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Recent Advances in Imported Malaria Pathogenesis, Diagnosis, and Management

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Abstract

Purpose of Review Malaria is an important human parasitic disease affecting the population of tropical, subtropical regions as well as travelers to these areas.

The purpose of this article is to provide clinicians practicing in non-endemic areas with a comprehensive overview of the recent data on microbiologic and pathophysiologic features of five *Plasmodium* parasites, clinical presentation of uncomplicated and severe cases, modern diagnostic methods, and treatment of malaria.

Recent Findings Employment of robust surveillance programs, rapid diagnostic tests, highly active artemisinin-based therapy, and the first malaria vaccine have led to decline in malaria incidence; however, emerging drug resistance, disruptions due to the COVID-19 pandemic, and other socio-economic factors have stalled the progress.

Summary Clinicians practicing in non-endemic areas such as the United States should consider a diagnosis of malaria in returning travelers presenting with fever, utilize rapid diagnostic tests if available at their practice locations in addition to microscopy, and timely initiate guideline-directed management as delays in treatment can lead to poor clinical outcomes.

Keywords Plasmodium · Imported malaria · Severe malaria · Malaria transmission · Rapid diagnostic test · Artemisinin-based therapy

Introduction

Malaria is a mosquito-borne disease caused by the parasites of the genus *Plasmodium*. Five species that infect humans include *P. ovale, P. vivax. P. malariae, P. falciparum,* and *P. knowlesi.* Transmission occurs via a bite of an infected female mosquito of *Anopheles* genus that serves as a vector. Human-to-human transmission, although extremely rare, may occur through a blood transfusion, organ transplantation, needlestick injuries in healthcare settings, or vertically from mother to newborn. Malaria remains an important human disease causing significant morbidity and mortality in countries within the geographic distribution of *Anopheles* mosquito, where disease elimination is challenged by various socio-economic factors. In the U.S., malaria remains an important diagnostic consideration in travelers returning from endemic areas who develop a febrile illness.

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Epidemiology

In 2021, 247 million malaria cases occurred worldwide, an increase from 245 and 232 million cases in 2020 and 2019, respectively. This recent uptrend was attributed to disruptions in malaria control efforts during the COVID-19 pandemic. More than 90% of malaria originates in the African Region and is caused by *P. falciparum*. *P. vivax,* on the other hand, is responsible for only 2% of malaria cases around the globe. Despite lower relative numbers, the prevalence of *P. vivax* cases has been increasing whilst *P. falciparum* has been decreasing in endemic regions where both species co-exist. In 2019–2021, deaths caused by malaria were estimated to be between 568,000 and 625,000. Most lethal cases occurred in children under the age of 5 and were caused by *P. falciparum* [1••].

In the United States and other non-endemic countries, malaria is the most common cause of acute undifferentiated fever in returning travelers from endemic areas [2•, 3]. In 2018, a total of 1,823 confirmed cases of malaria were reported to the Centers for Disease Control and Prevention (CDC), a 15.6% decline from the preceding year. Of these

cases, 85% were acquired in Africa. *P. falciparum* accounted for the most infections (69.8%), followed by *P. vivax* (9.5%), *P. ovale* (5.2%), and *P. malariae* (2.6%). In 2018, a case of *P. knowlesi* was identified for the first time since 2008 [4•].

Microbiology and Pathophysiology

The life cycle of *Plasmodium* species is completed in two hosts - mosquitoes and vertebrates. Transmission to humans occurs with *Plasmodium* sporozoites migrating from infected *Anopheles* mosquito's salivary glands into dermis during a mosquito bite. Within minutes to hours, sporozoites migrate to liver where they mature into liver-stage schizonts. The hepatocytic schizont stage usually lasts from 2 to 10 days. Each liver schizont produces from 2,000 to 40,000 merozoites that are released into the bloodstream to invade red blood cells. In erythrocytes, merozoites mature into trophozoites and, eventually, into blood-stage schizonts. The latter continue an asexual cycle by releasing more and more merozoites, multiplying the total number of parasites in the human host. Some trophozoites, however, do not undergo asexual stages, and instead, differentiate into female and male gametocytes – the sexual stage that is infectious for a mosquito. Once ingested by another feeding mosquito during a subsequent bite, gametocytes will generate zygotes within mosquito's gut and new parasites will migrate to its salivary glands to continue the cycle [5, 6].

Genetic and physiologic variations between *Plasmodium* species are responsible for differences in geographic distribution and clinical presentation. *P. falciparum*, the parasite causing most severe and fatal cases of malaria, produces unique proteins that are expressed on the surface of infected erythrocytes promoting their adhesion to endothelium, platelets, and uninfected erythrocytes. Clinically, this phenomenon promotes parasite sequestration, microcirculation obstruction, tissue hypoxia, and lactic acidosis [7–10]. Infected red blood cell binding or sequestration allows *P. falciparum* to be temporarily removed from the peripheral circulation, causing low-grade parasitemia sometimes undetectable on blood smears, posing a diagnostic challenge [7].

P. vivax is the most widespread malarial parasite in tropical and subtropical regions outside of Africa [1••]. Its limited presence on the African continent is believed to be due to a lower expression of the Duffy antigen on erythrocytes of the African population, a blood group antigen, although not obligatory, but commonly used by *P. vivax* for erythrocyte entry [11].

