Belgian Paediatric Malaria Treatment Guideline 2024

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Keywords

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Abstract

The Belgian Paediatric Malaria Treatment Guideline 2024 addresses the need for early diagnosis and specialized care in managing paediatric malaria, a potentially life-threatening disease. It outlines the protocol developed for the treatment of malaria in children in Belgium, shaped by an extensive collaborative process among paediatric infectious disease specialists across the country. The guideline highlights the importance of early recognition of malaria symptoms and rapid initiation of treatment and the need for specialized advice early onwards.

Introduction

Malaria remains a potential life- threatening disease caused by *Plasmodium* parasites transmitted by *Anopheles* mosquitoes. In 2022, there were 249 million malaria cases globally that led to 608 000 deaths in total. Of these deaths, 76% were children under 5 years of age (1).

The five *Plasmodium* species that can infect humans are *P. falciparum, P. vivax, P. ovale, P. knowlesi and P. malariae*. Incubation can range from six days until months and rarely years depending on the species. The majority of *P. falciparum* infections (85%) becomes clinically apparent within one month after infection, with less than one percent of cases presenting after 6 months. In contrast, only 25% of non-falciparum malaria cases present within one month after infection/travel, while 60% appear within six months and 90% within a year (2).

Severe malaria is a medical emergency. Children with malaria can deteriorate extremely quickly. Early diagnosis and prompt treatment initiation is vital. Malaria should always be ruled out in a child with fever (current or recent history) returning from a malaria-endemic area up to twelve months after return, regardless of any malaria chemoprophylaxis. Advise from a paediatric infectious diseases specialist should be obtained as early as possible, and cases of severe malaria should preferably be managed in a centre with paediatric intensive care facilities.

Method

During an interdisciplinary meeting focused on paediatric malaria treatment between Citadel Hospital and CHU St. Pierre, disparities in treatment practices came to light. Motivated by a desire to align with the latest advances in the field, we aimed at creating a unified Belgian protocol, receiving approval from the Belgian Study group of Travel Medicine.

We reached out to paediatric infectious disease specialists from various Belgian hospitals, requesting their local malaria treatment protocols. Twelve hospitals from all regions of Belgium contributed their protocols, allowing a comprehensive comparison of diagnostic and treatment practices.

A series of virtual meetings were held from February to July 2022 - a period still affected by the COVID-19 pandemic - during which we compared these protocols with the most recent guideline of the World Health Organisation (WHO, February 2022) and the United Kingdom National Malaria guidelines (2016) (3, 4).

This collaborative effort among paediatric specialists in paediatric infectious diseases and travel medicine culminated in the protocol presented, aiming to enhance our collective expertise and practice in treating paediatric malaria in Belgium.

Diagnosis

1. Travel history

A detailed travel history is paramount for children presenting with fever following their return from a malaria-endemic area. The travel should include travel dates, destinations including airport transfers, activities (e.g., trips to rural areas), chemoprophylaxis (medication, dosing and adherence), and (travel) vaccinations. Keep in mind that despite chemoprophylaxis, no preventive measure offers 100% protection against malaria.

To assist in assessing the malaria risk, the Belgian Study group of Travel Medicine provides an annually updated world map of the malaria risk. For

the most recent version of this map, please scan the provided QR code (Figure 1) to visit the website. https://artsen.wanda.be/en/a-z-index/malaria-world-map.

2. Symptoms and clinical examination

Symptoms in children can manifest as non-specific 'flu-like' symptoms, ranging from fever, malaise, headache, respiratory symptoms to abdominal complaints like vomiting and diarrhoea, mimicking infectious enteritis. The clinical examination is often non-specific but signs like pallor, petechiae, jaundice, tachypnoea, splenomegaly, lethargy or abnormal neurological examination can be present.

