



Review

Update on malaria

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ABSTRACT

Despite recent successful efforts to reduce the global malaria burden, this disease remains a significant global health problem. Only in 2018, malaria caused 228 million clinical episodes, 2–4 million of which were severe malaria cases, and 405,000 were fatal. Most of the malaria attributable mortality occurred among children in sub-Saharan Africa. Nowadays, rapid diagnostic tests and artemisinin derivatives are two of the main pillars for the management of malaria. However, considering the current situation, these strategies are not sufficient to maintain a reducing trend in malaria incidence and mortality. New insights into the pathophysiology of malaria have highlighted the importance of the host response to infection. Understanding this response would help to develop new diagnostic and therapeutic tools. Vector and parasite drug resistance are two major challenges for malaria control that require special attention. The most advanced malaria vaccine (RTS,S) is currently being piloted in 3 African countries.

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Actualización en malaria

RESUMEN

La malaria es la enfermedad parasitaria más importante del mundo, causando una enorme carga de morbimortalidad en aquellas zonas donde es endémica. Los primeros 15 años del siglo xx han visto como la incidencia de la malaria y las muertes atribuibles a esta enfermedad disminuían de forma significativa. Los enormes avances en los tratamientos y métodos diagnósticos, así como en las estrategias de prevención han contribuido, sin duda, a mejorar la situación de esta enfermedad a nivel global. Sin embargo, una serie de desafíos biológicos, que incluyen la aparición de resistencias por parte del parásito a los antimaláricos, así como por parte de los vectores a los insecticidas, y la aparición de parásitos mutantes que no expresan el gen de la proteína PfHRP2 (siendo, por tanto, «invisibles» a las pruebas diagnósticas rápidas basadas en esta proteína), han puesto en peligro los enormes avances observados. Si la comunidad global pretende continuar avanzando de forma firme hacia la erradicación global de esta enfermedad, será importante mejorar la actual cobertura de todas estas intervenciones, así como fomentar la innovación en las áreas de diagnóstico, prevención y tratamiento.

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Introduction

Malaria is a protozoan disease transmitted by *Anopheles* female mosquitoes and results from the infection of a vulnerable host by *Plasmodium* parasites. Of the more than 120 *Plasmodium* species known to exist, only five cause malarial infections in humans:

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Plasmodium falciparum, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. *P. falciparum* accounts for the overwhelming majority of mortality, accounting for over 99% of all malaria-associated deaths globally. Although *P. vivax* has been traditionally considered to cause uncomplicated malaria, there is evidence of its potential to cause severe disease.¹ *P. knowlesi* is a parasite transmitted from primates to humans that can also cause severe manifestations. *P. malariae* and *P. ovale* cause uncomplicated malaria, although rarely can associate other complications.

Epidemiology

Nearly half of the world's population is at risk of malaria which is currently endemic in 86 tropical and subtropical countries, encompassing all of sub-Saharan Africa (SSA) as well as large areas of South-East Asia, Eastern Mediterranean, Western Pacific, and the Americas.²

Malaria caused an estimated 228 million clinical cases and 405,000 deaths in 2018.² 94% of all deaths occurred in Sub-Saharan Africa. The greatest burden of severe disease is borne by children under 5 years of age which represent 67% of global deaths.²

The first 15 years of the millennium showed a stable and consistent reduction in the malaria burden, with important changes in its geographic distribution, and an overall reduction of around 60% in terms of malaria mortality. This led to a renewed enthusiasm, endorsed by the Global health community, toward a second push for malaria eradication. During the last 5 years, however, progress in terms of the malaria burden seems to have stalled, with a set of countries adequately progressing toward malaria elimination, but other countries showing an alarming increasing incidence of their malaria burden. *P. falciparum* accounts for the vast majority of malaria cases in the WHO African region (>99%), but is also a problem in regions of the Western Pacific (71.9%), the Eastern Mediterranean (69%) and South-East Asia (62.8%). *P. vivax* is the parasite driving the burden in the Americas and South-east Asia, and, apart from some specific regions of the Horn of Africa, is very uncommon across the rest of Africa due to the absence of Duffy antigen in human populations.³ *P. malariae* and *P. ovale* are globally distributed but their overall prevalence is low with *P. ovale* mainly present in Southeast Asia and West Africa. *P. knowlesi* is a zoonotic malaria, currently only transmitted to humans from macaques, and highly circumscribed in a small geographical region around Borneo in Malaysia. Malaria can be transmitted occasionally through other mechanisms that do not include the triad vector-parasite-human, namely through blood transfusions, organ transplant, or congenitally, but the relative contribution of these mechanisms to the overall burden is almost negligible.

