1 Section of Paediatric Infectious Disease and Centre for Paediatrics and Child Health, Imperial College London, UK

2 Imperial College Healthcare NHS Trust, London

3 Médecins sans Frontières OCA, Amsterdam, Netherlands

4 West African Centre for Cell Biology of Infectious Pathogens, Department of Biochemistry, Cell and Molecular Biology, University of Ghana, Accra, Ghana

5 Global Technical Team, Malaria Consortium, London

Correspondence to A J Cunnington

Cite this as: *BMJ* 2024;384:e077512

http://dx.doi.org/10.1136/bmj-2023-077512

Published: 13 March 2024

CLINICAL UPDATE

Identification and management of co-infections in people with malaria

Aubrey J Cunnington, [1,2] Aula Abbara, [2,3] Flavia Kaduni Bawa, [4] Jane Achan[5]

What you need to know

- Co-infections with malaria affect up to half of children in endemic countries and around one in seven travellers with malaria
- A positive diagnostic test does not mean malaria is the only, or even a contributing, cause of current illness
- In settings where resources are constrained, limited diagnostic capacity can influence the diagnosis of co-infections, so vigilance is required for clinical features atypical for malaria

A 16 year old Ugandan girl is brought to the emergency department with a three day history of fever, headache, cough, and myalgia. She has had several episodes of malaria in the past. On admission, she is febrile, tachycardic, tachypnoeic, and has oxygen saturations of 90% in air. A malaria rapid antigen test is positive for Plasmodium falciparum and a chest radiograph shows left sided pneumonia. She is admitted and treated with antimalarials, antibiotics, and oxygen. She makes a full recovery over five days. At discharge, the cause of the pneumonia and the contribution of malaria to the illness remain unresolved.

Introduction

Malaria is the symptomatic illness caused by the mosquito transmitted parasites *Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*. It is one of the most common causes of fever in many malaria endemic countries and in travellers returning from those countries.[1] The World Health Organization estimated 249 million malaria cases in 2022 worldwide, 94% attributable to *P falciparum* infections in Africa, where children have the greatest burden of severe disease.[2]

In patients who have evidence of acute or recent malaria infection, co-infections with other pathogens occur commonly.[3] In this article, we consider the challenges of diagnosing bacterial, viral, and parasitic co-infection in patients who have malaria, and the related challenge of attributing illness to malaria in endemic countries. We focus on how to assess and manage co-infection in children with severe *P falciparum* malaria in sub-Saharan Africa (who account for most deaths from malaria globally) and in travellers of all ages with imported malaria who present in non-endemic countries (where all age groups are at risk of severe illness). We do not focus on malaria endemic countries outside Africa, or non-falciparum malaria.

Does detection of malaria parasites always indicate a diagnosis of malaria?

Individuals living in malaria endemic areas can acquire "clinical immunity" to malaria through repeated infections, enabling persistent asymptomatic parasitaemia.[4] The age at which this tolerance is acquired depends on the frequency of exposure. In some African countries with high malaria transmission, asymptomatic *P falciparum* parasitaemia can be found in up to 80% of school age children[2] and symptomatic malaria is uncommon in adults. It is likely, therefore, that co-infection with non-malarial illnesses in these populations will be accompanied by incidental malaria parasitaemia.

How common are co-infections?

Although comprehensive data are lacking, co-infections are probably very common.[3] Prevalence is higher in populations living in malaria endemic countries than in those where malaria is imported, but estimates depend on how intensively co-infections are sought and availability of diagnostics. In one large observational study of outpatient children in Tanzania undergoing extensive diagnostic evaluation for a spectrum of causes of fever, half of patients with malaria had at least one co-infection.[5] A postmortem study of Malawian children who met diagnostic criteria for cerebral malaria at time of death found an alternative infectious cause of death in at least 19% (6/31).[6] Among imported malaria patients at specialist university hospitals in Italy and Germany, co-infection rates were 13% (9/70) and 16% (41/264), respectively.[7,8]

Bacteraemia

Risk of bacteraemic co-infection has been studied extensively. Malaria is thought to increase susceptibility to bacteraemia by impairment of gastrointestinal barrier defences and impairment of immune responses.[9,10] The most commonly reported bacterial co-infections are enteric Gram negative organisms (eg, *Salmonella* species, particularly non-typhoidal salmonella in African children) and *Staphylococcus aureus*.[11,12]

A large epidemiological study that used mendelian randomisation with malaria protective sickle cell trait to establish causality, provided strong evidence that malaria increases the risk of bacteraemia in Kenyan children, explaining 62% of cases when malaria prevalence was highest.[13] Systematic reviews report a pooled prevalence of bacteraemia in 7.6% (95% confidence interval (CI) 6.7% to 8.7%) of patients with malaria who were tested for bacteraemia,[12] and 6.4% (95% CI 5.8% to 7.0%) in African children with

severe malaria,[11] but noted substantial heterogeneity in prevalence between studies.

Large observational studies suggest the prevalence of bacteraemic co-infection is lower in those who do not reside in high malaria transmission settings. Bacteraemia was present in 1% (95% CI 0.4% to 1.8%) of Vietnamese adults with severe malaria,[14]1.4% (3/219) of adult patients with imported malaria at a German university hospital,[8] and 0.3% (2/417) of imported malaria cases in Sweden.[15] Overall rates of bacterial co-infection (including non-bacteraemic infections) were 4.3% (12/291) in Sweden[15] and 11% (29/264) in adults in Germany.[8] Higher rates of bacterial co-infection have been reported in patients with imported severe malaria: 20% (10/49) in German adults[8] and 14% (13/91) in a French intensive care unit.[16]

Viral

Acute viral co-infections are likely more common than bacterial co-infections, but they are frequently undocumented because of limited diagnostic testing capacity in malaria endemic countries. In outpatient children in Tanzania with malaria, about one third had concomitant viral upper respiratory tract infections or a systemic viral illness.[5] In Malawian children with a clinical diagnosis of cerebral malaria, 35% (27/78) also had a central nervous system viral infection.[17] Conversely, only 5% (14/264) of adults with imported malaria at a German university hospital were found to have a viral co-infection.[8]

The overlapping epidemiology of malaria transmission with areas of high prevalence of HIV and chronic hepatitis viruses means that these will also be common viral co-infections. A large cross sectional study in Mozambique, a country with high HIV prevalence and high malaria transmission, found malaria parasites in 33% of adult patients with HIV.[18] Viral haemorrhagic fevers are rare co-infections compared with respiratory viruses and bacteraemia, but can be more common in endemic areas and outbreaks. In an area of Nigeria where Lassa fever is endemic, Lassa virus was identified in 4.6% (4/87) of febrile children with malaria parasitaemia.[19]

