinfused(in 4hr)	Drop ratepermin
≤6	60	0.2 ml	50 ml	4 drops
6–10	90	0.4 ml	100 ml	8 drops
11–14	150	0.5 ml	100 ml	8 drops
15–18	180	0.6 ml	150 ml	13 drops
19–24	210	0.7 ml	200 ml	17 drops
25–35	300	1.0 ml	250 ml	21 drops
36–49	420	1.4 ml	350 ml	30 drops
50–60	540	1.8 ml	500 ml	42 drops
≥60	600	2.0 ml	500 ml	42 drops

3.3.1. Overview of the evidence

DHAP is another ACT that has been extensively researched for the treatment of uncomplicated malaria. While the drug is a relatively recent addition to the list of WHO-approved ACTs, there is consensus that DHAP exhibits high cure rates for uncomplicated malaria [12, 15]. A Cochrane systematic review comparing the effectiveness and safety of DHAP with AL in Africa found that both drugs met the WHO standard of 5% or less PCR‐adjusted treatment failure rate at day 28 in all trials [15]. The review concluded that DHAP represented an effective alternative, offering a simpler dose regimen and longer-lasting post‐treatment prophylaxis. A randomized controlled trial comparing the two drugs in central Sudan showed a 100% cure rate with DHAP [16]. Observed adverse events, such as nausea, vomiting, abdominal pain, rash, and/or dizziness, were mild, infrequent, and resolved spontaneously. Some concerns have been raised about the potential effects of DHAP on the QT interval, however, the Cochrane review reported no cardiac arrhythmias or differences in prolonged QTc when DHAP was compared to AL [15].

3.3.2. Decision criteria and other considerations

The evidence supporting DHAP's effectiveness in the treatment of uncomplicated malaria is of high quality. Furthermore, DHAP has been the recommended as the second-line treatment of uncomplicated malaria in Sudan since 2017 and the benefits of its continuation are comparable to those of AL and its first-line designation.

3.3.3. Conclusions and research priorities

The committee concluded that there is high-certainty evidence of a net health benefit from the continued use of DHAP as the second-line therapy for uncomplicated malaria in Sudan. DHAP has a high success rate in treating uncomplicated malaria with low rates of adverse reactions. The relative scarcity of recent data on DHAP's efficacy in Sudan highlights the need for the inclusion of second-line treatments in routine therapeutic efficacy studies conducted in the country.

3.4. Recommendation 4: Treatment of uncomplicated P. vivax malaria

In patients with uncomplicated *P. vivax* malaria, the committee recommends AL as the first-line treatment. With the exception of pregnant and breastfeeding women and children under six months of age, all patients with *P. vivax* malaria should receive a 14-day course of primaquine in addition to AL (strong recommendation based on high certainty evidence).

3.4.1. Overview of the evidence

The effectiveness of ACTs in treating the blood stage of *P. vivax* is well-established. At least four RCTs have compared the ACTs recommended by the WHO with chloroquine, consistently showing that ACTs, including AL, clear parasites faster than chloroquine [17–20]. Unlike *P. falciparum*, *P. vivax* has liver-stage forms that can lay dormant for extended periods and cause spontaneous relapses. These dormant parasites, or hypnozoites, are not susceptible to conventional antimalarials, and the only drug commonly used for their clearance is primaquine. The evidence supporting the use of primaquine in hypnozoite clearance is robust. Compared to no primaquine or placebo, a 14-day regimen of primaquine reduced relapses by about 40% over 15 months of follow-up. Shorter courses of primaquine are associated with higher frequency of relapses when the daily dose is held constant. No serious adverse events were reported in these trials, and non-serious events were mild and self-limiting [21]. Of note, however, most trials explicitly excluded people with G6PD deficiency, as primaquine is known to induce hemolysis in

this subgroup. The use of primaquine is thus contraindicated during pregnancy, breastfeeding, and in children less than six months old due to the risk of severe hemolysis to the fetus or infant. For patients with G6PD deficiency, a dose of 0.75 mg/kg of primaquine should be administered once a week for eight weeks under close medical supervision [5].

3.4.2. Decision criteria and other considerations

The quality of evidence supporting the use of AL to treat uncomplicated *P. vivax* blood infection and primaquine to prevent future relapses is high. The decision to recommend AL for the treatment of uncomplicated *P. vivax* malaria is augmented by its aforementioned status as the first-line treatment for uncomplicated *P. falciparum* malaria, the most prevalent species in Sudan.

3.4.3. Conclusions and research priorities

The committee determined that there is strong evidence of a net health benefit from the continued use of AL and primaquine for uncomplicated *P. vivax* malaria in Sudan, except in pregnant and breastfeeding women and infants under six months, for whom only AL should be prescribed. In light of the unstable supply and frequent shortages of primaquine in Sudan, future research should focus on addressing the procurement and supply bottlenecks for primaquine in the country.

3.5. Recommendation 5: Specific treatment of severe malaria

In patients with severe malaria, the committee recommends using parenteral artesunate as the first-line treatment, with parenteral quinine reserved as a second-line option (Tables 3 & 4; strong recommendation based on high certainty evidence).