Biology

The lifecycle of *P. falciparum* is summarized in Fig. 1. The female *Anopheles* mosquito requires protein for egg development and inoculates the infective form of the parasite (*sporozoites*) when feeding upon humans. The sporozoites circulate for a few minutes in the bloodstream and invade hepatocytes where they remain, replicating for 7–14 days. This is called the pre-erythrocytic stage, and equals to the incubation period, as no symptoms are yet present. For species like *P. vivax* or *P. ovale* this stage may last weeks, months and even years as some parasites can remain dormant in the liver as *hypnozoites*,⁴ to subsequently relapse. After emerging from the liver as *merozoites*, the parasite starts its erythrocytic stage, whereby leading to the appearance of clinical symptomatology. Each merozoite entering the bloodstream will try to invade a red blood cell (RBC) and multiply into what is known as an erythrocytic schizont which will burst and release merozoites which can re-invade

other RBCs and perpetuate the blood stage of the cycle. A small percentage of merozoites will differentiate into a different and parallel pathway and develop into the sexual stages or gametocytes. In order to ensure transmission to the next human being, the female and male gametocytes will need to be absorbed by a second mosquito where they will be able to complete the sexual reproduction in the vector's midgut. After a period of 9–14 days, the mosquito cycle ends up with the *sporozoite* migrating to the salivary glands, from where they will be ready for a new bloodstream inoculation during a subsequent blood meal, thus completing the transmission cycle.

Pathogenesis

Traditionally, malaria has been defined in relation to periodic fever paroxysms which coincide with the parasite's intraerythrocytic cycles of each species (24 h for *P. knowlesi* infection; 48 h for *P. falciparum*, *P. vivax* and *P. ovale*; and 72 h for *P. malariae*).

P. falciparum is the unique species able to cause multiple infections on a single RBC as well as to invade RBCs of any age, thus translating into a greater virulence and faster multiplication causing more severe disease. Both parasite and host determinants contribute to the onset and outcome of severe and cerebral malaria (CM) although why some individuals develop severe disease is still unknown.⁵ RBCs sequestration, inflammation and endothelial dysfunction are key components of the so called pathological triumvirate which leads to severe malaria (SM).⁶

First, sequestration is suggested to be mediated through the adherence of mature forms of infected RBCs to host receptors expressed on the endothelium lining host capillaries, on uninfected RBCs to form rosettes⁷ and on platelets to form platelet-mediated clumps.⁸ Cytoadhesion, a key feature of the pathogenesis of *P. falciparum* associated infections, is mediated by the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1),⁹ which binds to numerous host receptors. Secondly, SM, including SMA and CM, has been also co-related with an excessive host immune response and, consequently, a deregulated inflammatory state. In third place, endothelial dysfunction is gaining importance as a key component of SM pathogenesis linking sequestration and inflammation.¹⁰

High parasite biomass is also directly related to SM and the phenomena of RBC sequestration, inflammation and endothelial dysfunction.⁶ *P. falciparum* histidine-rich protein-2 (HRP2) is a water soluble protein produced by the parasite and released from RBCs, the measure of which provides a more robust estimate of the total body parasite biomass, particularly when comparing it to peripheral parasitaemia.^{5,11} High concentrations of HRP-2 are associated with SM and higher mortality.^{12,13}

Immunity

There is no sterilizing immunity to malaria infection. However, repeated exposure to infective mosquito bites leads to the progressive acquisition of clinical immunity and protects against severe disease and death. This is the case of children born in high-transmission areas, who after repeated exposure to infected bites, will acquire immunity to SM if they survive the first years of life.¹⁴ This does not mean that they will not suffer infections throughout their childhood or adult life, but the likelihood of those infections becoming clinically evident and severe will be drastically reduced. On the other hand, when transmission is low, and exposure less frequent, severe disease may be present at any age because of the lack of development of clinical immunity. In a context where there is a significant reduction of the malaria incidence, this should be taken into consideration, because reduced transmission may affect the acquisition of natural immune responses and therefore lead to