Parasites

Mixed infections of *P falciparum* and non-*P falciparum* malaria parasites are a common finding in sub-Saharan Africa, particularly when sensitive molecular techniques are used for the detection of non-*P falciparum* species. One recent study reported mixed infection in 25.8% (523/2027) of outpatients with malaria in Kenya.[20] Helminths (eg, hookworm, roundworm, *Schistosoma*) are widely distributed and also common co-infections in many malaria endemic regions, with a pooled prevalence of 17.7% (95% CI 12.7% to 23.2%) in a recent systematic review.[21] Many countries where malaria is endemic are also endemic for systemic parasitic diseases, with clinical features overlapping those of malaria (eg, visceral leishmaniasis, human African trypanosomiasis), and co-infections are well documented in populations with a high overlapping incidence.[22 23]

Fungi

Few data are available on malaria and fungal co-infections, but several case reports documented disseminated aspergillosis following malaria in individuals who were previously healthy, possibly as a result of immune dysfunction related to malaria.[24]

Do co-infections influence severity of illness?

The implication of assuming the diagnosis is *only* malaria can range from insignificant, usually for self-resolving viral co-infections, to severe and life threatening, for treatable invasive bacterial co-infections or viral haemorrhagic fevers.

Bacteraemia

A systematic review of studies in African children reported a higher pooled case fatality rate (24.1%) in severe malaria with invasive bacterial co-infection than in severe malaria alone (10.2%).[11] Another systematic review reported a mortality rate of 15% (95% CI 8.0% to 23.0%) across all patients with malaria and bacteraemic co-infection.[12] Bacterial co-infection was more common in fatal cases (40%, 4/10) of imported severe malaria than non-fatal cases (11%, 9/83) in a European intensive care unit.[16] Recent estimates suggest up to a third of the malaria deaths in African children may be the result of bacterial co-infection rather than the malaria parasites.[25]

Viral

Most acute viral co-infections are self-limiting, but incorrect diagnosis can result in missed opportunities to detect, treat, and prevent transmission of more significant viral diseases such as dengue, viral haemorrhagic fevers, or covid-19. The clinical consequences of viral co-infections in individuals with severe malaria and, conversely of malaria co-infection in individuals with severe viral diseases, are less well established. In Malawian children with suspected central nervous system infection, mortality was higher (38%, odds ratio 3.6 (95% CI 1.6 to 8.0)) for children with *P falciparum* parasitaemia and central nervous system viral infection than in those with parasitaemia alone (14%).[17] Conclusive data for the most common or severe viral infections, including Ebola virus[26] and SARS-CoV-2, are lacking.[27 28]

Parasites

Data on the impact of malaria and co-infections with *Leishmania* or *Trypanosoma* on severity of illness and survival are inconclusive.[22 23] Helminths transmitted in soil may contribute to the severity of anaemia associated with malaria.[21]

What are the challenges for diagnosing malaria and co-infections?

Presentation

Malaria usually presents as an acute febrile illness with systemic symptoms such as chills, headache, and body aches.[29] Most clinical features of the disease are indistinguishable from many other systemic febrile illnesses (table 1), including some non-infectious causes. Only one clinical finding, malarial retinopathy, is highly specific for malaria (up to 100% specificity for diagnosis of cerebral malaria[30]), but it does not exclude co-infection with other pathogens.[17]

Table 1 | Clinical features of malaria, severe malaria, and their overlap with other causes of fever in children and adults

Malaria	Clinical features	Examples of other causes of fever with overlapping clinical features
Uncomplicated malaria	Rigors, myalgia, headache	**Influenza, covid-19**, Epstein-Barr virus **Typhoid and non-typhoidal Salmonella bacteraemia** Leptospirosis, scrub typhus, tuberculosis African trypanosomiasis *Multi-system inflammatory syndrome in children*
	Abdominal pain, vomiting, diarrhoea,	**Viral gastroenteritis, Campylobacter, salmonellosis, shigellosis,** cryptosporidiosis, amoebiasis
	Cough	**Respiratory viruses, bacterial pneumonia** (pneumococcal, mycoplasma), tuberculosis
Severe malaria	Prostration, multiple convulsions, coma (cerebral malaria)	**Viral meningitis or encephalitis, acute bacterial meningitis,** cerebral abscess, tuberculous meningitis, cryptococcal meningitis, *Reye's syndrome*
	Acidosis, hypoglycaemia	**Sepsis**
	Severe anaemia	Haemolytic uraemic syndrome, visceral leishmaniasis, haemolytic crisis (sickle cell, G6PD deficiency), malignancy
	Renal impairment	Lassa fever, Ebola virus disease, **urinary tract infections**, sepsis, leptospirosis, haemolytic uraemic syndrome
	Jaundice	Acute cholecystitis, cholangitis, leptospirosis, haemolytic crisis (sickle cell, G6PD deficiency), *Kawasaki disease*
	Hypoxia, respiratory distress	**Bacterial or viral pneumonia**
	Abnormal bleeding	Sepsis, viral haemorrhagic fever (Ebola virus disease, Lassa fever), dengue, haematological malignancy
	Shock	**Sepsis,** dengue, hypovolaemia associated with gastrointestinal infections

Diseases in bold are most common. Those in *italics* are specific to children

In box 1 and figure 1, we outline features of other infections (and selected non-infectious febrile illnesses) which do not usually occur in malaria. Focal symptoms and signs, such as lymphadenitis or unilateral lung crepitations, are not typical of malaria and should prompt consideration of an additional cause. In a setting with low resource healthcare, WHO's Integrated Management of Childhood Illness guidelines recommend assessing for stiff neck, runny nose, localised tenderness, oral sores, refusal to use a limb, hot tender swelling, red tender skin or boils, lower abdominal pain, pain on passing urine, and signs of measles, which may suggest a diagnosis other than malaria.[31] At the end of this article we highlight additional sources of guidance for evaluation of travellers from malaria endemic countries (box 'Guidelines'), which should include a detailed history, considering risk factors for other infections and the chronology of illness.

