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Swiss TPH
Centre for Tropical and Travel Medicine
National Reference Centre for Malaria

Malaria Treatment Recommendations 2026

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I. Clinical assessment / triage of malaria patients

Patients diagnosed with malaria must be assigned to one of the following two treatment groups / modes of treatment:
- «Uncomplicated malaria» = ambulatory/out-patient peroral therapy and follow-up
- «Severe malaria» = hospitalisation and parenteral therapy

Criteria of «severe malaria» – treat as «severe malaria» if ≥1 of the following complications is present:	
Prostration	Generalized weakness, unable to sit, stand or walk without assistance
Cerebral malaria	Impaired consciousness (GCS <11 in adults; BCS <3 in children), seizures
Respiratory distress	Hypoxia, pulmonary oedema, acute respiratory distress syndrome (ARDS)
Acute renal failure	Urine output <0.4 ml/kg/h or creatinine >265 µmol/l [>3 mg/dl] or urea >20 mmol/l
Acidosis	Arterial pH <7.3, plasma bicarbonate <15 mmol/l, lactate ≥5 mmol/l or BE <8 mmol/l
Circulatory collapse	Shock (compensated [no hypotension but capillary refill time ≥3 sec or temperature gradient on leg (mid to proximal limb)]; decompensated shock [syst. RR <80 mmHg in adults or <70 mmHg in children])
Jaundice	Bilirubin >50 µmol/l [>3 mg/dl] with a parasite count >100'000/µl (>2%) in *P. falciparum* or >20'000/µl (0.4%) in *P. knowlesi* malaria
Hypoglycemia	Blood glucose level <2.2 mmol/l [<40 mg/dl]
Severe anaemia	*Adults*: Hb <4.8 mmol/l [<7 g/dl] or Hct <20%, *Children*: <12 years: Hb 3.1 mmol/l [<5 g/dl] or Hct <15% together with a parasite count >10'000/µl
Impaired coagulation	Spontaneous bleedings, disseminated intravascular coagulation (DIC)
Repeated vomiting	Inability to take oral medication
Hyperparasitaemia*	≥2% (parasite count 100'000/µl)
≥3 days symptoms**	As indirect surrogate marker of potentially high parasitaemia in the absence of quantified parasitemia

Criteria adapted from WHO[1]

* Swiss threshold, see comment below.

** Swiss criterion defined for the situation in which parasitemia is not timely available.

In unclear cases, consult a specialist with experience in the clinical management of malaria. The Swiss TPH Centre for Tropical and Travel Medicine provides expert advice 24/7: Tel. 061-284-8144.

Comment on the clinical assessment / triage of malaria patients

The hyperparasitaemia threshold and the concept of isolated «*uncomplicated hyperparasitemia*»

Background:

The Swiss threshold of 2% is based on a large study (retrospective analysis of 2793 malaria cases imported to Sweden 1995-2015) that showed an association between oral treatment and progression to severe malaria in patients with more than 2% parasitaemia at presentation.[2] However, the threshold value of hyperparasitemia defining severe malaria varies considerably between international guidelines and also WHO has repeatedly revised this threshold (between 2–10%) over time. The recently updated German malaria treatment guideline e.g. refers to a parasitemia level of ≥5% as cut-off to define severe malaria.[3]

In addition, WHO has introduced the differentiation between «*hyperparasitaemia*» (= ≥10% of red blood cells parasitized; defining «*severe malaria*» irrespective of epidemiological setting) and «*uncomplicated hyperparasitaemia*» (= ≥4–<10% of red blood cells parasitized in the absence of other signs defining «severe malaria»). In «*uncomplicated hyperparasitaemia*», WHO recommends hospitalisation and close monitoring (due to «increased risk for treatment failure, severe malaria and death») but advocates oral treatment with an artemisinin-based combination therapy (ACT) in this situation.[1] Since the WHO has introduced the concept of «*uncomplicated hyperparasitemia*» for endemic populations (with partial immunity)[1], it remained unclear whether this concept would also applicable to travelers from non-endemic areas (without partial immunity) or to migrants who have left endemic areas and now live in non-endemic areas (with partial immunity declining over time). With regard to the latter group, it deserves noting that it is currently not possible to reliably quantify *partial immunity* or its decline over time.[4] Recent publications from non-endemic countries (Germany[5], Spain[6]) France[7]) have readdressed the question whether hyperparasitaemia, as well as other criteria for severe malaria, may need reevaluation.

Recommendation:

- Physicians with limited experience in the clinical management of malaria should generally adhere to the 2% threshold when triaging malaria cases and treat all patients with a parasitaemia ≥2% as having «*severe malaria*».
- Physicians experienced in the clinical management of malaria may opt to treat selected patients with isolated «*uncomplicated hyperparasitaemia*» with peroral artemisinine-based combination therapy (ACT). However, given the caveats outlined above, we currently recommend restricting this approach to patients who (i) reliably adhere to treatment, (ii) plausibly present partial immunity, and (iii) have a parasitaemia of <4%. To maximise safety, these patients should be monitored in the clinic until at least two doses of oral treatment have been administered (= 8 hours) before they are discharged and followed up as outpatients. Note that the option of peroral treatment of «*uncomplicated hyperparasitaemia*» is limited to artemisinin-based combination therapy (ACT) and that other treatment regimens should not be used in this situation!