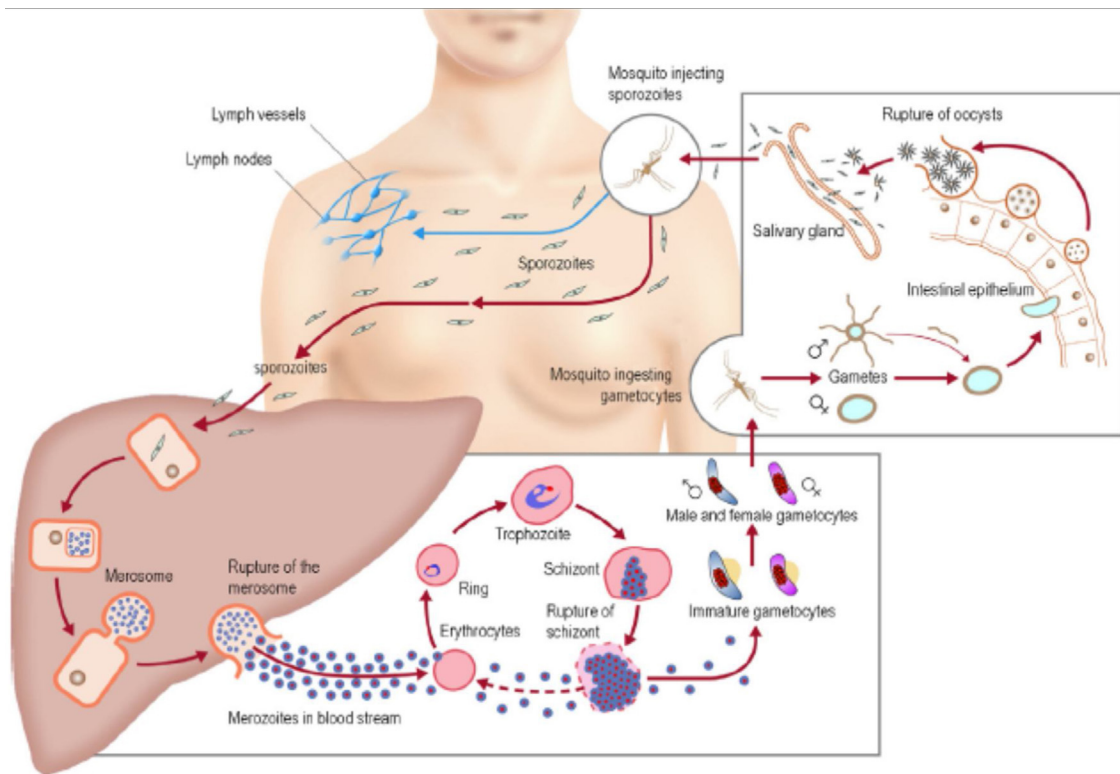


Fig. 1. Lifecycle of *Plasmodium falciparum* in human body and anopheline mosquito.

changes in the clinical spectrum of the disease.¹⁵ Those responses and the mechanisms associated are far from being completely understood.¹⁶

Clinical features of malaria

The vast majority of malaria infections do only cause mild disease with only ~1% of *P. falciparum* infections causing severe clinical manifestations. An uncomplicated malaria case is defined as a patient with a clinical diagnosis of malaria with a *Plasmodium* asexual parasitaemia >0 parasites/ μL and not fulfilling the criteria for SM. The cardinal sign of malaria is fever, an abnormally elevated body temperature. In addition to this, the first symptoms of disease are non-specific including general malaise, fatigue, arthralgia, myalgia, headache, abdominal discomfort, nausea, vomiting or orthostatic hypotension. In malaria-endemic areas, malaria is the most common cause of fever and most patients will only have few abnormal physical findings. In non-endemic areas, malaria needs to be suspected in patients with a travel history to endemic countries.