3.5.1. Overview of the evidence

Multiple randomized controlled trials have demonstrated that parenteral artesunate significantly reduces mortality compared to parenteral quinine in the treatment of severe malaria [22–24]. While parenteral quinine remains a viable treatment alternative in resource-limited settings, where artesunate may not be readily available, there is a notable deficiency in recent evidence comparing the two drugs in Sudan. However, a randomized trial in eastern Sudan found that artesunate led to significantly shorter parasite and fever clearance times when compared to quinine, although no difference in coma resolution time between the two groups was observed [25].

3.5.2. Decision criteria and other considerations

The recommendation is supported by high-certainty evidence. The superior effectiveness, safety, tolerability, and ease of administration of artesunate supports its designation as the first-line treatment of severe malaria in Sudan.

3.5.3. Conclusions and research priorities

The committee determined that there is strong evidence of a net health benefit from the use of parenteral artesunate as the first-line treatment for severe malaria in Sudan. Quinine may be used as a second choice when artesunate is unavailable or contraindicated. Further research is needed to investigate the efficacy, safety, and long-term outcomes of severe malaria treatments in the specific context of Sudan.

3.6. Recommendation 6: Pre-referral treatment of severe malaria

In patients presenting with severe malaria at peripheral units, the committee recommends using one dose of parenteral artesunate followed by

immediate referral. If parenteral artesunate is unavailable, rectal artesunate should be used for children under six years of age (strong recommendation based on moderate certainty evidence).

3.6.1. Overview of the evidence

A Cochrane review of randomized controlled trials indicated that pre-referral treatment with rectal artesunate reduces mortality by 26% in children less than six years when compared to placebo. However, pre-referral rectal artesunate was shown to paradoxically increase mortality when used in older children and adults [26].

While no direct evaluation of the effects of parenteral artesunate as a pre-referral treatment has been performed, the WHO recommends parenteral artesunate as the first choice for pre-referral treatment based on its established benefits in hospitalized patients [5].

3.6.2. Decision criteria and other considerations

The committee's decision is based on the available moderate-certainty evidence. The preference for parenteral artesunate over rectal artesunate is further supported by the underutilization of rectal artesunate in Sudan.

3.6.3. Conclusions and research priorities

The committee concluded that parenteral artesunate should be used as the first-line pre-referral treatment for severe malaria at peripheral units, with rectal artesunate as a second-line alternative for children under six years of age. Patients should be referred to the nearest hospital without delay. Proper documentation and follow-up of the deployment of this recommendation are needed to generate further evidence on this approach.

3.7. Recommendation 7: Treatment of uncomplicated malaria in pregnancy

In pregnant women of all trimesters presenting with uncomplicated malaria, the committee recommends AL as the first-line treatment (strong recommendation based on high certainty evidence for the second and third trimesters, and low certainty evidence for the first trimester).

3.7.1. Overview of the evidence

The evidence supporting the use of AL in the second and third trimesters of pregnancy is robust. AL has been extensively studied in women in their second and third trimesters and was determined to be effective, safe, and well-tolerated [27, 28]. While the evidence for AL use in the first trimester is less robust, trial outcomes are increasingly assuring. A systematic review conducted in 2023 demonstrated no evidence of embryotoxicity or teratogenicity associated with ACT use during the first trimester of pregnancy [29].

3.7.2. Decision criteria and other considerations

The evidence to support the continued use of AL as the first-line treatment for uncomplicated malaria in the second and third trimesters of pregnancy is strong. While the evidence for AL use in the first trimester of pregnancy is less robust, the committee reviewed updated evidence comparing the risks and benefits of using AL versus oral quinine in the first trimester, concluding that AL should be adopted as the first-line treatment. As AL is the recommended first-line in other trimesters as well as in non-pregnant patients with uncomplicated malaria in Sudan, this recommendation is likely to confer logistical and practice benefits.

3.7.3. Conclusions and research priorities

The committee concluded that AL is the first-line treatment for uncomplicated malaria in all trimesters of pregnancy. Continued clinical studies and close surveillance are needed to improve the evidence base for the safety of AL and DHAP in the first trimester of pregnancy.

3.8. Recommendation 8: Intermittent preventive treatment of malaria in pregnancy (IPTp)

In high transmission settings, the committee recommends that pregnant women of all gravidities be given SP at regular intervals (strong recommendation based on moderate certainty evidence).

3.8.1. Overview of the evidence

This recommendation builds on evidence from systematic reviews on intermittent preventive treatment of malaria in pregnancy (IPTp). The evidence showed that, when compared to placebo, IPTp with SP reduces the risk of maternal anemia, antenatal parasitemia, and low birthweight. The effects are particularly pronounced in the first and second pregnancies, and with the administration of three or more doses of SP [30, 31].

3.8.2. Decision criteria and other considerations

The certainty of evidence varies depending on multiple factors such as gravidity and studied outcomes. However, the evidence is robust for key outcomes like severe maternal anemia. Cost-effectiveness analysis also supports the incorporation of IPTp-SP into national guidelines as part of a comprehensive package for tackling malaria in pregnancy.