II. Treatment of uncomplicated malaria

	1st-line treatment	Alternative treatment
P. falciparum	▪ **Artemether/lumefantrine (A/L)**[1,2,3,4] 2 doses/day for 5 days[5] 0, 8, 24, 36, 48, 60, 72, 84, 96, 108 h: RIAMET *Baby* (1 tabl. = 2.5/30 mg): 2 –<5kg: 2 tabl./dose[6] [total 20 tabl.] RIAMET (1 tabl. = 20/120 mg): 5–14 kg: 1 tabl./dose [total 10 tabl.] 15–24 kg: 2 tabl./dose [total 20 tabl.] 25–34 kg: 3 tabl./dose [total 30 tabl.] ≥35[7] kg: 4 tabl./dose [total 40 tabl.] OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**[1,2,4,8,9] (1 tabl. = 40/320 mg) 1 dose/day for 3 days = at 0, 24, 48 h: 5[6]–<7 kg: ¼ tabl./dose [total ¾ tabl.] 7–<13 kg: ½ tabl./dose [total 1½ tabl.] 13–<24 kg: 1 tabl./dose [total 3 tabl.] 24–<36 kg: 2 tabl./dose [total 6 tabl.] 36–<75 kg: 3 tabl./dose [total 9 tabl.] >75 kg: 4 tabl./dose [total 12 tabl.]	▪ **Atovaquone/proguanil (A/P)**[3] 1 dose/day for 3 days = at 0, 24, 48 h: <11kg: paediatric formulation: 1 tabl.= 62.5/25 mg: 5–<9 kg 2 tabl./dose [total 6 tabl.] 9–<11 kg 3 tabl./dose [total 9 tabl.] ≥11kg: adult formulation: 1 tabl. = 250/100 mg ; 11–20 kg: 1 tabl./dose [total 3 tabl.] 21–30 kg: 2 tabl./dose [total 6 tabl.] 31–40 kg: 3 tabl./dose [total 9 tabl.] >40 kg: 4 tabl./dose [total 12 tabl.][7] OR ▪ **[Mefloquine**[10] (1 tabl. = 250 mg) 25 mg/kg given in 1–4 doses (if ≥2 doses[#] separate doses by 6–8 h and give the tablets of each dose over 30 min): 5–10 kg: ½–1 tabl. 10–20 kg: 1–2 tabl. 20–30 kg: 2–3 tabl. (#2 + 1 tabl.) 30–45 kg: 3–4 tabl. (#2 + 2 tabl.) 45–60 kg: 5 tabl. (#3 + 2 tabl.) >60 kg: 6 tabl. (#3 + 2 + 1 tabl.) >90 kg: 9 tabl. (#3 + 3 + 3 tabl.) >120 kg: 12 tabl. (#3 + 3 + 3 + 3 tabl.)**]**
P. vivax ***P. ovale*** ***P. cynomolgi***	▪ **Artemether/lumefantrine (A/L)**[1,3,4,11] Dosage analogue to *P.f.*, but 3 day regimen: 0, 8, 24, 36, 48, 60 h OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)** (see *P.f.*)[1,3,4,8,9,11] OR ▪ **Chloroquine**[4,12] Initially 10 mg base[13]/kg p.o. [adult: 600 mg] followed by 5 mg base[13]/kg p.o. [adult: 300 mg] after 12, 24, 36 h (alternatively: 6, 24, 48 h) ***followed by*** (after ruling out G6PD-deficiency) **Primaquine** <70kg: 0.5 mg base[14]/kg/day [max. 30 mg] for 14 days ≥70kg: 30mg/day until a cumulative dose of 6 mg base/kg body weight is reached[15] **+ if initially treated with A/L: Chloroquine**[16] adults: 100–150 mg/day for 14 days; children: 5–25 kg: 25mg/d, 25–35 kg: 50mg/d, 35–45 kg: 75mg/d for 14 days	▪ **Atovaquone/proguanil (A/P)**[3] (see *P.f.*) OR ▪ **[Mefloquine** (see *P.f.*)[10]**]** ***followed by*** (after ruling out G6PD-deficiency) **Primaquine** <70kg: 0.5 mg base[14]/kg/day [max. 30 mg] for 14 days ≥70kg: 30mg/day until a cumulative dose of 6 mg base/kg body weight is reached[15] **+ Chloroquine**[16] adults: 100–150 mg/day for 14 days; children: 5–25 kg: 25 mg/d, 25–35 kg: 50mg/d, 35–45 kg: 75 mg/d for 14 days
P. malariae	▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**[4] (see *P.f.*) OR ▪ **Chloroquine**[4] Initially 10 mg base[13]/kg p.o. [adult: 600 mg] followed by 5 mg base[13]/kg p.o. [adult: 300 mg] after 12, 24, 36 h (alternatively: 6, 24, 48 h)	▪ **[Mefloquine** (see *P.f.*)[10]**]** OR ▪ **[Artemether/lumefantrine (A/L)** (see *P.f.*)**]**[17] OR ▪ **[Atovaquone/proguanil (A/P)** (see *P.f.*)**]**[17]
P. knowlesi	▪ **Artemether/lumefantrine (A/L)**[18] (see *P.f.*) OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)** (see *P.f.*)[18]	▪ **Atovaquone/proguanil** (see *P.f.*) ▪ **Chloroquine** (see *P.v./o./c./m.*) ▪ **[Mefloquine** (see P.f.)[10]**]**

In the case the infecting Plasmodium species cannot be determined, treat as P. falciparum malaria.

[1] A/L and DHA/PPQ provide more rapid symptomatic and parasitological recovery and a shorter hospitalisation compared to A/P.[8]

[2] Prefer A/P if the *P.f.* infection was acquired in the Greater Mekong Subregion (Thailand, Laos, Cambodia, Myanmar, Vietnam): resistance related A/L treatment failure rates of ~20% are reported from the Thai-Cambodian border region and resistance related DHA/PPQ treatment failure rates of 44–87% are reported from Cambodia, Thailand, and Vietnam.

[3] Intake with fatty food or milk to ensure adequate bioavailability!

[4] When treating breakthrough infections following recent chemoprophylaxis with mefloquine, monitor ECG because of increased risk of QTc prolongation.

[5] High rates of late treatment failures have been observed in (non-immune) European travellers with uncomplicated *P.f.* malaria receiving the licensed standard 3-day A/L treatment regimen (see comment ① below).

[6] The dispersible *Riamet Baby* tablets are dissolved in ~10 mL of water/tablet (roughly 2 teaspoons). The cup should then be rinsed with a further 10 ml of water, which should also be given to the child to ensure that the full dose is taken.

[7] Consider adjusting dose in patients >90 kg (see comment ③ below).

[8] Intake with water on an empty stomach, at least 3 h before or after a meal to ensure adequate bioavailability!

[9] Risk of QT_c prolongation. Avoid in patients at risk (cardiac comorbidities) and with comedication known to prolong QT_c. Check ECG before first dose and 4–6 h before and after third dose. If QT_c intervall >500ms, change to A/P.

[10] Due to its unfavourable side-effect profile, mefloquine is nowadays only used if no alternative drug regimen is available.

[11] A/L and DHA/PPQ provide more rapid symptomatic and parasitological recovery compared to chloroquine.[9]

[12] While *P. ovale* and *P. cynomolgi* are generally sensitive to chloroquine, chloroquine resistant *P. vivax* is widespread (see section IV). Consider chloroquine for *P. vivax* only if chloroquine resistance is epidemiological unlikely.