Box 1: Features in history that may suggest co-infection with other pathogens

Symptoms

- Insidious onset, gradual weight loss
- Prolonged fever (>7 days)
- Profuse vomiting, diarrhoea (including presence of blood or mucus)
- Coryza, conjunctivitis, sore throat, stridor, prominent/productive/whooping cough
- Focal musculoskeletal symptoms
- Rash, skin or mucosal lesions
- Strong or foul smelling urine, dysuria

Risk factors

- Recent exposure to others with transmissible infections
- Presence of HIV, other immunodeficiencies, or immunosuppression
- Malnourished state
- Presence of sickle cell disease
- Congenital or acquired heart disease
- Pregnancy
- Close contact with animals
- Positive travel history (including within malaria endemic countries)
- Presence of indwelling medical devices (eg, catheters, ventriculoperitoneal shunts) or recent surgery

Drug history (which may modify risk or influence diagnostic test results)

- Recent use of antibiotics and antimalarials
- Vaccinations
- Immunosuppressive medication

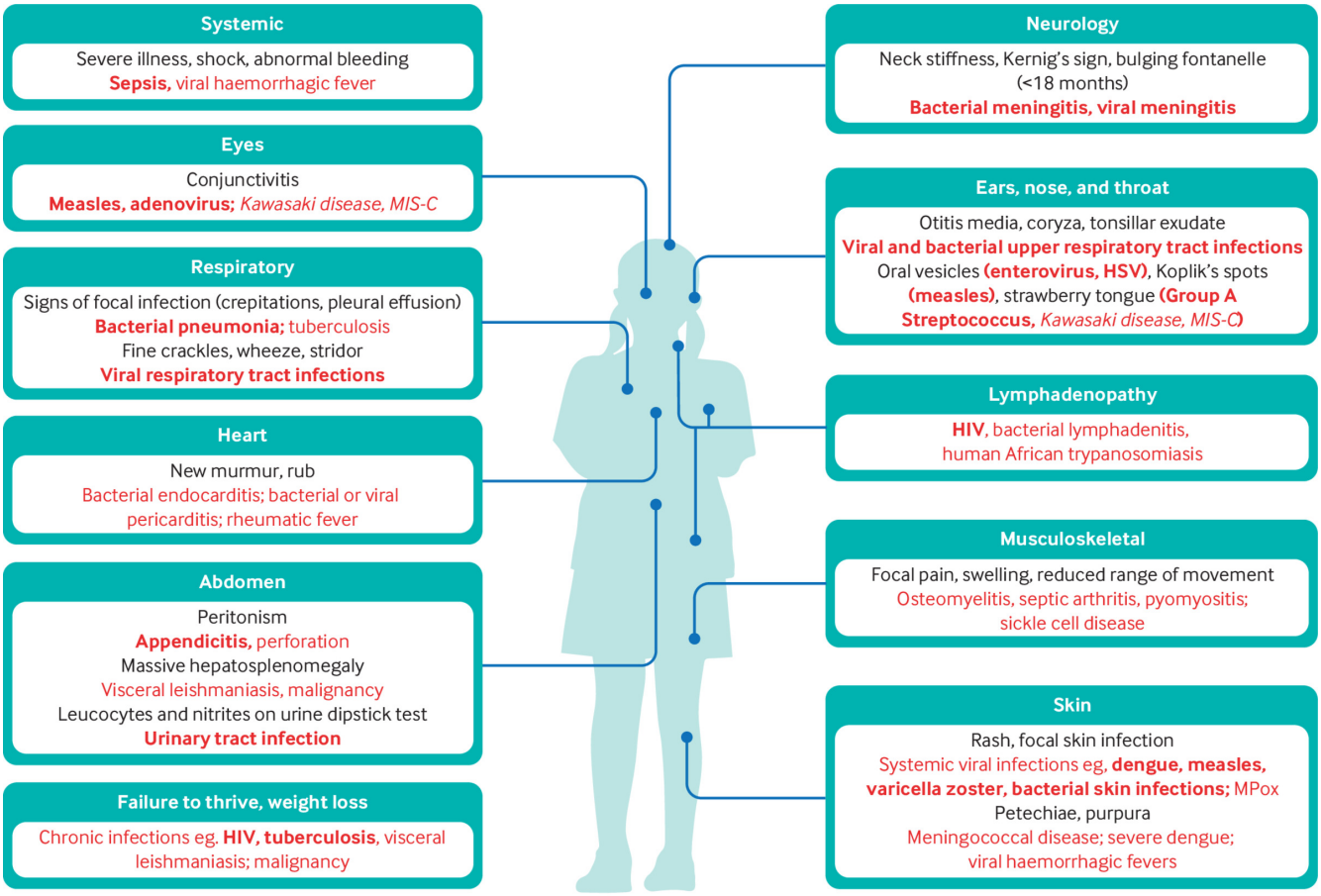

Fig 1 | Features on physical examination that may suggest malaria is not the only cause of illness. Example non-malarial causes are provided under respective clinical features (in red text). Those in bold are most common. Those in *italics* are specific to children. MIS-C=multisystem inflammatory syndrome in children

Testing

Malaria must be confirmed by diagnostic testing, most commonly microscopy for parasites within red blood cells and/or the detection of one or more parasite antigens in blood using lateral flow rapid diagnostic tests (RDTs).[29] A full blood count is also helpful, with thrombocytopenia being a typical finding in malaria. In Africa, common RDTs based on the detection of the parasite antigen PfHRP2 are around 95% sensitive and 95% specific for symptomatic *P falciparum* malaria,[32] but with caveats:

- Sensitivity is diminished in low parasitaemia asymptomatic infections[33]
- Results from PfHRP2 RDTs can remain positive for several weeks after successful treatment of malaria[29 33]:
  - They can detect malaria even if treatment was given before testing in the current illness
  - A false positive test may arise from a previous malaria infection, especially in settings with high transmission rates
- Increasingly, false negative PfHRP2 RDT results occur because of deletions of the parasite PfHRP2/3 genes.[33]

Current RDTs for malaria have lower sensitivity for non-falciparum parasite species, and their detection by microscopy may be challenging because parasitaemia is often lower than that of *P falciparum*.[34]

Rapid multiplex molecular assays for efficient syndromic testing (table 2) are increasingly available in resource rich settings,[35] but diagnostics for infections other than malaria can be scarce in resource limited settings.[36] Diagnostics for bacterial co-infection usually require the culture of bacteria from sterile site samples before starting antimicrobial therapy. Presenting features and patient age determine appropriate microbiological samples, which can generally be performed in line with context appropriate guidelines for management of fever or sepsis (eg, guidance from WHO[37] or the National Institute for Health and Care Excellence[38]). Diagnostics for rarer pathogens are often available only in reference laboratories and should be requested only after expert consultation, in parallel with any necessary infection prevention and control processes (box 'Guidelines').