SM is a complex multi-system disease that may be differently defined according to the age group it affects. Most children with SM can be identified by a combination of just three overlapping syndromes which differ in biological, clinical and epidemiological characteristics: Cerebral malaria (CM), Severe malarial anemia (SMA) and acidosis/hyperlactatemia (clinically manifested as respiratory distress). Other manifestations include hypoglycaemia, acute kidney injury, jaundice, repeated convulsions, pulmonary edema, significant bleeding, hyperparasitaemia, or shock (Table 1).¹⁷ Clinical manifestations of malaria differ between adults and children, with multiorgan failure and shock being more frequent in the former. New insights, such as the demonstration of high prevalence of acute kidney injury in children,¹⁸ are however confirming that some clinical features considered more typical of adults are also frequent in children. Irrespective of the age, neurological involvement, acidosis and renal

impairment are associated with poor outcomes and the combination of them may worsen the prognosis.^{19–21}

CM is characterized by severe impairment of consciousness (deep coma) in the absence of other alternative explanations or diagnoses. CM can also present with repeated seizures or other neurological abnormalities and is associated with different long-term cognitive and neurological deficits in up to one-third of survivors.^{22–27} CM, both in adults and children, may reach case fatality rates (CFR) of 20%, being brain swelling a key pathogenetic event to explain these high percentages.^{28–31} Respiratory distress is a common manifestation of SM which develops in up to 25% of adults and 40% of children with severe falciparum malaria.³² It usually presents with deep (acidotic) and labored breathing, tachypnea, low chest indrawing and sustained nasal flaring. Although SM is mainly caused by *P. falciparum*, SMA may present in all types of malaria.³³ Prevalence of anemia in malarial endemic areas is very high, particularly in children, and has a multifactorial etiology.³⁴ Malaria associated anemia decreases with age and increases with exposure.⁶ Albeit its lower associated CFR, but due to its high incidence, SMA is the principal cause of malaria attributable mortality globally.

In the last decade, the pathogenic potential of other species such as *P. vivax* or *P. knowlesi* has also become evident. These two species should no longer be considered benign, and should be approached more vigorously in terms of their management.

Diagnosis

Malaria manifestations are non-specific and difficult to distinguish from other illnesses only based on a clinical approach. Current guidelines recommend to confirm the parasite presence in all suspected malaria cases before starting early, specific and appropriate treatment. Table 2 summarizes the current available tools for malaria diagnosis. Thick and blood films are still the gold standard for malaria diagnosis. Thick films are highly sensitive to

Table 1
Clinical defining features of severe malaria.

Impaired consciousness	A Glasgow Coma Score < 11 in adults or a Blantyre coma score < 3 in children
Acidosis	A base deficit of >8 meq/l or, if unavailable, a plasma bicarbonate of <15 mM or venous plasma lactate >5 mM. Severe acidosis manifests clinically as respiratory distress – rapid, deep and labored breathing
Hypoglycaemia:	Hypoglycaemia: Blood or plasma glucose < 2.2 mM (<40 mg/dl)
Severe malarial anemia:	Severe malarial anemia: A hemoglobin concentration < 5 g/dl or a haematocrit of <15% in children <12 years of age (<7 g/dl and <20%, respectively, in adults) together with a parasite count >10,000/μl
Renal impairment (acute kidney injury):	Plasma or serum creatinine >265 μM (3 mg/d) or blood urea >20 mM
Jaundice:	Plasma or serum bilirubin >50 μM (3 mg/dl) together with a parasite count >100,000/μl
Pulmonary edema	Radiologically confirmed, or oxygen saturation < 92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding	Including recurrent or prolonged bleeding from nose gums or venipuncture sites; haematemesis or melena
Shock	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia:	<i>Plasmodium falciparum</i> parasitaemia >10%

Source: Severe malaria. Trop Med Int Health. 2014;19 Suppl. 1:7–131.

Table 2
Diagnostic tools for detection of malaria, benefits and limitations.

Method	Principle	Benefits	Limitations
Clinical diagnosis	Recognition of symptoms	Rapid and cheap	Very unspecific (over diagnosis and overtreatment)
Microscopy	Observation of malaria parasites in blood smears (thick and thin films)	Species differentiation and quantification Follow-up of patients	Labor and time consuming Requires trained staff and equipment maintenance
Rapid diagnosis test (RDT)	Detection of malaria antigens in blood samples	Fast (5–20 min) and simple to perform and interpret Affordable and stable in extreme conditions No need of high qualified staff and equipment	Possible false positives and negatives No species differentiation or quantification Limited performance for mixed-infections
Polymerase chain reaction (PCR)	Identification of malaria DNA in blood samples	High sensitivity and specificity Species differentiation and quantification Antimalarial resistance detection	High cost Need of highly technical expertise and equipment maintenance

Adapted from: Rubio M, Bassat Q, Estivill X, Mayor A. Tying malaria and microRNAs: from the biology to future diagnostic perspectives. Malar J. 2016;15:167.