[13] Oral chloroquine formulations: Plaquenil®: 1 tabl. = 200 mg hydroxychloroquinesulfate = 155 mg base (600 mg = 4 tabl.); Nivaquine®: 1 tabl. = 136 mg chloroquinesulfate = 100 mg base (600 mg = 6 tabl.); Hydroxychloroquine Zentiva®: 1 tabl. = 200 mg hydroxychloroquinesulfate = 155 mg base (600 mg = 4 tabl.);

[14] Primaquine tablets are usually composed of 26.3 mg primaquine phosphate = 15 mg primaquine base. The recommended dose range of primaquine varies from 0.25 to 0.75 mg base/kg/d; since lower doses are associated with treatment failure in *P. vivax* malaria, especially in Eastern Indonesia/Papua New Guinea, 0.5 mg/kg is the dose most widely recommended. Although a lower primaquine dose of 0.25 mg/kg/day is sufficient for the eradication of *P. ovale* hypnozoites, a uniform dosage for *P.v.* and *P.o.* is recommended for pragmatic/practical reasons.

[15] Due to reduced efficacy of primaquine in patients ≥70 kg, the total dose of primaquine should be adjusted in these patients to 6 mg/kg body weight, then divided into daily doses of 30 mg for the number of days needed to complete the total dose (i.e. more than the standard 14 days to complete treatment).

[16] Chloroquine and PPQ synergistically enhance the efficacy of primaquine. Thus, add chloroquine to primaquine if (1) neither chloroquine nor DHA/PPQ was used for treatment and if (2) primaquine treatment is delayed >3 weeks beyond chloroquine or DHA/PPQ treatment (see comment ② below).

[17] Considering the longer erythrocytic cycle of *P. malariae*, regimens/drugs with longer serum half-lives (DHA/PPQ, mefloquine) should be preferred over regimens/drugs with shorter serum half-lives (A/L, A/P) to avoid treatment failure.[10]

[18] The asexual cycle of *P. knowlesi* is the shortest of all human-pathogenic malaria species (24h) which potentially leads to high levels of parasitaemia. Therefore, the fast parasite clearance of artemisinin compounds makes them the favoured 1st line option.

Comments on the treatment of uncomplicated malaria

1. Late treatment failures in (non-immune) travellers with uncomplicated *P. falciparum* malaria receiving the standard 3-day treatment regimen of artemether/lumefantrine (A/L):

Background:

Retrospective studies from Sweden[11] and the Czech Republic[12] showed that the standard 3-day A/L treatment regimen may be associated with a high rate of late treatment failures in returning travellers (5.3[11]–13.9%[12]), whereas in the same studies no failures were observed with mefloquine or atovaquone/proguanil. Of note, already in the only ever conducted prospective study of A/L in nonimmune patients, published in 2008[13], a failure rate of 5.3% (3/57) was observed in the unpublished subgroup analysis of nonimmune European travellers. Limited pharmacokinetic data from the Swedish study indicate that the observed treatment failures may be attributable to low lumefantrine plasma concentrations. It is known, that the area under the curve (AUC) of plasma lumefantrine concentration versus time, or its correlate, the plasma concentration on day 7, is the main determinant for eradication of residual parasites not eliminated by artemether and, thus the determinant of the combination's clinical efficacy.[14] It should be noted, however, that in a more recent retrospective study [*Musumeci et al. Univ. Hospital Geneva, not yet published*], the recurrence rate in non-immune travellers was lower (~4%) but also occurred in the presence of factors that may have reduced lumefantrine exposure: body weight >100 kg or the presence of diarrhea. Pragmatically, considering that (i) nonimmune patients, lacking acquired partial immunity, have a higher risk of treatment failure compared to patients from endemic regions and that (ii) the observed treatment failures with A/L are very likely attributable to low lumefantrine plasma levels, the use of the 3-day A/L standard treatment regimen has to be seen critical.[15] The safety of an extended 5-day A/L treatment regimen has been demonstrated[16] and it has also been shown that besides *extending* the standard regimen from 3 to 5 days, *expanding* the 3-day regimen to 5 days by adapting the dosing intervals to 0, 8, 24, 48, 72, 96 h can also ensure sufficient lumefantrine plasma concentration on day 7[17-19]. In 2026, the US CDC extended the recommended duration of A/L treatment for uncomplicated *P. falciparum* malaria from 3 to 5 days.[20]

Recommendation:

We pragmatically recommend extending the licensed standard 3-day treatment regimen (see table above) by 4 additional doses (at 72, 84, 96, and 108 h) to 5 days.

2. Non-chloroquine treatment of *P. vivax* malaria:

Background:

(I) ACTs for non-*falciparum* malaria:

- The treatment of choice for non-*falciparum* malaria was chloroquine until chloroquine-resistant *P. vivax* emerged in the late 1980s and consecutively spread around the globe. Today, chloroquine-resistant *P. vivax* malaria is reported from many countries (see section IV). Therefore, chloroquine should only be used if the infection was acquired in an area with known chloroquine sensitivity.
- *P. ovale, P. malariae, P. knowlesi*, and *P. cynomolgi* parasites are generally chloroquine-sensitive and no chloroquine-resistance has ever been reported (see section IV).
- As in *P. falciparum* malaria, ACTs clear non-*falciparum* parasites and symptoms more rapidly than chloroquine and are at least equivalently effective in treating non-*falciparum* blood-stage infections.[21,22]
- Universal ACT treatment of all uncomplicated malaria cases, regardless of species, has the advantage of being a pragmatic and simple one-for-all solution and ensures that overlooked *P. falciparum* co-infections (which are mostly chloroquine-resistant in all regions of the world) would also be covered.

(II) The pro-drug issue of primaquine:

Primaquine is a pro-drug that is converted by cytochrome P450 2D6 (CYP2D6) to its active (hypnozoitocidal) form carboxyprimaquine. In patients with genetically determined low CYP2D6 activity, this conversion may be insufficient, leading to relapse(s).[23,24]

(III) "Hypnozoitocidal co-drug synergy":

- Coadministration of chloroquine and primaquine leads to significantly higher plasma levels of primaquine and its active metabolite carboxyprimaquine when compared to administration of primaquine alone.[25] This effect is explained by pharmacokinetic interactions between chloroquine and primaquine and is considered to be responsible for the observation that coadministration of the two drugs enhances the efficacy of primaquine against relapses (i.e. the eradication of hypnozoites).[26] Due to the extreme long plasma half-life of chloroquine (ranging from 70 to 300 hours and resulting in therapeutic blood drug levels for between 3 weeks to 3 months[27]), it can be assumed that primaquine administration may be delayed up to 3 weeks beyond chloroquine treatment without losing this synergistic effect.
- Artemisinins have no effect on the metabolism of primaquine.[28]
- Analogous to chloroquine, coadministration of PPQ and primaquine leads to significantly higher plasma levels of primaquine and its active metabolite carboxyprimaquine when compared to administration of primaquine alone.[29] A clinical trial has confirmed the co-drug synergy of PPQ and primaquine against relapses.[30] Like chloroquine, the elimination half-life of PPQ is extremely long (~22 days) and it can be assumed that primaquine administration may be delayed up to at least 3 weeks beyond PPQ treatment without loosing this synergistic effect.
- To date, neither pharmacological nor clinical studies have assessed pharmacokinetic interactions or co-drug synergy of lumefantrine and primaquine or atovaquone/proguanil and primaquine.