3. Differential diagnosis

Given the wide range of potential aetiologies for fever in children returning from tropical countries, clinicians must maintain a broad differential diagnosis. This approach ensures that other conditions, such as sepsis, pneumonia, influenza, meningo-encephalitis, dengue and other arboviruses, enteric fever, rickettsiosis, leptospirosis, tick-borne relapsing fever (various *Borrelia* species in several tropical areas) or other commonly acquired viral infections are considered alongside malaria.

4. Laboratory investigations

To confirm malaria and identify the infecting species a rapid diagnostic test (RDTs), detecting *Plasmodium* antigens), AND a thin/thick blood smear are recommended.

An RDT does not exclude formally a diagnosis of malaria because of the risk of a false negative test in case of very high parasitaemia (prozone effect), low parasitaemia (below level of detection), the possibility of mutant *P. falciparum* parasites (with some antigen deletion) or the lower sensitivity in case of non-falciparum malaria. A positive RDT always needs to be completed by a thick and thin smear to allow the determination of species, diagnosis of mixed infections, the staging and quantification of parasites. If despite a negative result a high index of suspicion for malaria persists (e.g., persistent fever, exposure in sub-Saharan Africa, presence of splenomegaly, unexplained thrombocytopenia,…) a thick smear must be repeated every 12-24 hours; this is especially relevant in cases where partial chemoprophylaxis has been given. In case of three negative thick smear tests performed over a 72 hours' time- period malaria is considered to be unlikely. Nucleic acid tests (e.g., PCR) for malaria are available but only performed in reference laboratories for confirmation of the microscopic results or in case of doubts.

Clinicians should be aware that fever in a returning traveller can be caused by other infections than malaria and that co-infections can occur. So alongside diagnostic testing for malaria it remains important to perform routine baseline testing and other explorative investigations (Table 1).

Figure 1: QR code linking to world map of malaria risk (https://artsen.wanda.be/en/a-z-index/malaria-world-map).

Table 1: Laboratory investigations to perform in case of fever after a stay in the tropics (suspected malaria infection).

Baseline tests to be taken in case of a suspected malaria		
	Probable test result if malaria +	**Remarks**
Rapid malaria antigen test Thin smear Thick smear	positive	range of sensitivity % and specificity % depends on the species and the used test
C- reactive protein (CRP)	< 10	
Full blood count including Reticulocytes	anaemia thrombocytopenia reticulocytosis	anaemia can be delayed white blood cells are often normal, so consider alternative diagnosis or coinfection if abnormal
Liver function test	hyperbilirubinemia (direct) transaminitis	
Glycaemia	frequently low	
Signs of haemolysis	hyperbilirubinemia (indirect), LDH, AST : high haptoglobin : low	
Coagulation	sometimes (but certainly not always) deranged in severe malaria	
Blood gas : pH lactate	acidosis increased lactate	
Renal function Electrolytes	deranged in acute phase or severe cases	proteinuria, haematuria hyponatremia is a sign of severe malaria
Blood culture		differential diagnoses
Blood group + cross-matching		if severe anaemia (transfusion preparation)
Additional investigations to consider based on clinical features and differentials		
G6PD	expedite results if *P. vivax* / *P. ovale* is confirmed	deficiency of G6PD = contra-indication of primaquine administration
Urine: microscopy and culture		differential diagnoses
Chest X-ray	lung oedema	differential diagnoses: pneumonia
Lumbar puncture		differential diagnoses: to perform if suspicion of meningitis
Storage serum	serology and virology	differential diagnoses
ECG		long QTc
Cerebral Magnetic resonance imaging (MRI)	cerebral malaria : oedema, ischemia (rarely)	
Fundoscopy	severe malaria: malarial retinopathy (retinal whitening, vessel discoloration, retinal haemorrhages optic disc oedema)	In 25-30% of cases of cerebral malaria

Management

Criteria for severe malaria

Severe malaria occurs when the infection is complicated by severe haemolysis or end- organ failure. It is important to distinguish between uncomplicated 'non-severe' and 'severe' malaria since this will guide the management (Figure 2). The criteria for severe malaria reported in Table 2 are those of the WHO guideline for malaria except for the cut-off values for severe anaemia and parasitaemia which are adapted to the Belgian standards based on expert opinion (3).