Table 2 | Examples of diagnostic tests for co-infections with clinical features overlapping those of malaria

		Recommended tests for different levels of care		
Test category (example)	Gold standard diagnostic	Community or health facility without a laboratory (LMIC)	Facility with a clinical laboratory (LMIC)	Facility with an advanced laboratory
Invasive bacterial infections (non-typhoid Salmonella bacteraemia)	Culture based detection from sterile site	**Usually none**	Staining procedures (eg, Gram stain) *Culture based methods.* *Antimicrobial susceptibility*	Culture based detection and bacterial identification from many specimen types. Antimicrobial sensitivity. Molecular diagnostics (eg, PCR)
Parasitic infection (malaria, visceral leishmaniasis)	Microscopy	Malaria RDT. *Visceral leishmaniasis (rK39) RDT*	Malaria RDT and microscopy. *Visceral leishmaniasis (microscopy, direct agglutination)*	Malaria RDT and microscopy, visceral leishmania (microscopy, serology, PCR)
Viral infection	NATs (+/- antigen based tests). Serological assays	*HIV (RDT), Influenza (RDT)* *SARS-CoV-2 (RDT)*	*Viral NAT: SARS-CoV-2, influenza, dengue virus, measles, HIV.* RDT: HIV, *dengue* Serological immunoassay: HIV, measles, rubella	NATs for many viruses, often in multiplex syndromic panels; antigen tests; serological assays
Mycobacterium tuberculosis	Culture based detection	*Urinary Lipoarabinomannan RDT (in patients with HIV)*	Microscopy, *culture, NAT (eg, gene expert), drug susceptibility testing*	Microscopy, culture, NAT. Drug susceptibility testing
Severity assessment	Clinical chemistry and haematology tests	*Haemoglobin (hemoglobinometer); glucose (glucometer); Urinalysis (dipstick)*	Complete blood count (automated analyser) *Liver function, renal function, electrolytes (semi-automated or automated analyser)* *Blood gas/pH/lactate/ glucose (portable analyser)* *CRP (RDT, immunoassay)*	Extensive range of automated analysers for haematology and biochemistry

Tests shown in italics vary in availability, meaning that they will often not be available at a health facility. LMIC=low and middle income countries; RDT=rapid diagnostic test; NAT=nucleic acid test; PCR=polymerase chain reaction.

Assessing risk of clinically significant co-infection

To our knowledge, there are no validated prediction rules or prospective studies of risk stratification for clinically significant co-infection in patients with malaria. In a retrospective study of adult patients with imported malaria in Germany, multivariate analysis showed that clinical evidence of an alternative focus of infection was associated with an odds ratio of 3.9 (1.5 to 11.5) for bacterial co-infection, while C reactive protein was not significantly different in those with and without bacterial co-infection.[8]

Bacteraemia

Some risk stratification may be possible based on patient and clinical factors. One large systematic review identified bacteraemia as most common in high transmission settings, in younger children, and in those with severe malarial anaemia.[11] However, retrospective observational studies indicate that laboratory measurements can help to identify two groups of patients who appear to have severe malaria and are at highest risk of bacterial co-infection (fig 2).

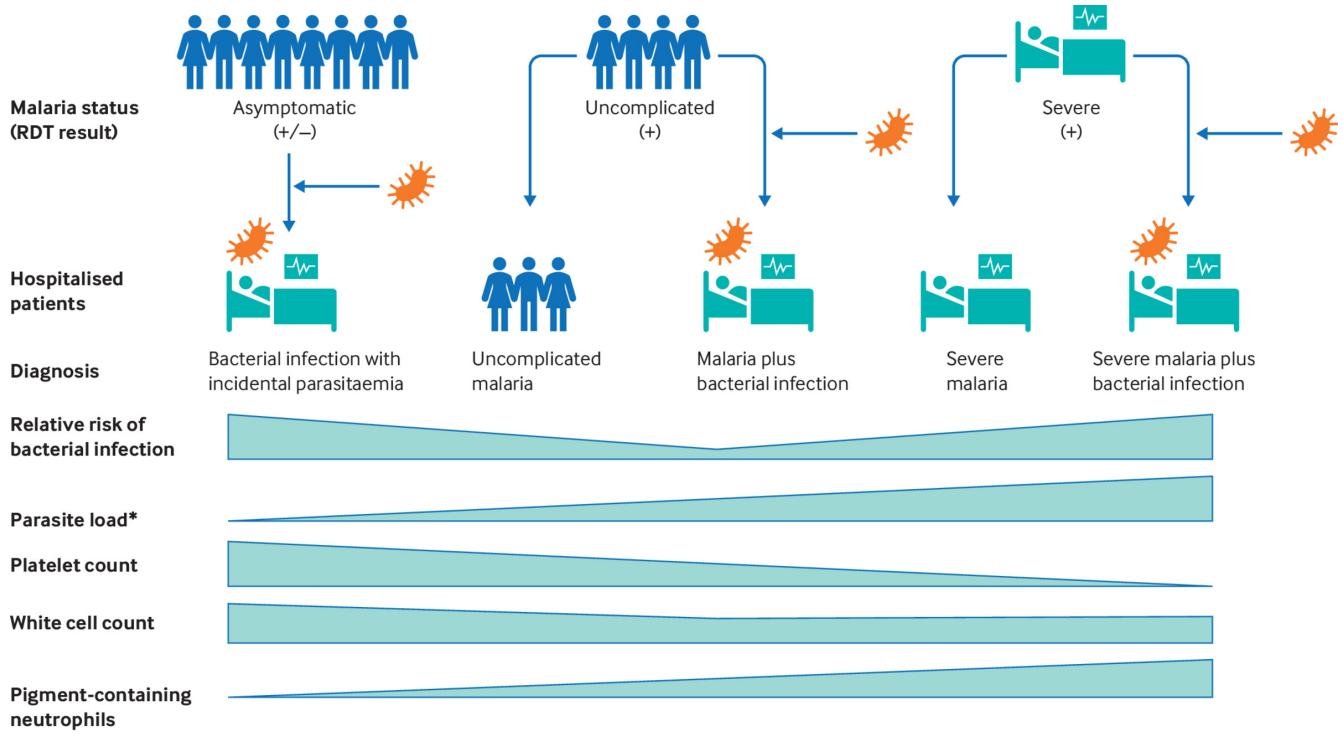

Fig 2 | Malaria and bacterial co-infection. Bacterial co-infection can occur in individuals with incidental (asymptomatic) parasitaemia, or individuals with symptomatic malaria. In malaria endemic countries it is common for individuals to have asymptomatic parasitaemia. In those sick enough to require admission to hospital, bacterial co-infection is most common among those with the lowest and highest parasite loads. Those with the lowest parasite load are likely to have been asymptomatically infected with malaria parasites and the cause of their illness is more likely to be a bacterial infection. Those with the highest parasite load are most likely to have severe malaria and are at highest risk of bacterial co-infection. *Parasite load is correlated with percentage parasitaemia and parasite density, but these can underestimate the total number of parasites in severe malaria when many parasites are sequestered in the microvasculature. In research settings, *P falciparum* parasite load is often estimated by quantification of the plasma concentration of the parasite antigen PfHRP2

These include:

- Individuals who have incidental parasitaemia and another cause of severe illness, characterised by low parasite load and absence of polymorphonuclear leucocytes containing malaria pigment (determined by microscopy), high white cell count for age, and normal platelet count[39-41]
- Individuals who have true severe malaria with very high parasite load,[42] low platelet count, lower white cell counts,[40] and often >5% of polymorphonuclear leucocytes contain malaria pigment,[39] at increased risk of bacterial co-infection as a direct consequence of their malaria infection.