- Coadministration of mefloquine and primaquine does not increase plasma levels of primaquine or carboxyprimaquine.[31]

Recommendation:

To assure "hypnozoitocidal co-drug synergy" we recommend adding chloroquine to primaquine if (i) neither chloroquine nor DHA/PPQ has been used for initial treatment or if (ii) primaquine treatment is delayed >3 weeks beyond chloroquine or DHA/PPQ treatment. [Note: in the case that mefloquine has been used for treatment, check QT_c-time before administering primaquine together with chloroquine as all three drugs, and especially their combination, may lead to QT_c-prolongation].

3. Treatment of uncomplicated malaria in overweight/obese patients:

Recommendation:

Due to possibly skewed pharmacokinetics in obese patients either (i) prefer DHA/PPQ (the long half-life of PPQ should outweigh potential underdosing) or (ii) consider extending treatment: e.g. A/L to 6 days and A/P to 4–5 days.

4. Treatment of uncomplicated malaria in pregnancy:

Background:

In the pre-artemisinin era, quinine and chloroquin were the recommended antimalarial drugs in pregnancy. As evidence accumulated for the safety of ACTs, they replaced these drugs as first-line treatment in the 2nd and 3rd trimesters, while quinine + clindamycin (*P.f.* malaria) and chloroquin (non-*P.f.* malaria) remained the recommended first-line regimens in the 1st trimester. In 2022, following a meta-analysis,[33] the WHO finally endorsed the recommendation to not only use an ACT in the 2nd and 3rd trimester of pregnancy but to also extend the use of artemether-lumefantrine (A/L) to the 1st trimester. The recommendation to use an ACT is currently limited to A/L only, as there is (i) insufficient data for other ACTs and (ii) ACTs containing antifolates (e.g. sulfadoxine-pyrimethamine) are contraindicated during pregnancy. Data on A/P in pregnancy are still limited but its use may be considered if no other treatment option is available.

Recommendation:

***P. falciparum* malaria:** 1st-line: A/L for 5 days[34]; 2nd-line: quinine + clindamycin OR mefloquine. Due to the potential risk of recrudescence after completion of therapy, we recommend secondary prophylaxis with mefloquine [250 mg once weekly] until delivery.[35]

Non-*P.falciparum* malaria: 1st-line: A/L for 3 days; 2nd-line: chloroquine (quinine may be used if there is concern about chloroquine resistant *P. vivax* malaria). *P. vivax, P. ovale*: primaquine is contraindicated during pregnancy as the G6PD-status of the foetus is not determinable. Primaquine is contraindicated during pregnancy because the G6PD status of the foetus cannot be determined. Radical cure with primaquine for eradication of hypnozoites should therefore be deferred until after delivery. Following treatment of the blood-stage infection, we therefore recommend secondary prophylaxis with chloroquine (500 mg once weekly) for the remainder of pregnancy to prevent relapse until radical cure with primaquine can be administered postpartum.[35] In breastfeeding women, primaquine should only be administered from 1 month postpartum and after the infant has been confirmed to have sufficient G6PD activity.

5. Primaquine treatment of patients with Glucose-6-Phosphate-Dehydrogenase (G6PD)-deficiency:

Background:

- G6PD protects erythrocytes from oxidative stress. G6PD deficient individuals are prone to sustain haemolysis if they are exposed to oxidative stresses, e.g. certain drugs like primaquine. The severity of haemolysis depends upon the degree of enzyme deficiency (which is G6PD-variant-dependent), the nature and total dose of the oxidative agent, the time course of exposure, the presence of additional oxidative stresses and pre-existing factors such as age, haemoglobin concentration and concurrent infection.
- The phenotypes of G6PD-deficiency are highly variable (reflecting ~300 genotypes): The African variant (A^-) mostly shows mild deficiency (>10% enzyme activity) and is relatively resistant to severe primaquine-induced haemolysis. Among Caucasians and Asians, however, the enzymatic activity in homozygotes is relatively low with a higher risk of severe primaquine-induced haemolysis. The Mediterranean variant (B^-) has especially minimal G6PD activity (often <1%) with a very high risk of sustaining severe haemolysis.
- The hypnozoitocidal efficacy of primaquine is determined by its cumulative total dose rather than by peak plasma levels. Extending the dosing regimen has shown to reduce toxicity in G6PD deficient individuals. In addition, extending the dosing schedule allows discontinuing treatment before the severity of haemolysis becomes critical. The most widely used regimen is a weekly single dose of 45 mg primaquine for 8 consecutive weeks.[36-38]
- In most cases with mild G6PD deficiency, haemolysis is self-limiting and ends a few days after stopping treatment. However, in patients with the Mediterranean variant (B^-), serious haemolysis may even be caused by extended dosing regimens of primaquine and, unlike with the A^- variant, haemolysis is not self-limiting. Therefore, primaquine administration to severely G6PD deficient patients remains controversial (e.g. WHO recommends against primaquine treatment). If treatment is considered, the dosage regimen should be modified to weekly doses of 30 mg primaquine for 15 weeks and patients should be closely monitored for haemolysis.[39]
- G6PD enzyme activity cut-off values for primaquine treatment: *Men: >30%*: no risk; *<30%*: significant risk; Women: *>80%*: low risk; *30–80%*: potential risk; *<30%* significant risk. Levels >30% are generally considered to confer an acceptably low risk when administering primaquine in the normal therapeutic dose.[40]

Recommendation:

- *Mild to moderate G6PD deficiency (≥30% activity) / non-Mediterannean G6PD variants:* give primaquine in a weekly single dose of 45 mg (below 60 kg of body weight give 0.75 mg/kg) for 8 consecutive weeks and closely monitor haemolysis parameters. In affected patients, the haemoglobin level starts falling 1–2 days after starting treatment, reaches a nadir after 5–6 days and then starts rising again despite continued treatment (by then old RBCs with low G6PD concentrations have been depleted and young RBCs with highter G6PD concentrations enter the circulation).
- *Severe G6PD deficiency (<30% activity) / Mediterranean G6PD variant:* there are two options:
  - (1) If the patient does not want to risk haemolysis, abstain from primaquine treatment and inform the patient about the possibility of future relapse(s). If there is a risk that the patient may sustain a relapse without timely access to appropriate health care, the patient should receive malaria emergency stand-by self medication (i.e. A/L or A/P).
  - (2) If primaquine treatment is agreed upon, give primaquine in a weekly single dose of 30 mg (below 60 kg of body weight give 0.5 mg/kg) for 15 consecutive weeks and closely monitor haemolysis parameters.
- Case reports of severe haemolysis in only mildly G6PD deficient individuals highlight that even extended dosing regimens cannot eliminate the risk: closely monitor haemolysis parameters!