Hospital admission versus ambulatory care

It is highly recommended to admit all children diagnosed with *P. falciparum* malaria for at least a period of 24h as the infection can rapidly evolve.

Figure 2 : Management.

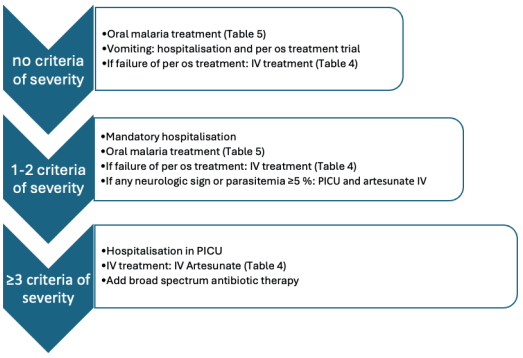


Table 2 : Overview of criteria for severe malaria.

Criteria for severe malaria	
Neurologic signs	impaired consciousness or prostration seizures
Severe anaemia	Hb < 7 g/dl
Metabolic acidosis	Ph < 7.3 or BE > 8 mEq/L or HCO3 < 15 mmol/L or lactate ≥ 5 mmol/L
Coagulation	significant bleeding (nose, gums, venipuncture site...) thrombocytopenia < 20.000/mm^3 signs of disseminated intravascular coagulopathy (DIC)
Renal failure	oligo-anuria:< 1 ml/kg/h in infants and < 0.5 ml/kg in 6 h for older children creatinine (plasma or serum) > 3 mg/dl
Hypoglycaemia	glucose < 40 mg/dl
Respiratory failure	hypoxemia SaO2 < 92 % signs of respiratory distress
Jaundice	total bilirubin > 3 mg/dl
Signs of shock	compensated or not compensated: tachycardia, altered peripheral perfusion, capillary refill > 3 sec, hypotension
Parasitaemia	> 2 % parasites in red blood cells

After discussion with a paediatric infectious diseases specialist, some children who fulfil ALL the outpatient criteria (Table 3) may be treated in an ambulatory setting after taking the first dose of treatment at the emergency unit and after supervision of minimum 4 hours. Those patients should receive at least two more treatment doses in hand before going home to complete the full 3-day treatment. They should be seen at the consultation or at the emergency service the next day to insure the tolerance of the treatment.

Table 3 : Criteria for outpatient treatment.

Criteria to be met before considering outpatient treatment
• Age ≥ 5 years
• Parasitaemia <1%
• Normal bilirubinaemia (<1.3mg/dl)
• No co-morbidity
• Possibility of close follow-up
• AND absence of any criteria of 'severe malaria'

Treatment

The choice of treatment depends on the species and the severity of the malaria. The first choice for the treatment of severe malaria is Artesunate IV. If artesunate IV is likely to be delayed/not available, IV quinine could be administered (as soon as possible) but as a second line antimalarial drug. This should be switched to IV artesunate as soon as it is available.

In case of non-severe malaria, the first choice of treatment is an artemisinin-based oral combination therapy (ACT). For an infection with *P. ovale* or *P. vivax* this should be followed by primaquine (after G6PD deficiency has been ruled out) to prevent relapse from liver hypnozoites.

In the event of vomiting, the oral medication may be re-administered within 60 minutes of ingestion or if the treatment is visible in the vomit. If persistent vomiting occurs, consider switching to IV treatment.

Tables 4 and 5 provide an overview of the treatment regimen and dosing.

Table 4 : Treatment of severe malaria.