Malaria parasitaemia is quantified as the percentage of infected red blood cells. Parasitaemia is lowest in asymptomatic infections, intermediate in uncomplicated malaria, and highest in severe malaria, but the groups overlap considerably.[2] In severe *P falciparum* malaria, many parasites are sequestered in the microvasculature and not visible on blood film. Research studies quantify the total parasite load of circulating and sequestered parasites by using plasma or serum PfHRP2 concentration, which discriminates better between asymptomatic, uncomplicated, and severe groups,[41 42] but these are not available in routine clinical practice. Parasitaemia and PfHRP2 concentrations are only moderately correlated, and their relations with symptomatic or severe disease can vary with age and endemicity, making it challenging to set generalisable risk thresholds. Nevertheless, very high parasitaemia indicates a high parasite load, and in a study of 845 adults with severe malaria in Vietnam, bacteraemia was 8.1 (95% CI 2.2 to 29.5) times more common in those with >20% parasitaemia than in those with lower parasitaemia.[14]

Prolonged fever, recurrence of fever, or deterioration after starting antimalarial treatment, all warrant evaluation for acquisition of bacterial infection and antibiotic treatment, as well as consideration of antimalarial resistance.

Viral

Consider the potential for viral haemorrhagic fever co-infection in patients from areas where such diseases are endemic (eg, Lassa fever in West Africa) or when outbreaks occur. Test patients with suspected viral haemorrhagic fever for malaria to rule out a treatable co-infection, and consider viral haemorrhagic fever co-infection in patients with malaria to enable appropriate measures of infection control. Risk of viral haemorrhagic fever can be stratified by a detailed travel history, including dates of travel to endemic areas (most have an incubation period under 21 days), exposures, and contacts (box 'Guidelines'). Risk factors for other significant viral infections may be identified through careful history taking and attention to current epidemiology. In areas with a high prevalence of HIV, it may be appropriate to screen all individuals with severe malaria for HIV.

Parasitic and fungal

Consider significant parasitic or fungal co-infections when the patient has a high risk of exposure or clinical features that are atypical for malaria (fig 1) or which fail to respond fully to antimalarial treatment.

How to manage possible co-infection

Figure 3 shows an algorithm for assessment and management of possible co-infection, based on our experience and in line with international guidelines.[43-50] Our recommendations apply to the management of possible co-infection in children with malaria in sub-Saharan Africa and in travellers with malaria in non-endemic settings. Antimalarial treatment is always indicated in a patient with a positive test for malaria and compatible symptoms, even if a co-infection is suspected or there is uncertainty about whether malaria is causing illness. If the patient has obvious focal infection, empirical treatment is indicated after taking appropriate diagnostic samples.

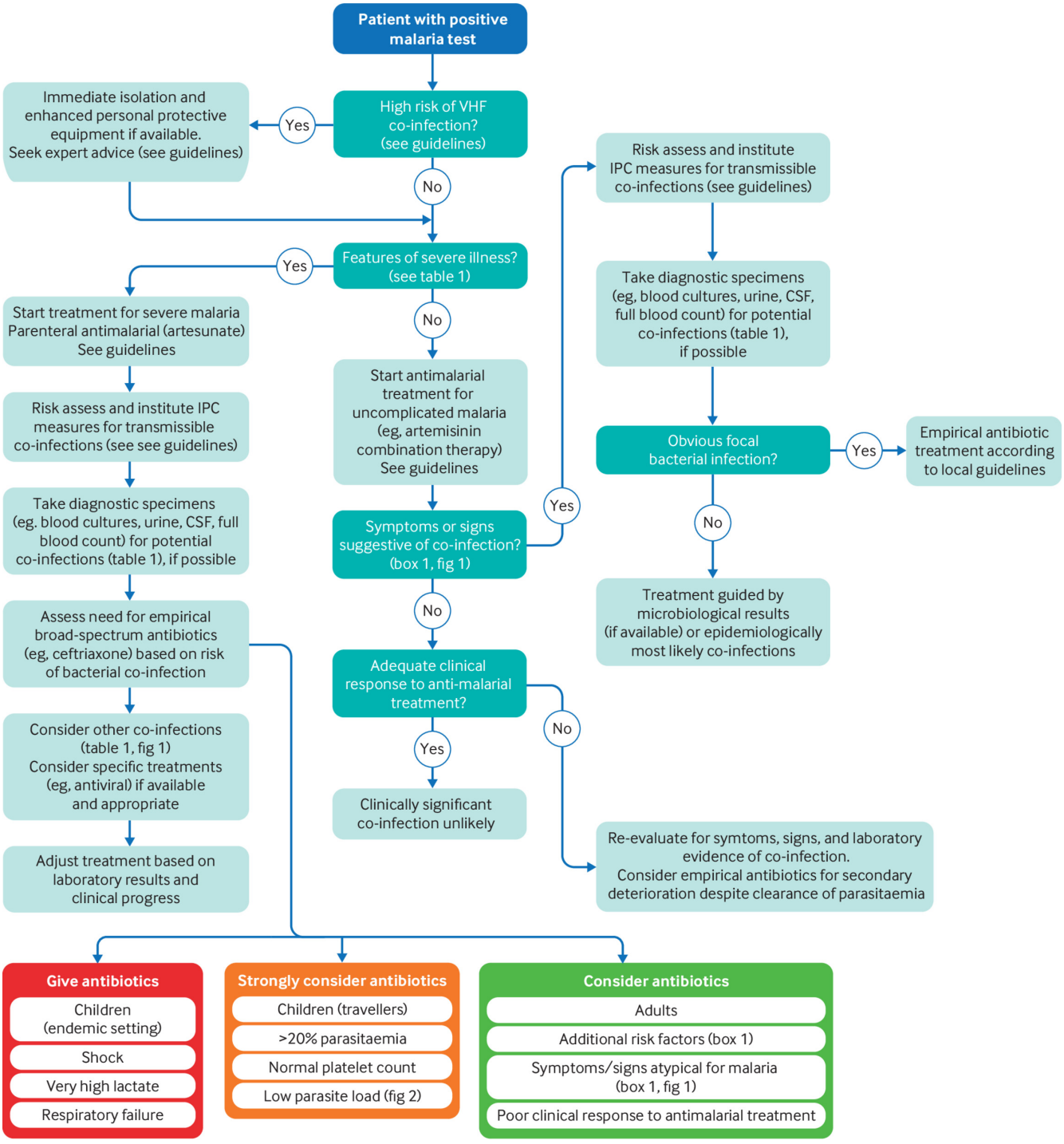

Fig 3 | Suggested algorithm for assessment and management of possible co-infection in patients with malaria. The algorithm is for care of children with malaria in sub-Saharan Africa and travellers of all ages presenting with malaria in non-endemic countries. VHF=viral haemorrhagic fever; IPC=infection prevention and control