define the presence or absence of infection, and thin films allow differentiation of species and quantification of malaria parasites with a limit of detection between 50 and 500 parasites/μL which can reach 5 parasites/μL with expert microscopists. However, rapid diagnostic tests (RDTs) are now the most widely available option and often the first-line investigation method, as they provide simple, sensitive and specific diagnosis based on the detection of HRP-2, pan-malaria or species-specific lactate dehydrogenase (LDH), or aldolase antigens in finger-prick collected blood samples.⁴ They are an affordable, cost-effective and easy to use technology with minimal training required and limited or no need of instrumentation; they can be stored without refrigeration and provide rapid results. Indeed, the RDTs have stirred a diagnostic revolution, allowing the endemic areas to escape from empirical treatment based on suspected malaria diagnosis. Altogether, these characteristics make RDTs a great option to improve the management of malaria cases, especially in areas with limited laboratory resources. They are also a valuable option in epidemic investigations and surveys. However, these tests are mainly qualitative and some of them do not differentiate between species giving less information than microscopy for an adequate management of the disease. RDTs may remain positive for several weeks after acute infection and complete parasite clearance, thereby presenting the possibility of them providing false positive results which merely reflect a recent infection. Another important problem has been recently identified regarding

HRP2-based diagnostic tests, whereby, the test may produce negative results in infections caused by *P. falciparum* parasites lacking the PfHRP-2/3 genes, a genetic evolution of the parasite that renders these RDTs useless. Such a phenomenon is being increasingly evidenced, and in countries such as Eritrea or Peru, up to 80% of the circulating falciparum strains may be HRP2/3 deficient,² thus triggering the need to include non-HRP2 based RDTs in their diagnostic arsenal. Additionally, some RDTs may also fail to work in the presence of very high *P. falciparum* parasitaemias (prozone effect), or be unable to detect low parasitaemias (threshold of detection is around 100 parasites/μL).³ Nucleic acid amplification based-tests can detect low density malaria infections but in endemic countries their use is restricted for epidemiological research and surveys mapping and they do not have a practical role in the clinical management of malaria.³⁵ In high income countries they might be used for accurate species diagnosis of imported malaria.

Case management

Effective case management is based on early and accurate diagnosis and treatment. The discovery of the artemisinin derivatives from the *Artemisia annua* plant³⁶ changed the paradigm of malaria treatment shifting from quinolone-based to artemisinin-based therapies, which are now the first choice to treat uncomplicated and severe *P. falciparum* malaria given their speed, potency and

Table 3

Main principles for the drug treatment of malaria.

Severe malaria*Treatment of choice*

- Artesunate (i.v. or i.m.) 2.4 mg/kg* immediately, then at 12, 24 h and daily until patient is able to drink and eat (*For children < 20 kg the parenteral artesunate dose is 3 mg/kg)

Alternatives

- Artemether (i.m.) 3.2 mg/kg initial dose followed by 1.6 mg/kg daily until oral medication can be taken reliably
- Quinine dihydrochloride (20 mg salt/kg) by slow intravenous infusion over 4 h or by i.m. injection split to both anterior thighs, followed by 10 mg salt/kg 8 h until patient is able to swallow.

Uncomplicated malaria*Uncomplicated P. falciparum malaria*

- Artemether 1.4–4 mg/kg body weight + lumefantrine 10–16 mg/kg body weight twice daily for 3 days
- Artesunate 4 mg/kg body weight + amodiaquine 10 mg/kg body weight once daily for 3 days
- Artesunate 4 mg/kg body weight + mefloquine 8.3 mg/kg body weight once daily for 3 days
- Dihydroartemisinin 4 mg/kg body weight + piperaquine 18 mg/kg body weight once daily for 3 days (for children < 25 kg the dose of dihydroartemisinin is at least 2.5 mg/kg per day)
- Artesunate 4 mg/kg body weight + sulfadoxine–pyrimethamine 25/1.25 mg/kg body weight, once daily for 3 days
- Artesunate 4 mg/kg body weight + pyronaridine 7.5–15 mg/kg body weight, once daily for 3 days

Uncomplicated Chloroquine-sensitive^a P. vivax, P. ovale^b, P. malariae, P. Knowlesi

- Chloroquine dose of 10 mg base/kg body weight at days 1 and 2 followed by 5 mg base/kg body weight at day 3.