Severe malaria	
Drug	Comment
FIRST CHOICE: **Artesunate (Malacef® IV)*:** < 20 kg: 3 mg/kg/dose IV ≥ 20 kg : 2.4 mg/kg/dose IV at t0h, t12h, t24h, then 1x/day **As soon as PO treatment possible: ALWAYS complete by a full oral ACT treatment** of 3 days	- Given by slow IV injection at a maximum rate of 3 ml/min of the 10 mg/ml solution (30 mg/min) - Administer for at least 24 h, during maximum 7 days, or until switch to oral therapy is possible. - No need for dose adaptation in case of kidney or liver failure.
SECOND CHOICE (if Artesunate not available): **Quinine hydrochloride IV** Loading dose: 20 mg/kg (max 1000 mg) slow IV over 4-6h diluted in 10 ml/kg G5% (or G10% if hypoglycaemia at the start) Then 8h after start: 10 mg/kg (max 500-600 mg) over 2-4 h in 10ml/kg G5% (max 250 ml) 3 x/d for first 48h or until switch to artesunate IV (ASAP in PICU) **As soon as PO treatment possible: ALWAYS complete by a full oral ACT treatment** of 3 days	- ECG prior administration is preferable - The infusion rate should not exceed 5 mg/kg/h. - Concentration of infusion fluid should be 2 mg/ml. - Monitor glycaemia/4h during treatment and provide continuous cardiac monitoring during administration (cave arrhythmias and hypotension). - Frequency of dosing should be reduced to 2x/day if IV quinine continues for more than 48h(maximal a total of 5-7 days). - In case of renal or liver failure: same dosing but the frequency of administration is reduced (1x/24h).
THIRD CHOICE (in case of non-availability of the 1e or 2nd choice): **any oral antimalarial treatment awaiting transfer to centre where IV treatment is possible**	- 1st choice of oral treatment: ACT - 2nd choice: Atovaquone/Proguanil (Malarone®)

*Artemisinin resistance is seen in some countries such as Cambodia, Laos, Myanmar, Thailand, Vietnam and there are signals of emerging resistance in some countries in East Africa. In travellers returning from areas with documented evidence of artemisinin resistance, contact a malaria expert to discuss treatment.

Monitoring and follow-up

Hospital admissions

There should be a very low threshold to admit patients with severe malaria to a paediatric intensive care unit. Monitoring of vital signs, Glasgow coma scales and urinary output are important. Glycaemia should be monitored at least every four hours, particularly in unconscious patients. Be careful with fluid administration and give maximum 70% of the maintenance fluid.

It is difficult to rule out sepsis in a shocked or severely ill child so a low threshold to start empirical parenteral broad-spectrum antibiotics (e.g., ceftriaxone) together with the anti-malarial treatment should be applied.

Daily monitoring of parasitaemia and laboratory parameters (full blood count) is essential for assessing treatment efficacy and identifying potential complication. The parasitaemia may increase over the first 24 hours, especially in severe malaria, and does not usually indicate treatment failure or resistance. Continue monitoring until asexual blood stage parasites are no longer seen on the blood film. Gametocytes (sexual stages) may persist or appear during or after treatment and does not indicate treatment failure. The rapid diagnostic test and Polymerase Chain Reaction (PCR) for malaria can remain positive during treatment. In case the parasites are not cleared at Day 3 after the start of the treatment (corresponding to Day 0), the possibility of (partial) resistance to artemisinin should be considered and expert advice must be sought since no clear recommendations exists in those specific cases.

Clinicians should be aware of the risk of delayed haemolysis with IV artesunate treatment, usually between day 7 and 21 and especially seen in cases of initial hyperparasitaemia. Note that this risk also exists (but much less frequently) after oral ACT (see below). Inform the patient about warning signs for haemolysis before discharge and organise a full blood count and blood film 14 to 28 days for all severe cases who had to be treated with IV artesunate. After discharge all patients with severe malaria should therefore receive a follow-up consultation (day 7 to day 14) and the patient should be informed to seek urgent medical advice in case of recrudescence of fever up until 28 days after initiation of treatment in view of potential therapy failure. During this consultation chemoprophylaxis measures for any next travel to a tropical area should be discussed with the patient.

