

1 **Review of UK malaria treatment guidelines 2016 (Public Health England**
2 **Advisory Committee on Malaria Prevention in UK Travellers)**

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1 **Information about current guideline**

2 This guideline covers the diagnosis and management of malaria, and was
3 published in the Journal of Infection in June 2016.[1] It was written by the
4 Public Health England Advisory Committee on Malaria Prevention (PHE
5 ACMP) based on review of available evidence and expert consultation (using
6 a modified GRADE criteria for assessment of evidence and strength of
7 recommendation), to be in line with World Health Organization guidelines on
8 management of malaria.[2] It relates to malaria in both adults and children in
9 the UK although here we focus on the diagnosis and management of children
10 returning to the UK with suspected malaria. Malaria is the most common
11 imported tropical pathogen in the UK, and children comprise about 10% of the
12 1300-1800 UK cases per annum. *Plasmodium falciparum* is by far the most
13 common (around 75% of cases) and is associated with more severe disease.
14

15 **Previous guideline**

16 This guideline replaces the previous PHE ACMP UK malaria treatment
17 guideline (2007),[3] and suggested guidance/recommendations from Maitland
18 *et al.* (2005), which advocated more aggressive fluid resuscitation in severe
19 malaria than now suggested.[4]
20

21 **RESOURCES (BOX)**

- 22 • [http://www.journalofinfection.com/article/S0163-4453\(16\)00047-5/fulltext](http://www.journalofinfection.com/article/S0163-4453(16)00047-5/fulltext) Full guideline
- 23
- 24 • <https://www.ncbi.nlm.nih.gov/pubmed/26880088> Executive summary
- 25 • http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1 World Health Organization (WHO) guidelines for the
26 treatment of malaria (2015)
- 27
- 28 • <https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk> Public Health England malaria
29 prevention guidelines
- 30
- 31 • <http://travelhealthpro.org.uk> Country-specific information on malaria
- 32 • www.fitfortravel.nhs.uk Public access website providing health
33 information for people travelling abroad from the UK

1

2 **Key issues that the guideline addresses**

3

4 **When to suspect malaria?**

5 Malaria should be considered in any unwell or feverish child who has visited
6 an endemic country regardless of whether prophylaxis was taken. *P.*
7 *falciparum* usually presents within 1 month of exposure (minimum 6 days),
8 although later presentations can occur. Other species may present over a
9 year post-travel.

10

11 **Clinical Features**

12 Malaria in children can be notoriously non-specific, even without fever.
13 Although fever, malaise and lethargy are the most common symptoms,
14 children can present with gastrointestinal symptoms (including diarrhoea),
15 jaundice, breathing difficulties or sore throat. Examination may reveal hepato-
16 and/or splenomegaly and lethargy.

17

18 **Diagnosis**

19 Thick and thin blood films remain the gold standard for detection and
20 speciation of malarial parasites, but rapid diagnostic tests (RDTs) are almost
21 as accurate for *P. falciparum* and *P. vivax*. If there is ongoing clinical
22 suspicion with negative blood films, these should be repeated at 12-24 hours
23 and again after a further 24 hours, particularly if fever is persistent. Empirical
24 therapy in the context of negative tests should only be given with symptoms of
25 severe malaria and on expert advice. Thrombocytopenia is common in
26 children with malaria; although not diagnostic, it should increase the index of
27 suspicion.

28

29 **Treatment**

30 Even in uncomplicated malaria, with *P. falciparum* there can be rapid
31 deterioration during the first 24 hours of treatment, so admission is
32 recommended initially. Uncomplicated *P. falciparum* malaria should be treated
33 with oral artemisinin combination therapy (ACT), e.g. artemether-lumefantrine

1 dosed according to weight (see BNF or Box 8 of guideline [1]). Admission will
2 also ensure that the oral ACT is tolerated as some children can vomit.

3
4 Features of severe malaria are:

- 5 1. Cerebral malaria
- 6 2. Respiratory distress/metabolic acidosis
- 7 3. Severe anaemia
- 8 4. Prostration (a child unable to sit if normally able to do so, or the inability
9 to drink in a younger child)
- 10 5. Hypoglycaemia
- 11 6. Electrolyte disturbance
- 12 7. Circulatory shock

13
14 Severe malaria should be managed in a paediatric intensive care or high
15 dependency unit with advice from a paediatric infectious diseases specialist
16 with malaria expertise. Intravenous artesunate gives a clear survival
17 advantage over quinine and is the drug of choice.[5] Following the results of
18 the FEAST trial showing a detrimental effect of fluid boluses, fluid
19 resuscitation should be cautious even in the context of shock.[6] Glucose
20 monitoring is crucial, and broad spectrum antibiotics should be given until
21 bacterial co-infection is excluded.

22
23 For non-*P. falciparum* malaria, both ACT and chloroquine are effective for
24 acute infection, although there is growing resistance to chloroquine in some
25 Indonesian areas. ACT may clear parasites faster and covers for *P.*
26 *falciparum* in case mixed infection cannot be excluded. To prevent relapse for
27 *P. vivax* and *P. ovale*, primaquine treatment should overlap with ACT to
28 ensure eradication of hypnozoites in the liver, after exclusion of G6PD
29 deficiency.