^a In areas with chloroquine-resistant infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) can be treated with an artemisinin derivative (except artesunate–sulfadoxine–pyrimethamine for *P. vivax*).

^b If there are no contraindications (pregnancy, children <6 months, glucose-6-phosphate-dehydrogenase deficiency) treatment of *P. vivax* and *P. ovale* must be followed by a radical cure with primaquine 0.5–1 mg/kg body weight once daily during 7–14 days. Alternatively, a single dose treatment with tafenoquine has already been FDA approved in patients ≥16 years of age (dose 300 mg), although not yet widely implemented or recommended by WHO.

safety (Table 3 summarizes the drug treatment options for treating malaria)

Uncomplicated malaria

The main objectives of the treatment of uncomplicated malaria are to prevent progression to severe disease and death, reduce clinical symptoms and cure the infection as soon as possible.² In endemic regions, correct and prompt treatment should also help to prevent antimalarial drug resistance and to reduce onward transmission to others. In the past decades, this has relied essentially in the use of inexpensive and widely available antimalarial drugs in combination treatments, rather than as monotherapies.

Current recommendations state that children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) should be treated with one of the following Artemisinin-based combination therapies (ACTs): artemether–lumefantrine, artesunate–amodiaquine, artesunate–mefloquine, dihydroartemisinin–piperaquine, artesunate–sulfadoxine–pyrimethamine, and artesunate–pyronaridine. They combine two active drugs with different mechanism of action and different half-lives. ACTs are administered orally in regimens which must in all cases cover a 3-day full course.

Chloroquine is the recommended treatment for uncomplicated malariae, vivax and ovale infections which should be followed by a radical cure with a drug with specific effect upon the liver hypnozoites. For this purpose, primaquine has been used globally for nearly seven decades, although its toxicity in G6PD deficient individuals (whereby it can cause severe or even life-threatening haemolysis) and compliance issues associated with the duration of recommended treatment (14 days) have made the treatment of *P. vivax* and *P. ovale* suboptimal.³⁷ More recently, tafenoquine, a single dose compound with similar antihypnozoitic potential to the complete primaquine treatment, has been approved by stringent regulatory authorities, although its toxicity liabilities regarding G6PD deficient individuals remain the same, and require its use obligatorily associated with the screening and quantification of G6PD activity.^{38,39} In case of resistance to chloroquine, or in countries where both falciparum and vivax coexist frequently, ACTs have become the first line drugs also for the treatment of vivax.

Pregnant women

Pregnant women are a particularly vulnerable group as malaria infection may lead to develop pregnancy loss, severe anemia, pulmonary edema and hypoglycemia. Mortality in pregnant women with SM may reach 50% and is more likely to occur during 2nd and 3rd trimester, especially in the first pregnancy. Furthermore, pregnant women are at higher risk of treatment failure. In the first trimester of pregnancy it is recommended to use oral quinine and clindamycin, during 7 days.⁴⁰ The recommended drugs during 2nd and 3rd terms of pregnancy are ACTs which have proven to be safe and effective and it is expected that in a near future they will be also indicated during the first trimester.⁴¹ Congenital malaria is rare in endemic countries where mothers have high level of antibodies which they transmit to their offspring, however this complication needs to be taken into consideration when naïve pregnant women with no immunity whatsoever against malaria travel to endemic areas and get infected there. Congenital malaria in newborns behaves as a systemic disease, and needs to be in the differential diagnosis of neonatal sepsis.

Non-immune travelers

Non-immune travelers are individuals from areas without malaria transmission who travel to malaria endemic areas and get exposed to infective bites there. They are generally malaria-naïve and, consequently, a high-risk group that can easily develop SM. They should receive early diagnosis and prompt treatment according to national policies. In non-endemic areas appropriate diagnosis and management can be difficult due to the lack of familiarity of practitioners, the poor recall of travel as a risk factor, and the limited availability of some antimalarials. Chemoprophylaxis using antimalarial drugs before, during and immediately after the trip is currently considered the best recommendation to prevent malaria in this particular vulnerable group. In case of infection, ACTs or atovaquone–proguanil are the currently recommended regimes for treating uncomplicated malaria in these patients.