6. **Recommended treatment monitoring of uncomplicated malaria:**
   - Treatment efficacy is assessed by clinical improvement, clearance of asexual parasite forms from the blood and normalisation of abnormal laboratory parameters (excellent surrogate marker: platelets).
   - Full blood count and parasitaemia assessment by microscopy every 24h until negative. Note that:
     - Parasite count may temporarily increase in the first 24–36h of treatment (due to the fluctuation of parasitaemia and the timepoint of blood sampling during the parasite's erythrocytic cycle) without demanding action.
     - Only the asexual trophozoite/ring stage parasites are relevant; gametocytes may still be present even in cured patients.
   - If treating with DHA/PPQ: ECG (QT_c assessment) before starting treatment and 4–6h before and after third dose.
   - Consider monitoring for *post-Artesunate delayed haemolysis (PADH)* in patients treated with ACT who are at risk for anaemia.

III. Treatment of severe malaria

	1st-line treatment	2nd-line treatment
P. falciparum **(*P. vivax*[1], *P. knowlesi*)**	**Artesunate i.v.** Adults and children >20kg: 2.4 mg/kg Children <20kg[2]: 3.0 mg/kg at 0, 12 and 24 h, then every 24 h[3] by slow i.v. bolus injection over 5 minutes; *switch to oral therapy once the patient is stable, tolerates oral medication, and parasitemia is <1% (but not before completing at least 24 h of i.v. treatment) and give a complete course (to be started 8–12 h after the last i.v. dose of artesunate) of:* ▪ **Artemether/lumefantrine (A/L)**[4] OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**[4] OR ▪ **Atovaquone/proguanil (A/P)** (*regimens: see uncomplicated malaria*) *if the situation does not allow for switching to oral therapy, continue Artesunate for a total of 7 days and add* **Doxycycline i.v.** adults: 100 mg BID; children (only if ≥8 years old): 2–4 mg/kg divided in 2 doses for a total of 7 days OR **Clindamycin i.v.** adults: 10 mg/kg loading dose, followed by 5 mg/kg every 8 h for a total of 7 days; children: 15–20 mg/kg divided in 3 doses for a total of 7 days	**Quinine dihydrochloride i.v.**[5,6] 1. loading dose[7]: 20mg salt[8]/kg over 4 h[9,10] Note: Quinine is increasingly unavailable! 2. continuation phase: 10 mg salt[8]/kg over 4 h starting 8 h after initiation of treatment followed by 10 mg/kg over 4 h every 8h (=alternate 4 h drug administration and 4 h drug free interval), max. dosage 600 mg TID *switch to oral medication as soon as possible (but not before completing at least 24–48 h of i.v. treatment) and give a complete course (to be started 8–12 h after the last i.v. dose of quinine) of:* ▪ **Artemether/lumefantrine (A/L)**[4] OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**[4] OR ▪ **Atovaquone/proguanil (A/P)** (*regimens: see uncomplicated malaria*) OR ▪ **Quinine sulfate** 10 mg salt/kg TID max. dosage: 600–650 mg TID for 7 days **+ Doxycycline p.o.:** adults: 100 mg BID; children (only if ≥8 years old): 2–4 mg/kg divided in 2 doses for a total of 7 days OR **+ Clindamycin p.o.:** adults and children: 5 mg/kg every 8 h for a total of 7 days

1 In the case of *P. vivax* malaria: sequential treatment with primaquine to eradicate hypnozoites (see *uncomplicated malaria*).
2 Pharmacokinetic modelling and the absence of potential toxicity supports dose adjustment in children <20 kg.[41]
3 *Artesunate*: no dose adjustment in the case of hepatic or renal impairment.
4 If the infection was acquired in areas with artemisinin-resistant *P.f.* strains (see section IV), consider A/P as the preferred follow-up treatment.
5 *Quinine*: in the case of hepatic or renal impairment (GFR <10 ml/min): no dose adjustment in the first 48 h of treatment; >48 h: reduce the dose by ⅓, to 10 mg salt/kg every 12 h. No dose adjustment in the case of haemodialysis or haemofiltration.
6 «Cinchonism»: comprising tinnitus, deafness, headache, nausea and visual disturbance, affects most conscious patients with therapeutic levels and does not warrant dose reduction!
7 Loading dose must not be used if patient received mefloquine within preceding 24 h.
8 Drug is labelled with the mass of drug expressed in salt rather than base (the active drug). Quinine dihydrochlorid is available as solution of various strengths in distilled water: 500 mg salt = 413 mg base in vials à 1 ml; 600 mg salt = 496 mg base in vials à 2 ml; 1000 mg salt = 826 mg base in vials à 2 ml; 1200 mg salt = 1000 mg base in vials à 5 ml.
9 The rational to infuse each dose of quinine within 4 h is based on the instability of quinine solution when exposed to light.
10 The quinine solution is diluted in isotonic fluid (e.g. 5% dextrose, normal saline) but preferably in 5% dextrose because of the quinine-induced insulin liberation leading to hypogycemia. Controlled infusion by infusion pump only! Monitor hypoglycaemia, hypotension, and cardiac arrhythmia!

Comments on the treatment of severe malaria

1. **Treatment of severe malaria in pregnancy:**

Background:

In the pre-artemisinin era, i.v. quinine + clindamycin used to be the standard treatment regimen for severe malaria in pregnancy. However, artesunate gradually replaced quinine for this indication and today WHO[1] as well as most national guidelines recommend i.v. artesunate as first-line treatment for severe malaria in pregnancy regardless of trimester. Note however that, although artesunate is recommended for the treatment of severe malaria in pregnancy, the drug is not approved for this indication, neither by the EMA in Europe nor by the FDA in the USA.