30
31 All children receiving intravenous artesunate need a repeat full blood count at
32 2 weeks post-therapy as it is associated with delayed haemolysis.

33 Families should be informed about mandatory notification of Public Health
34 England, reassured that the child is not infectious to others (although other

1 family members who also travelled may be at risk), and informed that
2 relapse/recrudescence is a risk, and so medical attention should be sought
3 with recurrent fevers. Finally, they should be directed to seek up to date
4 advice on malarial prevention when travelling in future (see *Resources* box).

6 **UNDERLYING EVIDENCE BASE (BOX)**

- 7 • Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus
8 quinine in the treatment of severe falciparum malaria in African children
9 (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;376:1647-
10 57.[5]
- 11 • Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in
12 African children with severe infection. *N Engl J Med* 2011;364:2483-
13 95.[6]
- 14 • Meremikwu M, Smith HJ. Blood transfusion for treating malarial
15 anaemia. *Cochrane Database of Syst Rev* 2000:CD001475.[7]

17 **What do I need to know?**

18 *What should I start doing?*

- 19 1. Use intravenous artesunate instead of quinine for treatment of severe
20 malaria [5]
- 21 2. If intravenous artesunate is not immediately available, do not delay
22 initiating treatment with intravenous quinine
- 23 3. Use artesunate combination therapy (ACT) orally as first line treatment
24 for uncomplicated malaria (both *P. falciparum* and non-*P. falciparum*)

26 *What should I not do?*

- 27 • Do not give rapid fluid boluses. For patients with shock, cautious and
28 slow volume resuscitation should be used – the FEAST trial found an
29 increased risk of death in children receiving crystalloid or colloid fluid
30 boluses.[6]
- 31 • Do not give routine blood transfusions except in severe anaemia, as
32 they can increase adverse events without reducing mortality.[7]

1 *What should I continue doing as before?*

- 2 • Malaria should be suspected in anyone with a history of fever and
3 return from a malaria endemic area even if prophylaxis was taken
- 4 • Thick and thin blood smears are still the gold standard for diagnosis
- 5 • Rapid diagnostic tests (RDT) detect parasite antigens, and are a useful
6 addition to blood smears but can miss non-*P. falciparum* malaria
- 7 • If there is ongoing clinical suspicion of malaria but the initial blood films
8 are negative, two further films should be assessed
- 9 • All children with malaria should have at least 24 hours of inpatient
10 observation
- 11 • Severe or complicated malaria should be managed in an intensive care
12 or high dependency setting, with support from a paediatric infectious
13 diseases specialist
- 14 • Broad spectrum antibiotics should be used in addition to anti-malarial
15 treatment until bacterial co-infection has been excluded
- 16 • Notify all malaria cases to Public Health England
- 17 • Remember eradication of liver stage hypnozoites with primaquine in *P.*
18 *vivax* and *P. ovale* malaria

20 **Unresolved controversies**

21 1. *Potential management of uncomplicated malaria as an outpatient*

22 Adults with *P. ovale*, *P. vivax* and *P. malariae* are often managed in an
23 outpatient setting, and in specialist centres *P. falciparum* is sometimes
24 managed in outpatients by experienced clinicians with clear protocols. In
25 children, at least 24 hours of observation in hospital is recommended due to
26 the risk of rapid deterioration and vomiting ACT. Data are currently lacking
27 around the potential safety of more rapid discharge in the UK context.

29 2. *Three films to exclude malaria*

30 The evidence underlying the requirement of three negative films over a 36-48
31 hour period to exclude malaria has recently been reviewed by Wilson *et al.*[8]
32 Most published literature relates to adult data, but the combination of one
33 blood film and one RDT is extremely sensitive for malaria. The authors

1 concluded that it is safe to exclude malaria in a well-appearing, afebrile child
2 with one negative RDT in addition to one negative blood film, although
3 appropriate safety netting advice should be provided.[8]

4 5 *3. Definition of severe malaria in non-endemic countries*

6 The precise definitions of severe malaria, which predict morbidity or mortality,
7 and which justify PICU admission or additional interventions such as blood
8 transfusion, are not based on firm evidence from non-endemic populations.
9 For example, whether a 2% parasitaemia in a child with otherwise
10 uncomplicated malaria justifies PICU/HDU admission is widely debated. It is
11 worth noting that the WHO guideline [2] has a more extensive list of severity
12 features, including renal impairment, which is a strong predictor of death in
13 African settings, and the addition of base excess $<-8\text{mEq/L}$ or lactate
14 $>5\text{mmol/L}$ to the definition of acidosis. However, the relative importance of
15 these features in the non-endemic setting remains unclear; the threshold for
16 admission to PICU/HDU is likely to be dependent on the experience of the
17 particular unit of managing malaria in children in the UK.

18 19 **CLINICAL BOTTOM LINE (BOX)**

- 20 • Malaria should be suspected in all children with fever and travel to a
21 malaria endemic region
- 22 • Children with severe/complicated malaria should be managed in an
23 intensive care/high dependency setting
- 24 • Intravenous artesunate should preferentially be used to treat
25 severe/complicated malaria, and oral ACT for non-severe cases
- 26 • Broad spectrum antibiotics should be used until bacterial co-infection
27 has been excluded
- 28 • Fluid resuscitation should be cautious

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