Treatment failure

When malaria treatment is not successful, symptoms may recur with an associated positive parasitemia 2–6 weeks after initial

regimen. There are some issues which may explain this failure as high parasite burden, the limited availability of pediatric friendly formulations, impaired or reduced drug absorption due to severe disease and vomit, the limited shelf-life of the artemisinin derivatives, the emerging resistance to artemisinin derivatives or existing resistance to the partner drug, and the lack of new drugs/partner drugs. In endemic countries there are additional challenges as difficulties in access to health system; drugs costs, distribution and stock out challenges, and the worrying and under assessed threat provoked by “counterfeit” or substandard drugs.^{42,43}

Antimalarial drug resistance

Emergence of antimalarial drug resistance threatens effective antimalarial drug treatment, malaria control, and elimination. It has been observed for all antimalarials and, more recently, also for the artemisinins. Artemisinin resistance appears to be “partial”, is characterized by a slower parasite clearance, and has emerged (like all other resistances documented for antimalarial drugs) in the Greater Mekong Subregion.⁴⁴ Although sporadic case reports of delayed clearance times for artemisinins have also been reported in SSA, there is no evidence that such a phenotype has reached the most vulnerable continent.⁴⁵ Polymorphisms in the kelch13 (k13) propeller gene of *P. falciparum* have been associated with artemisinin resistance.⁴⁶

Of the five human malaria species, *P. falciparum* and *P. vivax* have developed resistance to antimalarial drugs. There is no conclusive evidence about chloroquine resistance in *P. malariae*.⁴⁷

Management of severe and cerebral malaria

Parenteral artesunate is now widely accepted as the standard of care for the treatment of SM, both in adults and children, following the landmark SEAQUAMAT and AQUAMAT trials that demonstrated its superiority over quinine.^{48,49} The main advantage of artemisinin derivatives is their potency leading to a rapid reduction of the parasite biomass. Although artesunate is more effective than quinine for the treatment of SM, this drug remains highly efficacious in its parenteral form and is still indicated in the treatment of malaria during the first trimester of pregnancy.⁴⁰ Intramuscular artesunate administration has proven to be non-inferior to intravenous artesunate in reducing parasitemia $\geq 99\%$ at 24 h in children with SM.⁵⁰ Intramuscular artemether seems to be inferior to parenteral artesunate in adults but is more effective than quinine in adults and children, thus being another valuable option when artesunate is not available.⁵¹ Parenteral treatment must be shifted to oral when the patient improves and is able to eat and drink. Artesunate is also indicated in its rectal form as a pre-referral option for children under six years of age living in remote areas waiting for immediate transfer to a higher-level.⁵²

Malaria complications may develop very fast, and may lead to death only a few hours after the first symptoms. Patients with SM may be adequately monitored with frequent measures of vital signs and hematological and biochemical parameters such as glycaemia, hemoglobin or renal and hepatic function. Whenever feasible, monitoring parasite density is desirable until confirming parasite clearance.¹⁷

Adjunctive therapies for severe malaria

Even with the improved efficacy of artesunate, CFR for SM and CM remain high.^{48,49} Therefore, treatment with potent artemisinin-derivatives alone is insufficient to prevent death or neurological disability in all patients with SM. Adjunctive therapies are used in combination with primary antimalarial treatment, with the aim of improving clinical outcomes, reducing mortality, and

preventing neurocognitive impairment. Several adjunctive therapies as steroids, immunoglobulin, anti-TNF therapies, antiepileptic drugs, mannitol, nitric oxide or blood transfusions have been evaluated without proving any success.^{53,54}

Prevention of malaria

Vector control or bite prevention

Measures to reduce the mosquito population or to limit the contact between humans and mosquitoes are the best preventive measures against malaria.² Scale up of Insecticide-based, home-centered interventions such as long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are surely important contributors to the significant decline in the malaria burden witnessed globally from 2000 to 2015.⁵⁵ However, such success is threatened by the emergence of mosquitoes resistant to pyrethroids,⁵⁶ the only insecticide currently used in LLINs, and to other insecticides used as part of other vector control strategies. Additionally, several mosquito behavioral changes are important biological challenges in our fight against malaria, including shifts to outdoor or early biting, quick house exiting right after feeding and even partially feeding upon animals. Such behavioral changes may allow vectors to avoid insecticide and keep transmission high even in the presence of good LLINs or IRS coverage in a phenomenon known as residual transmission.⁵⁷ Innovative approaches are needed to control residual transmission, some options being considered include the use of drugs (such as for example ivermectin, a potent endectocide⁵⁸) that kill mosquitoes feeding upon treated people or animals, attractive targeted sugar baits and spatial repellents.⁵⁹