***Recommendation*:**

1st-line treatment: artesunate followed by A/L for 5 days[34]

2nd-line treatment: quinine + clindamycin

Note: *P. falciparum*: Due to the potential risk of recrudescence after completion of therapy, we recommend secondary prophylaxis with mefloquine [250 mg once weekly] until delivery.[35]

P. vivax/ovale: Primaquine is contraindicated during pregnancy as the G6PD-status of the foetus is not determinable. Primaquine therapy to eradicate hypnozoites has to be delayed until after birth. To prevent relapses after completion of therapy, we recommend secondary prophylaxis with chloroquine [500mg once weekly] until delivery.[35]

2. Post-Artesunate Delayed Haemolysis (PADH):[42,43]

Background:

Malaria parasites killed by artesunate are removed from erythrocytes by the spleen and the «cleaned» erythrocytes are released back into circulation. These morphologically altered («pitted») erythrocytes (or «once-infected erythrocytes», «o-iE») remain in circulation but with a considerably decreased life span of 7 to 21 days. Artemisinins are more likely than quinine to result in the creation of significant numbers of o-iEs. Patients with higher initial parasitaemia have higher numbers of o-iEs after treatment with artemisinin drugs. When these erythrocytes with decreased lifespan are simultaneously cleared en masse, it results in a brief haemolytic episode that does not recur. PADH has been observed in ~27% of European travellers receiving i.v. artesunate and some required blood transfusion. Therefore, monitoring of haemolysis parameters following i.v. artesunate treatment of severe malaria is generally recommended. PADH has also been observed after oral artemisinin treatment of uncomplicated malaria.[44]

***Recommendation*:**

- Monitor for delayed haemolysis in patients treated with i.v. artesunate at day 7, 14, 21, and 28.
  (Note: the higher the initial parasitemia, the higher the number of o-IEs, the higher the risk of sustaining significant PADH; in rare cases prolonged haemolysis over >4 weeks has been described)
- Although the lower initial parasitaemia in uncomplicated malaria leads to lower numbers of o-IE after treatment and PADH is less pronounced and clinically irrelevant in most cases, analogous monitoring of haemolysis parameters should be considered in patients with predisposing risk factors for anaemia.

3. Adjunct treatment of severe malaria:

- ***Empirical antibiotic therapy for possible concomitant sepsis***
  - In contrast to children, the prevalence of concomitant bacteraemia in adults with severe malaria is low.[45]
  - Hypotensive shock may occur but is not typical for malaria and should raise the suspicion of concomitant bacterial sepsis.

  ***Recommendation*:**
  - The administration of empirical antibiotics in addition to artesunate is not generally indicated in adults with severe malaria, but is justified in the few patients with very high parasitemia.
  - If the patient is in shock, obtain blood cultures and empirically start antibiotic treatment to cover for gram-negative sepsis.
- ***Renal failure:***
  - Frequent complication of severe malaria.
  - Adjunct acetaminophen/paracetamol treatment shows a kidney-protective effect in patients with severe malaria.[46,47]

  ***Recommendation*:**
  - Patients with severe malaria should receive adjunct acetaminophen/paracetamol (1g 6-hourly for the first 72 h of treatment) for kidney protection.
  - Avoid NSARDs and other nephrotoxic medication.
- ***Respiratory failure:***

  Malaria patients are prone to fluid overload and pulmonary oedema (pathophysiological correlate: endothelial damage).

  Recommendation:
  - Limit fluid replacement to diuresis and compensation for perspiration/fever: 2–3 ml/kg/h during the first 24 hours without bolus therapy, unless the patient is hypotensive.[48]
  - No intravenous fluid bolus resuscitation in children with malaria.[49]
  - In low resource settings, bedside sonography of the vena cava is a simple tool to evaluate the patient's volume status and guide volume therapy. In high resource settings a central venous catheter (monitoring of CVP) or a PiCCO catheter (monitoring of extravascular lung water, lung oedema) may be used.
- ***Cerebral malaria:***
  - If patient is unconscious: rule out hypoglycaemia, consider cranial imaging and diagnostic lumbar puncture.
  - The use of prophylactic anticonvulsants is contraindicated as their use is associated with increased lethality.
  - Seizure control: use benzodiazepines or benzodiazepine-derivatives; phenobarbital increases lethality.
  - Corticosteroids and mannitol are contraindicated in adult patients with cerebral malaria and cranial hypertension. Both drugs prolong coma and worsen prognosis.
- ***Metabolic acidosis:***

  Metabolic acidosis usually corresponds to lactic acidosis due to microcirculatory disturbance and hypovolemia. Other metabolic causes are possible. Under antiparasitic therapy, there is usually a rapid equalization of the shifts.

  Recommendation:
  - Careful treatment of hypovolemia (see *respiratory failure* above)
  - Alkalizing therapy should only be given in exceptional cases (i.e. if the arterial pH falls below 7.2 despite correction of hypovolaemia and hypoxaemia) as sodium bicarbonate administration can lead to an increase in intracerebral pH and pressure.[1]
- ***Exchange transfusion/erythrocytapheresis for severe malaria:***
  - Exchange transfusion (ET) has been used as an adjunct treatment of severe malaria presenting with hyperparasitaemia and organ failure since its first reported use in 1974. The rationale of ET is based on its biological plausibility: The accelerated parasite clearance time (PCT) is supposed to prevent further sequestration of infected RBCs, thus preventing further microvascular blockage and organ failure. The techniques used included traditional/manual ET and, more recently, erythrocytapheresis (automated RBC ET). While traditional ET is a time-consuming process involving intermittent or continuous venesection and transfusion, with inherent risks of haemodynamic compromise, erythrocytapheresis allows for the rapid removal of altered RBCs and replacement with normal cells (usually in <2 h) by maintining haemodynamic stability and retaining platelets and plasma components such as clotting factors. In the absence of scientific evidence, ET has been recommended, based on pathophysiological plausibility.[50] Up to 2012, 37 clinical case reports on the use of automated RBC exchange as an adjunctive treatment option for severe malaria have been published in the form of case series and case reports. All but one report included patients with hyperparasitaemia (>10%) and critical organ dysfunction. RBC exchange was most often considered in cases with extremely high parasite counts (median 30%) and the presence of neurological symptoms suggestive of cerebral malaria.[50] In the absence of randomized controlled trials the benefit of ET

remains unproven. Furthermore, the introduction of i.v. artesunate with its rapid clearance of parasites from the blood (PCT: i.v. quinine: 49 h; i.v. artesunate: 20 h) has questioned the benefit of ET.
- In 2013, a retrospective Dutch cohort study on ET adjunct to i.v. quinine and i.v. artesunate therapy was published. The study concluded that ET does not significantly contribute to parasite clearance in patients treated with artesunate (there could be a small effect of ET on parasite elimination under quinine treatment).[51]
- In 2013, the US CDC published an analysis and review of ET and concluded «despite rapid parasite clearance times resulting from ET, there is no evidence for efficacy of ET as adjunctive therapy in severe malaria. Adjunct ET cannot be recommended. When rapidly acting antimalarials, specifically artemisinins, become more widely available, the biologic plausibility argument for ET will become less relevant».[52]

Recommendation:
- Treated with i.v. artesunate: there is no evidence that ET is beneficial.
- Treated with i.v. quinine: if available, change to i.v. artesunate; if i.v. artesunate is unavailable but erythrocytapheresis is available, discuss the option of exchange transfusion with a malaria specialist.