Ambulatory care

A close follow-up is warranted and a clinical review (or at least a telephone contact) around day 2-3 is advised to ensure treatment adherence, subsidence of fever and clinical improvement. Preferably at day 3 or 4 and or the latest at day 7 a full blood count and blood film should be performed. At day 7 a follow-up consultation should be done and the patient should be informed to seek urgent medical advice in case of recrudescence of fever up until 28 days after initiation of treatment in view of potential therapy failure. During this consultation chemoprophylaxis measurements for any next travel to tropical area should be discussed with the patient.

Therapy failure

If *P. falciparum* parasitaemia persist (>3 days) or in case of evolution towards severe malaria or an increase in parasitaemia on day 2 or 3 despite adequate treatment, one should consider an early treatment failure, which could be due to partial resistance to artemisinin. Recurrence of fever and parasitaemia from 1 to 4 (6) weeks after initial treatment (with no new exposure) corresponds to late treatment failure, which could reflect resistance to any of both drug component, but also (and more likely) bad compliance or insufficient dosing or absorption of treatment (vomiting, unusual pharmacokinetics of a patient, drug interaction). Therapy failure seems on the increase in Belgium in the past few years (5).

In both scenarios (persistence or recurrence of parasitaemia), expert opinion (at least of the paediatric infectious diseases specialist) should be sought and preferably the Institute of Tropical Medicine in Antwerp (Prof. dr. Emmanuel Bottieau or the infectious disease specialist on call) should be contacted to discuss the appropriate treatment and the performance of genomic analysis of the parasite to better understand the underlying reasons for treatment failure and to properly guide management decisions.

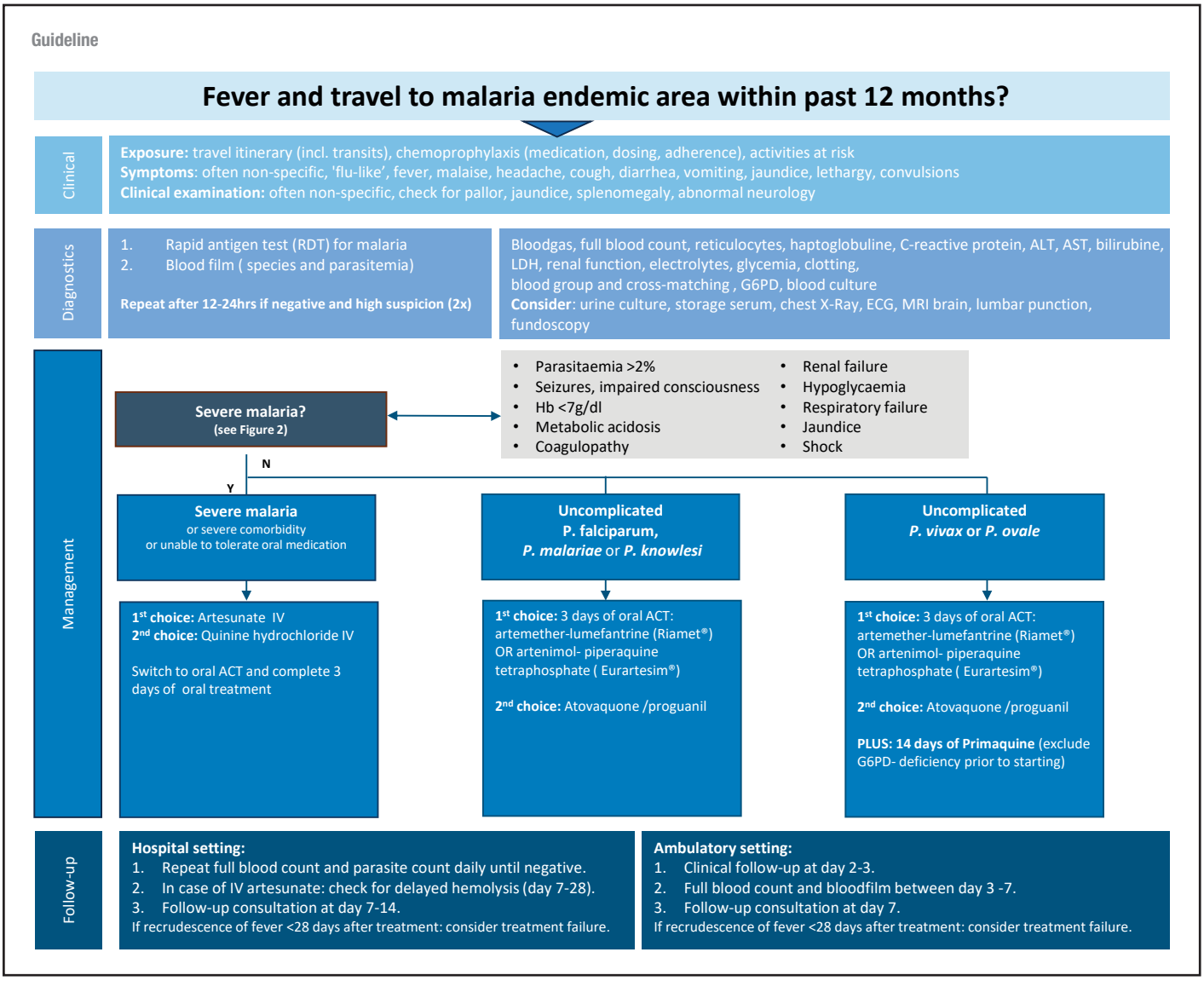
Table 5 : Treatment of uncomplicated malaria.