Bacteraemia

In children with malaria in an endemic country:

- Initiate antimalarial treatment
- Examine and investigate, if possible, for focal bacterial co-infection
- Commence broad spectrum antibiotic treatment in all children with severe malaria.

In returning travellers:

- Initiate antimalarial treatment
- Examine and investigate for focal bacterial co-infection
- Commence broad spectrum antibiotic treatment in all severely ill children and in adults with signs of shock or respiratory failure.

Consider empirical treatment also for patients with severe illness who have inconsistent clinical or laboratory findings, and those with very high parasitaemia (>20%). Some national guidelines recommend more restrictive approaches to empirical antibiotic treatment, focusing on patients with circulatory shock, respiratory failure, very high lactate.[46-48]

Treatment with a third generation cephalosporin (eg, ceftriaxone) is likely to be effective against the most common bacterial co-infections, non-typhoidal *Salmonella* and *S aureus*, but this may not be feasible for every child with severe malaria in endemic countries because of cost and limited availability. Alternative empirical treatment regimens using gentamicin plus narrower spectrum β lactam antibiotics may not provide adequate cover. Even third generation cephalosporins may sometimes be inadequate because of increasing prevalence of resistant organisms.[43] Some guidelines for imported malaria recommend broader spectrum treatment with piperacillin/tazobactam or carbapenems, plus an aminoglycoside.[47 48]

Viral

Diagnostics and specific treatments for many viral infections are rarely available outside advanced healthcare facilities. If viral co-infections of public health importance are suspected, such as measles or a viral haemorrhagic fever, take available infection control precautions, and notify appropriate authorities according to local and national procedures. Post-exposure vaccination or immunoglobulin may protect and prevent further spread for specific infections.[51]

After stratifying risk for viral haemorrhagic fevers and other transmissible infections, follow standard local infection control policies for patients at low risk. Isolate patients at high risk immediately, and use enhanced personal protective equipment while urgently seeking specialist guidance (box 'Guidelines').

Treatment of specific viral co-infections with antiviral agents and/or adjunctive treatments depends on the virus detected.

Parasitic and fungal

Treatment of specific parasitic and fungal co-infections depend on the organism. Empirical treatment with albendazole or mebendazole may be given to anaemic children with malaria, if not received in the last six months, to treat soil transmitted helminths.

Areas of uncertainty

- What is the burden of different clinically significant co-infections with malaria in different settings and different age groups?
  - What are their prevalences in patients with a positive malaria test?
  - Are they more common in patients with malaria than in the general population?
  - What are their impacts on morbidity and mortality in different settings?
- How can we identify patients with a positive malaria test who are at greatest risk of having clinically significant co-infections?
- Which additional diagnostic tests for co-infection should be performed in different geographical and healthcare settings?
- Which patients with malaria should receive empirical antibiotics?
  - Which empirical antibiotics are most appropriate in which settings?
- What is the impact of giving empirical antibiotics on antimicrobial resistance?

Patient perspective

There are times when I am convinced that I have malaria. During those times, I am okay when I visit the hospital and get tested for malaria and start my antimalarial drugs. There are other times I am convinced it is something else, but then, I still must test for malaria. On these occasions, I become worried because I might be receiving treatment for just a part of my symptoms and risk infecting my family members if the second cause is infectious. Being able to test for different pathogens puts my mind at ease and makes me trust the doctor's final diagnosis. Although this is more expensive, it saves me from multiple trips to the hospital, and makes me confident in the healthcare system.

Kambe, university student, Ghana

How patients were involved in the creation of this article

Patients were not directly involved in in the writing of this article, but a representative patient story has been included.

How this article was made

We searched PubMed using combinations of the terms: "Malaria", "Plasmodium", "Co-infection", "Coinfection", and names of specific infections. We supplemented this with personal archives of references, and references within identified articles.

Guidelines

Management of malaria

- WHO Malaria management guideline. https://app.magicapp.org/#/guideline/7661
- UK Malaria treatment guideline. https://doi.org/10.1016/j.jinf.2016.02.001
- Canadian malaria treatment guideline. https://www.canada.ca/en/public-health/services/catmat/canadian-recommendations-prevention-treatment-malaria/chapter-7-treatment.html#a7
- French guidelines for management of imported malaria in children. https://doi.org/10.1016/j.medmal.2019.02.005, and severe imported malaria in adults https://doi.org/10.1016/j.medmal.2018.08.003

Assessment and management of infections acquired in malaria endemic countries

- Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions. https://www.bmj.com/content/363/bmj.k4766.long
- Fever in the returning traveller. https://www.bmj.com/content/360/bmj.j5773.full

Management of suspected severe infection in children in resource limited settings

- WHO pocket book of hospital care for children: Second edition. https://www.who.int/publications/i/item/978-92-4-154837-3
- Integrated management of childhood illness for primary health care services. https://cdn.who.int/media/docs/default-source/mca-documents/child/imci-integrated-management-of-childhood-illness/imci-in-service-training/imci-chart-booklet.pdf

Risk assessment and approach to viral haemorrhagic fever

- World Health Organization. Clinical management of patients with viral haemorrhagic fever: a pocket guide for front-line health workers. https://www.who.int/publications/i/item/9789241549608
- Assessment of fever in the returning traveller. https://www.bmj.com/content/360/bmj.j5773
- UK Advisory Committee on Dangerous Pathogens (ACDP) viral haemorrhagic fever guidance. https://www.gov.uk/government/publications/viral-haemorrhagic-fever-algorithm-and-guidance-on-management-of-patients
- United States CDC TOUR (Treat patient, Obtain history, Urine/ blood work, Rule out malaria) approach to risk-assessment for VHF. https://www.cdc.gov/vhf/abroad/assessing-fever-returning-traveler-no-risk-viral-hemorrhagic-fever.html
- United States CDC CALM (Consider, Act, Laboratory, Monitor) approach to VHF. https://www.cdc.gov/vhf/abroad/assessing-vhf-returning-traveler.html

Specialist advice on diagnostic testing and management

- UK Imported Fever Service. https://www.gov.uk/guidance/imported-fever-service-ifs

Information about outbreaks of infectious diseases around the world

- The International Society for Infectious Diseases' ProMed and HealthMap are useful and up to date resources for current outbreaks. https://www.healthmap.org/en/

Education into practice

- How do you assess for additional or alternative infection diagnoses in patients with a positive malaria test?
- Of your patients with severe malaria, what proportion had blood cultures taken and received empirical broad spectrum antibiotic treatment?