4. Recommended treatment monitoring of severe malaria:
- Treatment efficacy is primarily assessed by clinical improvement, clearance of asexual parasite forms from the blood and normalisation of abnormal laboratory parameters (excellent surrogate marker: platelets).
- Full blood count and parasitaemia assessment by microscopy every 24h until negative. Note that:
  - Parasite count may temporarily increase in the first 24–36h of treatment (due to the fluctuation of parasitaemia and the timepoint of blood sampling during the parasite's erythrocytic cycle) without demanding action.
  - Only the asexual trophozoite/ring stage parasites are relevant; gametocytes may still be present even in cured patients.
- Blood gas analysis (BGA) latest every 6h (+ in the case of quinine therapy additionally at 3h after starting therapy) until patient's conditions have stabilised.
- If treated with quinine: monitor for hypoglycemia (due to quinine-induced hyperinsulinemia) 2-hourly during quinine infusion, 4-hourly during infusion-free interval, and each time altered consciousness is noted.
- Monitor for delayed post-artesimate haemolysis (see comment ②) in patients with predisposing risk factors for anaemia.

IV. Treatment failure: recrudescence / relapse / resistance

Recrudescence	• = situation in which parasitaemia falls below detectable levels and then increases to detectable levels again due to incorrect dosing, incompliant drug intake, compromised intestinal drug absorption, poor drug quality, drug interactions, unusual drug metabolization or drug resistance. • May occur in malaria due to any species. • Most recrudescence episodes occur more than 2 weeks (mostly between 2–6 weeks) after treatment, but up to 10 weeks following treatment with long-halflife drugs like mefloquine or piperaquine (in DHA/PIP).
Relapse	• = recurrence due to activation of hypnozoites in *P. vivax*, *P. ovale or P. cynomolgy* malaria. • May occur weeks, months and up to a maximum of ~5 years following primary infection. • The proportion of cases relapsing and the interval between relapses vary between parasite strains (tropical *P. vivax* strains: 3–6 weeks; subtropical and temperate region *P. vivax* strains: often >8 months–5 years).
Resistance	• ***P. falciparum:*** ▪ *Chloroquine: P. falciparum* remains sensitive to chloroquine only in Central America and Hispaniola (Dominican Republic and Haiti).[54] Nevertheless, genetic chloroquine resistance markers are reported from the region.[54] ▪ *Mefloquine:* mefloquine resistance is a concern in the Greater Mekong subregion, in particular in Thailand and in Cambodia. A case report on failure of mefloquine therapy due to drug resistance in a traveller returning from Benin has been published.[55] ▪ *Atovaquone/proguanil:* molecular analysis of recrudescent isolates showed that atovaquone resistance is associated with a single mutation in the parasite's cytochrome *b* gene.[56] Mutations in this gene have been reported in Burkina Faso, Cameroon, the Comoros, Ivory Coast, French Guiana, Guinea, India, Kenya, Mali, Mozambique, Nigeria, Senegal, Sierra Leone and Uganda.[57] ▪ *ACTs:* artemisinin-based combination therapies (ACTs) remain highly efficacious in most parts of the world. *Artemisisin partial resistance** emerged in the Greater Mekong Subregion (Laos, Thailand, Vietnam, Cambodia) in 2007 and more recently (since 2020) in Eastern Africa (Rwanda, Uganda, Ethiopia, Eritrea).[58] • ***P. vivax:*** Reported resistance of *P. vivax* is limited to chloroquine, sulfadoxine/pyrimethamine and (low dose) primaquine. Chloroquine reatment failure has been observed in Afghanistan, Bolivia, Brazil, Cambodia, China, Colombia, Democratic People's Republic of Korea, Ethiopia, French Guiana, Guyana, India, Indonesia, Madagascar, Malaysia, Myanmar, Nepal, Pakistan, Papua New Guinea, Peru, Republic of Korea, Solomon Islands, Sri Lanka, Thailand, Timor-Leste, Turkey, Vanuatu and Viet Nam.[54] • ***P. ovale, P. malariae, P. knowlesi:*** *P. ovale, P. malariae* and *P. knowlesi* are generally considered sensitive to chloroquine.[54] Only one report from Sumatra, Indonesia suggests local resistance of *P. malariae* to chloroquine.[59] • Up-to-date information on antimalarial drug resistance: http://www.wwarn.org/explorer/app

* *Artemisinin partial resistance* is characterized by (i) an increased parasite-clearance half-life of more than 5 hours and (ii) the presence of specific K13 mutations in the parasite's genome. Artesmisinine partial resistance does not mean that the parasite is completely resistant to the drug and cannot be treated with it, but only that the drug needs more time to kill the parasite. So far there have been no reports of *Artemisinin complete resistance*.

Recommendation:
- Inform all patients treated for malaria about the potential risk of recurrence/relapse!
- Uncomplicated *P. falciparum recrudescence:*
  - If initially a 3-day regimen of A/L was used, retreat with a 5-day A/L regimen (see section I., comment ①).
  - If initially a 5-day regimen of A/L was used and *artemisinin partial resistance* is suspected, retreat with either (i) a prolonged A/L course (i.e. 6–7 days; due to in-vitro data suggesting superiority of lumefantrine[61] in this situation we recommend to retreat with A/L and not with DHA/PPQ) or (ii) with A/P.
- *Severe P. falciparum malaria with suspected artemisinin resistance (delayed response to treatment / parasite clearance):*
  - Always consult a malaria specialist in such cases!