3.8.3. Conclusions and research priorities

The committee concluded that IPTp-SP should be administered to pregnant women of all gravidities in high transmission settings. The doses should be given with the objective of ensuring that at least three doses are received. The effectiveness of IPTp should be monitored in concomitance with roll-out to improve the existing body of evidence.

3.9. Recommendation 9: Malaria in children

In children and young infants, the committee recommends AL and DHAP as the first- and second-line treatments for uncomplicated malaria, and artesunate and quinine as the first- and second-line treatments for severe malaria (strong recommendation based on high certainty evidence).

3.9.1. Overview of the evidence

Systematic reviews have established the efficacy and safety of AL and DHAP in pediatric patients [32, 33]. In Shibeshi *et al*., the PCR-corrected treatment success rate for ACTs in pediatric patients was 96.3% and 93.9% for day 28 and 42, respectively [32]. Furthermore, ACT-related adverse drug reactions were uncommon and all were reported to resolve spontaneously.

The use of artesunate as a first-line treatment for severe malaria in children is also strongly supported by evidence. A Cochrane review indicated that artesunate significantly reduced mortality in both adults and children compared to quinine, and concluded that intravenous artesunate should be the first-line treatment for severe malaria in both adults and children, regardless of geographical location. The review additionally pointed out that treatment with artesunate was associated with an increased incidence of neurological sequelae in children at discharge. However, most of these sequalae were temporary, and no significant

difference in their incidence was reported during later follow-up [34].

3.9.2. Decision criteria and other considerations

The certainty of the evidence is graded as high. Additional considerations in the correspondence of the selected drugs to the management guidelines in adults.

3.9.3. Conclusions and research priorities

The committee concluded that the antimalarial drugs recommended for adults in this guideline are safe, effective, and well-tolerated by children. The only exception is primaquine, which is contraindicated in children under six months of age. Future research should address the safety and efficacy of these treatments in infants below 5 kg of weight.

3.10. Recommendation 10: Malaria prevention

The committee recommends using ITNs as a preventative measure against malaria (strong recommendation based on high certainty evidence).

3.10.1. Overview of the evidence

An increasing body of evidence, including systematic reviews [35, 36] and randomized clinical trials [37], supports the use of ITNs as an effective malaria prevention strategy. These studies have demonstrated that ITNs significantly reduce the incidence of malaria by providing both a physical barrier against mosquitoes and an insecticidal effect. In Sudan, ITNs are recommended as malaria preventive measures [38]. Research consistently confirms that regular use of ITNs decreases malaria cases among users. Additionally, this evidence highlights the critical role of healthcare providers in promoting ITN use through health education and counselling [39], especially among vulnerable populations such as pregnant women and children. ITNs can be used both indoors and outdoors, but it is essential to avoid hanging them in direct sunlight to preserve their insecticidal efficacy.

3.10.2. Decision criteria and other considerations

The quality of evidence supporting the use of ITNs to prevent malaria is robust. The recommendation for ITN use is further strengthened by its proven effectiveness in significantly reducing malaria incidence through both physical mosquito barriers and insecticidal effects. This recommendation is crucial for protecting vulnerable populations, particularly pregnant women and children, from malaria.

3.10.3. Conclusions and research priorities

The committee concluded that healthcare workers should encourage the use ITNs as a preventive measure in Sudan. Future research should address the issue of low ITN utilization among owners in the country.

4. External Review and Quality Assurance

The federal document produced from this guideline, the Sudan Malaria Case Management Protocol 2023, has been independently reviewed by the WHO's Global Malaria Programme.

5. Plans for Guideline Updates

The NMCP maintains regular surveillance for updates to WHO guidelines as well as locally generated evidence on the therapeutic efficacy of antimalarial drugs to assess the need for updates to malaria case management guidelines in Sudan.

6. Limitations

The limitations and research needs for each recommendation are detailed under the relevant subheadings in Section 3: Recommendations.

7. Guideline Dissemination

The official Sudan Malaria Case Management Protocol 2023 document is available on the FMOH's website [6].

Declarations

Acknowledgements

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Ethical Considerations

The recommendations in this guideline, as outlined in the Sudan Malaria Case Management Protocol 2023, have been approved and formally adopted by the Federal Ministry of Health in Sudan.

Competing Interests

None.

Availability of Data and Material

Not applicable.

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Abbreviations and Symbols

ACTs: Artemisinin-based combination therapy
AL: Artemether-lumefantrine
DHAP: Dihydroartemisinin-piperaquine
FMOH: Federal Ministry of Health
G6PD: glucose-6-phosphate dehydrogenase
HRP2: Histidine-rich protein
IPTp: Intermittent preventive treatment of malaria in pregnancy
ITNs: Insecticide-treated nets
NMCP: National Malaria Control Program
RDT: Rapid diagnostic test
SP: Sulfadoxine-pyrimethamine
TAC: Technical Advisory Committee
WHO: World Health Organization

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