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: AC, FKB, and JA are supported by a grant (NIHR134694) from the National Institute for Health and Care Research using UK aid from the UK government to support global health research to study novel diagnostics for malaria and other infections in Africa. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK government. AC is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No 848196 to study novel diagnostics for infectious diseases.

All four authors made substantial contributions to the conception and design of the article, drafting and revising it critically for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AC is responsible for the overall content as guarantor.

Consent: The case in this article is fictitious and therefore no consent was needed. The patient story in this article is real and written consent has been obtained.

Provenance and peer review: commissioned; externally peer reviewed.

1 Buss I, Genton B, D'Acremont V. Aetiology of fever in returning travellers and migrants: a systematic review and meta-analysis. *J Travel Med* 2020;27:taaa207. doi: 10.1093/jtm/taaa207 pmid: 33146395
2 World Health Organization. World Malaria Report, 2023. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023.
3 McArdle AJ, Turkova A, Cunnington AJ. When do co-infections matter? *Curr Opin Infect Dis* 2018;31:-15. doi: 10.1097/QCO.0000000000000447 pmid: 29698255
4 Phillips MA, Burrows JN, Manyando C, van Huijsduijnen RH, Van Voorhis WC, Wells TNC. Malaria. *Nat Rev Dis Primers* 2017;3:. doi: 10.1038/nrdp.2017.50 pmid: 28770814
5 D'Acremont V, Kilowoko M, Kyungu E, etal. Beyond malaria—causes of fever in outpatient Tanzanian children. *N Engl J Med* 2014;370:-17. doi: 10.1056/NEJMoa1214482 pmid: 24571753
6 Taylor TE, Fu WJ, Carr RA, etal. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med* 2004;10:-5. doi: 10.1038/nm986 pmid: 14745442
7 Antinori S, Galimberti L, Gianelli E, etal. Prospective observational study of fever in hospitalized returning travelers and migrants from tropical areas, 1997-2001. *J Travel Med* 2004;11:-42. doi: 10.2310/7060.2004.18557 pmid: 15710055
8 Küpper-Tetzel CP, Idris R, Kessel J, etal. Coinfections and antimicrobial treatment in a cohort of falciparum malaria in a non-endemic country: a 10-year experience. *Infection* 2023;•••. doi: 10.1007/s15010-023-02103-x. pmid: 37889376
9 Orf K, Cunnington AJ. Infection-related hemolysis and susceptibility to Gram-negative bacterial co-infection. *Front Microbiol* 2015;6:. doi: 10.3389/fmicb.2015.00666 pmid: 26175727
10 Nyirenda TS, Mandala WL, Gordon MA, Mastroeni P. Immunological bases of increased susceptibility to invasive nontyphoidal Salmonella infection in children with malaria and anaemia. *Microbes Infect* 2018;20:-98. doi: 10.1016/j.micinf.2017.11.014 pmid: 29248635
11 Church J, Maitland K. Invasive bacterial co-infection in African children with Plasmodium falciparum malaria: a systematic review. *BMC Med* 2014;12:. doi: 10.1186/1741-7015-12-31 pmid: 24548672
12 Wilairatana P, Mala W, Masangkay FR, Kotepui KU, Kotepui M. The prevalence of malaria and bacteremia co-infections among febrile patients: a systematic review and meta-analysis. *Trop Med Infect Dis* 2022;7:. doi: 10.3390/tropicalmed7090243 pmid: 36136654
13 Scott JA, Berkley JA, Mwangi I, etal. Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. *Lancet* 2011;378:-23. doi: 10.1016/S0140-6736(11)60888-X pmid: 21903251
14 Phu NH, Day NPJ, Tuan PQ, etal. Concomitant bacteremia in adults with severe falciparum malaria. *Clin Infect Dis* 2020;71:-70. doi: 10.1093/cid/ciaa191 pmid: 32107527
15 Sandlund J, Naucler P, Dashti S, etal. Bacterial coinfections in travelers with malaria: rationale for antibiotic therapy. *J Clin Microbiol* 2013;51:-21. doi: 10.1128/JCM.02149-12 pmid: 23052321
16 Bruneel F, Hocqueloux L, Alberti C, etal. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. *Am J Respir Crit Care Med* 2003;167:-9. doi: 10.1164/rccm.200206-631OC pmid: 12411286
17 Mallewa M, Vallely P, Faragher B, etal. Viral CNS infections in children from a malaria-endemic area of Malawi: a prospective cohort study. *Lancet Glob Health* 2013;1:-60. doi: 10.1016/S2214-109X(13)70060-3 pmid: 24748325
18 Di Gennaro F, Marotta C, Pizzol D, etal. Prevalence and predictors of malaria in human immunodeficiency virus infected patients in Beira, Mozambique. *Int J Environ Res Public Health* 2018;15:. doi: 10.3390/ijerph15092032 pmid: 30227677
19 Akhuemokhan OC, Ewah-Odiase RO, Akpede N, etal. Prevalence of Lassa Virus Disease (LVD) in Nigerian children with fever or fever and convulsions in an endemic area. *PLoS Negl Trop Dis* 2017;11:e0005711. doi: 10.1371/journal.pntd.0005711 pmid: 28671959
20 Akala HM, Watson OJ, Mitei KK, etal. Plasmodium interspecies interactions during a period of increasing prevalence of Plasmodium ovale in symptomatic individuals seeking treatment: an observational study. *Lancet Microbe* 2021;2:-50. doi: 10.1016/S2666-5247(21)00009-4 pmid: 35544189
21 Afolabi MO, Ale BM, Dabira ED, etal. Malaria and helminth co-infections in children living in endemic countries: A systematic review with meta-analysis. *PLoS Negl Trop Dis* 2021;15:e0009138. doi: 10.1371/journal.pntd.0009138 pmid: 33600494
22 Ornellas-Garcia U, Cuervo P, Ribeiro-Gomes FL. Malaria and leishmaniasis: Updates on co-infection. *Front Immunol* 2023;14:1122411. doi: 10.3389/fimmu.2023.1122411 pmid: 36895563
23 Kotepui KU, Masangkay FR, De Jesus Milanez G, Kotepui M. Prevalence and outcomes of malaria as co-infection among patients with human African trypanosomiasis: a systematic review and meta-analysis. *Sci Rep* 2021;11:. doi: 10.1038/s41598-021-03295-8 pmid: 34893680
24 Eckerle I, Ebinger D, Gotthardt D, etal. Invasive Aspergillus fumigatus infection after Plasmodium falciparum malaria in an immuno-competent host: case report and review of literature. *Malar J* 2009;8:. doi: 10.1186/1475-2875-8-167 pmid: 19619319
25 White NJ, Watson JA, Uyoga S, Williams TN, Maitland KM. Substantial misdiagnosis of severe malaria in African children. *Lancet* 2022;400:. doi: 10.1016/S0140-6736(22)01600-2 pmid: 36088944
26 Edwards HM, Counihan H, Bonnington C, Achan J, Hamade P, Tibenderana JK. The impact of malaria coinfection on Ebola virus disease outcomes: A systematic review and meta-analysis. *PLoS One* 2021;16:e0251101. doi: 10.1371/journal.pone.0251101 pmid: 34029352
27 Achan J, Serwanga A, Wanzira H, etal. Current malaria infection, previous malaria exposure, and clinical profiles and outcomes of COVID-19 in a setting of high malaria transmission: an exploratory cohort study in Uganda. *Lancet Microbe* 2022;3:-71. doi: 10.1016/S2666-5247(21)00240-8 pmid: 34723228