Uncomplicated malaria

P. falciparum, P. malariae or *P. knowlesi* malaria

Drug	Comment
FIRST CHOICE: **ACT (artemisinin-based combination therapy).** 2 options are available in Belgium: **Riamet®:** 6 doses in 3 days (t0h, t8h than t24h, t36h, t48h et t60h)	- An ECG is advised prior to administration only in patients at risk of QTc prolongation (co-medication, vomiting with subsequent hypokalaemia,...) † - If vomiting, the use of alizapride is permitted. **Riamet®: tablet of artemether 20 mg / lumefantrine 120 mg** Absorption is enhanced by fat; therefore recommended to use with milk/food. Can be crushed and mixed with food or milk.
< 5 kg (¥) — Dissolve 1 tablet 20/120 mg in 5 ml water and give 1 ml/kg body weight by mouth followed by normal feed.(WHO) 5 < 15 kg — 1 tablet 20/120 mg 15 < 25 kg — 2 tablets 20/120 mg 25 < 35 kg — 3 tablets 20/120 mg ≥ 35 KG — 4 tablets 20/120 mg	
Eurartesim®: 1x/day for 3 days	**Eurartesim®: tablet of artenimol 40mg / piperaquine tetraphosphate 320 mg** Mix tablets only with water and administer immediate after preparation. To take preferably on an empty stomach. Tablets can be cut in 2 and crushed.
< 5 kg (¥) — 2.5 mg/kg artenimol and 20 mg/kg piperaquine tetraphosphate/dose 5 < 8 kg — ½ tablet 40/320 mg 8 < 11 kg — ¾ tablet 40/320 mg 11 < 17 kg — 1 tablet 40/320 mg 17 < 25 kg — 1½ tablets 40/320 mg 25 < 36 kg — 2 tablets 40/320 mg 36 < 60 kg — 3 tablets 40/320 mg 60 < 80 kg — 4 tablet 40/320 mg ≥ 80 KG — 5 tablets 40/320 mg	
SECOND CHOICE If ACT treatment is not available or contra-indicated (e.g., long-QT)	
Malarone®: 1x/day for 3 days	**Malarone®: adult tablet atovaquone 250mg/proguanil 100mg, paediatric tablet atovaquone 62,5mg/proguanil 25mg** This treatment can only be taken if it was not used as chemoprophylaxis. Tablets can be crushed and mixed with food or milk. To be taken daily at the same hour.
5 < 9 kg — 2 tablets ped (62.5/25) 9 < 11 kg — 3 tablets ped (62.5/25) 11 < 21 kg — 1 tablets 250/100 21 < 31 kg — 2 tablets 250/100 31 < 40 kg — 3 tablets 250/100 ≥ 40 KG — 4 tablets 250/100	
ALTERNATIVE TREATMENT: **Oral Quinine** Quinine 10 mg/kg (quinine sulphate) 3x/day po for 4-5 days (max 500 mg)	Magisterial preparation Combined with - **Clindamycin** 20 mg/kg/d divided in 3x/d po for 7 days (max 600 mg/dose) **OR** - If older than 8 years: **Doxycycline** **<45 kg:** doxy 2.2mg/kg 2x/d po for 7 days (max 100 mg/dose) **>45 kg:** doxy 100 mg/d 2x/d po for 7 days