Chemoprophylaxis

Intermittent preventive treatment

These are innovative preventive schemes for the administration of different antimalarial treatment regimens separated in time to risk groups, benefitting with high coverage encounters of the malaria-endemic populations with the health system. Preventive treatment in pregnant women with sulfadoxine-pyrimethamine (SP) is a recommendation implemented in many African countries with high *P. falciparum* endemicity, and has clear benefits on the health of the pregnant mother and the newborn. WHO currently recommends at least three doses (one month apart) during pregnancy, although the coverage of such a recommendation still remains suboptimal.

Seasonal malaria chemoprevention

This is a strategy to protect children under five years of age in the Sahel, where malaria is highly seasonal and transmission occurs only during a few consecutive months of the year. It consists of administering a monthly dose of an artemisinin-free antimalarial (SP-Amodiaquine) during the malaria-transmission season (usually 3–4 months long). Such a strategy has demonstrated an 80% reduction in malaria episodes and almost 60% reduction in all-cause mortality when implemented appropriately. WHO also recommends intermittent prophylaxis in infants in areas where malaria transmission is moderate-high and *P. falciparum*'s resistance to SP is less than 50%,⁴⁰ but the lack of real-time data on the frequency of this phenotype has hindered this recommendation.

Fixed-term prophylaxis

Antimalarial chemoprophylaxis is recommended for everyone, especially children, traveling to malaria-endemic areas. This should be done with the most suitable drug or combination of drugs (atovaquone-proguanil, doxycycline, mefloquine, etc.) for the area to be visited and which best adapts to the idiosyncrasy of the

traveler, always following the current recommendations of the WHO or the US Centers for Disease Control and Prevention (CDC). The drug or combination of drugs should be started before the trip, with the aim of reaching good blood levels upon arrival at the destination, and should generally be continued for an additional 1–4 weeks after returning, to cover the incubation period of a possible infective bite received in the last days of the trip. HIV-infected patients receiving co-trimoxazole as prophylaxis for opportunistic infections are partially protected of malaria infections, but should consider taking additional drugs as this scheme is not sufficient to guarantee full protection.

Vaccines

The great antigenic variability shown by the malaria parasite throughout its life cycle has made the design of effective vaccines a titanic task. The RTS,S/AS01 malaria vaccine, approved by stringent regulatory authorities (European Medicines Agency) in the year 2015 is, currently, the only effective compound, and has shown consistently significant (albeit partial) levels of protection, both against clinical malaria and severe malarial disease.⁶⁰ A pilot and large-scale implementation program, promoted by the WHO, was launched in 2019 in three African countries, namely Ghana, Kenya and Malawi to evaluate its protective effective, the feasibility of administering 4 doses, the impact on overall infant mortality and the safety of its routine use in endemic countries. It is expected that after three years of implementing such pilot program, a clear recommendation will emerge on the need to include this vaccine as part of the expanded program of immunization throughout falciparum endemic settings. The development of a vaccine against *P. vivax* is far behind the development of vaccines against *P. falciparum*, with no recent clinical trials beyond phase II.

Another approach to the development of an effective vaccine, consists on the attempt to develop an immune response as a result of the inoculation of irradiated and therefore attenuated *P. falciparum* sporozoites. Such an approach, logistically more complex, has however provided initial promising results in human volunteers subject to an experimental malaria challenge, but the efficacy of such a vaccine needs to be confirmed in malaria-endemic areas.⁶¹

Conclusions and future perspectives

In the third decade of the 21st century, malaria remains a significant challenge to the health of humans living where it is transmitted. The encouraging trends observed in the first years of the millennium are now threatened by a stall in progress reducing malaria cases. The new push for malaria eradication, which monopolized most malaria efforts in the last decade seems to have been tampered by a renewed spirit of enhanced efforts in those countries with higher burdens, recognizing that lack of improvements there will thwart global progress. In this particular moment, innovation and research focussing on new therapeutics, diagnostics and insecticides need to continue at the forefront of global efforts, so as to overcome the biological challenges affecting the tools available, and thus creatively bypass the hurdles that are hampering our fight against this deadly disease.

Conflict of interest

The authors declare that they have no competing interests.

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