28 Hussein R, Guedes M, Ibraheim N, etal. Impact of COVID-19 and malaria coinfection on clinical outcomes: a retrospective cohort study. *Clin Microbiol Infect* 2022;28:doi: 10.1016/j.cmi.2022.03.028 pmid: 35367364

29 Ashley EA, Pyae Phyo A, Woodrow CJ. Malaria. *Lancet* 2018;391:-21. doi: 10.1016/S0140-6736(18)30324-6 pmid: 29631781

30 Beare NAV. Cerebral malaria—using the retina to study the brain. *Eye (Lond)* 2023;37:-84. doi: 10.1038/s41433-023-02432-z pmid: 36788363

31 World Health Organization. *Integrated Management of Childhood Illness. Chart Booklet.* World Health Organization, 2014.

32 Abba K, Deeks JJ, Olliaro P, etal. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. *Cochrane Database Syst Rev* 2011;2011:CD008122.pmid: 21735422

33 Martiáñez-Vendrell X, Skjefte M, Sikka R, Gupta H. Factors affecting the performance of HRP2-based malaria rapid diagnostic tests. *Trop Med Infect Dis* 2022;7:. doi: 10.3390/tropicalmed7100265 pmid: 36288006

34 Gimenez AM, Marques RF, Regiart M, Bargieri DY. Diagnostic methods for non-Falciparum malaria. *Front Cell Infect Microbiol* 2021;11:681063. doi: 10.3389/fcimb.2021.681063 pmid: 34222049

35 Dumkow LE, Worden LJ, Rao SN. Syndromic diagnostic testing: a new way to approach patient care in the treatment of infectious diseases. *J Antimicrob Chemother* 2021;76(Suppl 3):-11. doi: 10.1093/jac/dkab245 pmid: 34555157

36 Fleming KA, Horton S, Wilson ML, etal. The Lancet Commission on diagnostics: transforming access to diagnostics. *Lancet* 2021;398:-2050. doi: 10.1016/S0140-6736(21)00673-5 pmid: 34626542

37 World Health Organization. *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses.* 2nd ed. 2013.

38 National Institute for Health and Care Excellence. NICE guideline NG143. Fever in under 5s: assessment and initial management 2021. https://www.nice.org.uk/guidance/ng143.

39 Srinamon K, Watson JA, Silamut K, etal. The prognostic and diagnostic value of intraleukocytic malaria pigment in patients with severe falciparum malaria. *Nat Commun* 2022;13:. doi: 10.1038/s41467-022-34678-8 pmid: 36371433

40 Watson JA, Ndila CM, Uyoga S, etal. Improving statistical power in severe malaria genetic association studies by augmenting phenotypic precision. *Elife* 2021;10:. doi: 10.7554/eLife.69698 pmid: 34225842

41 Watson JA, Uyoga S, Wanjiku P, etal. Improving the diagnosis of severe malaria in African children using platelet counts and plasma *Pf*HRP2 concentrations. *Sci Transl Med* 2022;14:eabn5040. doi: 10.1126/scitranslmed.abn5040 pmid: 35857826

42 Hendriksen IC, White LJ, Veenemans J, etal. Defining falciparum-malaria-attributable severe febrile illness in moderate-to-high transmission settings on the basis of plasma PfHRP2 concentration. *J Infect Dis* 2013;207:-61. doi: 10.1093/infdis/jis675 pmid: 23136222

43 Tack B, Vanaenrode J, Verbakel JY, etal. Invasive non-typhoidal Salmonella infections in sub-Saharan Africa: a systematic review on antimicrobial resistance and treatment. *BMC Med* 2020;18:.

44 Ministry of Health (MOH), Ghana Health Service (GHS) and National Malaria Control Programme (NMCP). *Guidelines for case management of malaria in Ghana.* 4th ed. 2020.

45 Ministry of Health national malaria control program. National guidelines for diagnosis, treatment, and prevention of malaria in Kenya. 5th ed. 2016.

46 Committee to advise on tropical medicine and travel. Chapter 7—Treatment of malaria: Canadian recommendations for the prevention and treatment of malaria. 2019.

47 Bruneel F, Raffetin A, Corne P, etal. Management of severe imported malaria in adults. *Med Mal Infect* 2020;50:-25. doi: 10.1016/j.medmal.2018.08.003 pmid: 30266432

48 Leblanc C, Vasse C, Minodier P, etal. Management and prevention of imported malaria in children. Update of the French guidelines. *Med Mal Infect* 2020;50:-40. doi: 10.1016/j.medmal.2019.02.005 pmid: 30885541

49 Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PLPHE Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines 2016. *J Infect* 2016;72:-49. doi: 10.1016/j.jinf.2016.02.001 pmid: 26880088

50 Department of Health Republic of South Africa. *National guidelines for the treatment of malaria.* 2019.

51 Gallagher T, Lipsitch M. Postexposure effects of vaccines on infectious diseases. *Epidemiol Rev* 2019;41:-27. doi: 10.1093/epirev/mxz014 pmid: 31680134