P. vivax or P. ovale malaria	
Same initial treatment as for *P. falciparum, P. malariae or P. knowlesi* malaria (see above).	
FOLLOWED BY PRIMAQUINE **after determination of G6PD activity** 0.5 mg/kg (max 30 mg/dose) 1x/day for 14 days For a total of 7 mg/kg/cure(magisterial preparation) If mild-moderate G6PD deficiency (10-50%): Primaquine 0.75 mg/kg 1x/week for 8 weeks. If severe G6PD deficiency (<10%): contra-indication of Primaquine.	To clear the residual hypnozoites. Primaquine can cause gastrointestinal upset and should be given after food. If not well tolerated, reduce daily dose and increase the duration (to obtain the same total dose).

Caution: ¥ Children < 5 kg: prefer IV treatment over oral treatment (crushed tablets).
†If QTc >500msec, both ACT are contra-indicated (see alternative regimens). If QTc 450-500msec, consider drug administration under cardiac monitoring.
Possible interactions with other QT-prolonging drugs or anti-arrhythmic drugs are e.g. fluoroquinolones, macrolides, rifadine, depression treatment, triazoles, cisapride, anti-epileptic drugs (carbamazepine et phenytoin) or drugs that alter the concentration of piperaquine (antiretroviral treatment, domperidone...).



Conclusion

The Belgian Paediatric Malaria Treatment Protocol 2024 provides a comprehensive framework for the diagnosis, treatment, and monitoring of malaria in children. This guideline is summarised in the flowchart. Early recognition, appropriate treatment, and careful monitoring are key to improving outcomes in paediatric malaria cases.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

REFERENCES

1. World_Health_Organization. World malaria report 2023. Licence: CC BY-NC-SA 3.0 IGO. Geneva, Switzerland; 2023.
2. Sharland M, Butler K, Cant A, Dagan R, Davies G, de Groot R, et al. Manual of childhood infections: the blue book: Oxford University Press; 2016.
3. World_Health_Organization. Guidelines for malaria, 3 June 2022. Licence: CC BY-NC-SA 3.0 IGO. Geneva, Switzerland; 2022.
4. Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PL. UK malaria treatment guidelines 2016. J Infect. 2016;72(6):635-49.
5. Pierreux J, Bottieau E, Florence E, Maniewski U, Bruggemans A, Malotaux J, et al. Failure of artemether-lumefantrine therapy in travellers returning to Belgium with Plasmodium falciparum malaria: an observational case series with genomic analysis. J Travel Med. 2024;31(3).