- WHO recommends artesunate + quinine combination therapy in this situation.[3]
- Non-*P. falciparum* «recrudescence» and «relapse» episodes can generally be retreated with the first-line regimen or with any listed alternative regimen, taking the following considerations into account:
  - The above listed species-specific resistances
  - *P. vivax/ovale* relapses: the pro-drug issue of primaquine (see section II., comment ②(II)) and the hypnocoitocidal co-drug synergy (see II., comment ②(III)); in the case a patient sustains repeated relapses despite compliant intake of primaquine, consider
    - Testing the patient's CYP2D6 enzyme activity (see section II., comment ②(II); non-/hypometabolizers should be provided with a course of emergency self-treatment in the case they do not always have timely access to medical care.
    - Increasing the primaquine dose up to 60mg/day.[53]
  - *P. malariae* recrudescence: the parasite's long erythrocytic cycle supports the rational to prefer regimens/drugs with longer serum half-lives (DHA/PPQ, mefloquine) over regimens/drugs with shorter serum half-lives (A/L, A/P).[10]

V. Diagnostic

1. **Microscopy:**
   Thick and thin (EDTA) blood films/smears remain the gold standard in malaria diagnostic (thick smear = high sensitivity for establishing the diagnosis; thin smear = high specificity for identifying the species) and the only laboratory test suitable for follow-up/to assess treatment success (see section II. 6. Recommended treatment monitoring).
   - A reliably sensitive microscopic examination requires adequately trained and experienced personnel!
   - A single negative microscopy does not rule out malaria. In non-immune individuals (travellers), symptoms can occur even at very low parasitaemia levels, which are below the detection threshold of microscopy (and RDTs). Therefore, most guidelines require at least 3 negative tests at intervals of 8–24h to rule out malaria with sufficiently high sensitivity. However, the dogma of 3 negative test, which dates back to the days of exclusively microscopic diagnostics, was recently called into question by a study conducted at the university hospital of Lausanne, which retrospectively reviewed 4972 cases investigated for malaria by either by microscopy or with microscopy + RDT. The first test diagnosed malaria in 415 of the 4972 suspected cases (8.3%). Only 3 cases (0.06%) were diagnosed by the second test and only 1 case (0.02%) by the third test.[62]
2. **Rapid diagnostic tests (RDT):**
   RDTs are based on the detection of circulating parasite antigene(s). Depending on the test, different antigens are targeted alone or in combination: (I) Histidin-rich-protein-2/HRP2 (*P. falciparum*-specific); (II) Parasite lactate dehydrogenase / pLDH (either *P. falciparum-, P. vivax-*, or pan-[all species] specific); (III) Aldolase (pan-specific). *Pitfalls:*
   - False-negative results may occur in cases of very low or very high parasitaemia. HRP2-only RDTs are especially problematic in the case of very high parasitaemia as they can show a «prozone/hook effect» (which is not observed with pLDH- or aldolase-based tests).[63, 64]
   - False-negative results due *P.f.*-parasites with HRP2-deletions are increasing worldwide: http://apps.who.int/malaria/maps/threats/
   - False-positive RDT results may be seen in patients with high concentrations of rheumatoid factor.
   - *P. ovale*, *P. malariae* and *P. knowlesi* are not specifically targeted by the currently available RDTs and therefore RDTs are not suitable for diagnosing/excluding these infections (e.g. in *P. knowlesi* malaria pan-pLDH- and aldolase-based tests may be positive, *P. falciparum*-specific pLDH-based tests may be positive, and HRP2-based tests will be negative[65,66]).
   - HRP2-based tests may be false-positive in the case of acute schistosomiasis due to *S. mekongi*.[67]
   - HRP2- and pan-pLDH-based tests may be false positive in the case of African trypanosomiasis.[68]
   - HRP2 is cleared very slowly from the blood, therefore, HRP2-based tests may remain positive >1 month after successful treatment, particularly if initial parasitaemia was high. In addition, HRP2, pLDH and aldolase are also produced by gametocytes and, depending on the drug regimen used, gametocytes may circulate after successful treatment for days to weeks. Therefore, these tests are not useful to monitor treatment response/success!
3. **PCR:**
   PCR is the most sensitive diagnostic method available and the method of choice to diagnose extremely low parasitic cases and zoonotic malaria infections and to exclude mixed infections in cases that are difficult to assess microscopically. PCR can only detect blood stage infection but not hepatic hypnozoites. Thus, PCR cannot rule out asymptomatic/dormant *P. vivax/ovale/cynomolgi* infection. PCR may remain positive >1 months after successful treatment. Therefore, PCR is not useful to monitor treatment response/success!

Recommendation:
- Since microscopy can also detect differential diagnostically relevant pathogens (e.g. African trypanosomiasis, relapsing fever borreliosis, babesiosis), it should (i) be performed at least once in all patients with suspected malaria and (ii) be combined with an RDT test, especially if the laboratory's microscopic experience is limited. If microscopy is not conducted in the acute situation, because an RDT or PCR/LAMP is used, microscopy should be performed as soon as possible, preferably within 12h.
- A general necessity for serial microscopic testing in all cases is not supported by evidence, especially not in cases with low epidemiological, clinical and laboratory-chemical pre-test probablility. However, if no plausible alternative diagnosis can be made and the suspicion of malaria persists, serial microscopy more than three times may even be recommended.
- PCR is highly sensitive. However, due to the heterogeneity of PCR/LAMP tests available on the market, we advise against relying solely on a single PCR/LAMP test: In combination with a negative microscopy or a negative RDT, a single negative PCR reliably excludes symptomatic malaria.
- Positive PCR/LAMP results should be confirmed by microscopy or RDT to exclude false-positive results.
- Since RDTs and PCR may remain positive >1 month even after successful treatment, microscopy remains the only available diagnostic tool to assess (i) parasitemia and (ii) monitoring/confirming treatment success (clearance of parasitemia).
- Do not use RDTs that only test HRP2 but only use RDTs that test HRP2 + pLDH (or + aldolase).

VI. Zoonotic malaria

P. knowlesi: *P. knowlesi* is a primate malaria parasite endemic in some parts of Southeast Asia (map see below). *P. knowlesi* is morphologically (microscopically) difficult to differentiate from *P. falciparum* and *P. malariae*.[69] Cases of *P. knowlesi* infections in travellers have repeatedly been reported.[70]

P. cynomolgi: After a single case reported in 2014, a cluster of 5 patients infected with the primate malaria parasite *P. cynomolgi* has been reported from the Kapit region in the centre of Borneo in 2018.[71] *P. cynomolgi* is microscopically indistinguishable from *P. vivax* and even some widely used PCR methods show cross-reactivity with *P. vivax*.[72] *P. cynomolgy* show a similar geographic distribution to *P. knowlesi*.

P. simium: *P. simium* is a primate malaria parasite endemic in some parts of Brasil. *P. simium* is microscopically not differentiable from *P. vivax*.[73] In 2015-2016, 49 human *P. simium* infections were reported in the Atlantic forest region of Rio de Janeiro State (a region where *P. vivax* is not endemic).[74] (map see below)

P. brasilianum: *P. brasilianum*, causing quartan malaria in Uakari monkeys, was discovered in 1908. Recently it has been shown that *P. brasilianum* is not only microscopically but also genetically identical to *P. malariae*.[75]

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