Additionally, *P. vivax* demonstrates high affinity to reticulocytes. Due to a small number of reticulocytes in peripheral circulation, *P. vivax* causes a much lower degree of parasitemia than other *Plasmodium* species, although it triggers higher systemic inflammatory response than *P. falciparum* [12–14]. Both *P. vivax* and *P. ovale* produce dormant liver-stage hypnozoites, causing recurrent episodes of parasitemia months or even years after the initial inoculation. Malaria caused by *Plasmodium malariae* carries the lowest risk for severe disease of approximately 2% with a low mortality rate. Infrequent complications include severe anemia, respiratory and renal insufficiency [15].

P. knowlesi is a simian malaria parasite endemic to Southeast Asia, with the majority of human cases reported in Malaysia. Usual hosts are long-tailed and pig-tailed macaques, and humans can harbor the infection if bitten by a mosquito that has fed from a macaque. No human-to-human transmission has been reported to date. Despite continuous success in elimination of other *Plasmodium* species circulating in Southeast Asia, *P. knowlesi's* incidence has been rising in recent years [16–18, 19•]. On microscopy, *P. knowlesi* resembles *P. falciparum* and *P. malariae*, therefore, this method cannot be used to diagnose *P. knowlesi* malaria [20, 21]. A definitive diagnosis can be made using nested polymerase chain reaction (PCR); however, its use is limited in resource-poor areas. Rapid diagnostic tests (RDTs) can be used to rule out falciparum malaria in *P. knowlesi*-endemic areas. Therefore, it is recommended to presumably treat for *P. knowlesi* in cases originating from endemic areas for these parasites after ruling out falciparum malaria on RDTs [22, 23].

Immunity and Transmission

Certain genetic factors as well as innate and adaptive immunity play an important role in illness severity. Generally, malaria severity is affected by degree of parasitemia, host's age, immune response, chemoprophylaxis effects, and time to treatment [24]. Among important hereditary factors, as already described above, an absence of the Duffy antigen in the African population protects against *P. vivax*. Some hemoglobinopathies also demonstrate an advantage in combating malaria. Individuals with sickle cell trait and sickle cell disease typically do not develop significant illness in falciparum malaria despite having the same susceptibility to it as individuals without sickle cell disease. Evidence, although less compelling, also suggests protective features of ovalocytosis, thalassemias, hemoglobin E disease, and glucose-6-phosphatase (G6PD) deficiency against malaria [6, 25–27]. Acquired immunity develops over time in residents of malarious areas after repeated exposure. For this reason, in endemic areas, severe disease affects mostly infants and young children, with a higher proportion of milder and asymptomatic cases in adults [5, 6]. Traditionally, transmission and disease severity were believed to be inversely related: the risks of severe disease are lowest in populations with the highest transmission, while the highest severe disease risks are observed among populations with

low-to-moderate transmission [28]. Therefore, nonimmune travelers to malarious areas are at a high risk for severe disease due to lack of preexisting immunity. However, in recent studies this relationship was found to be more complex. First, it is challenging to correctly estimate malaria prevalence in a given population due to a large number of asymptomatic or mildly symptomatic individuals with submicroscopic parasitemia [29, 30]. Furthermore, multiple clones of parasites can be present within one host simultaneously, and sequencing methods are needed to track new genotypes acquired over time [31, 32]. Lastly, degree of parasitemia does not always represent high infectivity. For example, a study in Ethiopia showed that only 15% of *P. falciparum*- and 35% of *P.vivax*-infected persons were infectious [33]. All of these and other factors contribute to uncertainties in establishing immunity, routes of transmission, and a true malaria burden.

Clinical Presentation of Uncomplicated Malaria

Incubation period is variable for different *Plasmodium* species and can last from 7 to 30 days, with shorter periods observed in *P. falciparum* and longer periods in *P. malariae* disease. About 95% of individuals develop symptoms within 6 weeks after exposure [6]. In some individuals residing in endemic areas, the disease can manifest as "asymptomatic" - with no symptoms in the setting of parasitemia. Some experts propose to favor the term "chronic" over "asymptomatic" malaria due to the long-term negative implications of untreated cases [34].

The hallmark feature of malarial illness – fever – coincides with the cyclical release of parasites during schizont rupture of erythrocytes. Once parasites are released into the bloodstream, inflammatory cytokines including tumor necrosis factor, interleukins, complement factors, prostaglandins and other pyrogenic factors trigger febrile response [7, 35]. The classic clinical course includes febrile episodes alternating with symptom-free periods. The typical febrile malarial paroxysm includes 3 stages. The first stage, namely the cold stage, is characterized by rigors and feeling cold. It is followed by the hot stage that includes fever, sometimes reaching 40–41 °C, accompanied by malaise, nausea, vomiting, headache, myalgias, and possibly seizures, especially in the pediatric population. Finally, the paroxysm is completed by the sweating stage during which the fever subsides [6, 36]. Although rarely observed, the duration of febrile episodes was historically associated with different species. Thus, *P. falciparum*, *P. vivax, P. ovale* cause malarial paroxysm every 48 h ("tertian" fever), and *P. malariae* – every 72 h ("quartan" fever) [35, 37].

Physical examination findings are generally nonspecific and may include lethargy, anorexia, pallor, petechiae, jaundice, or mild abdominal tenderness. Children are more likely to present with hepatomegaly and splenomegaly than adults [38]. Notably, malaria does not produce lymphadenopathy [39].

Laboratory Investigations in Uncomplicated Malaria

All patients presenting with febrile illness in the setting of suspected malaria should have a complete blood count, metabolic panel, liver panel, coagulation panel, plasma lactate level, arterial blood gas analysis, urinalysis and chest imaging performed. Malaria-specific diagnostic tests are discussed separately. Laboratory abnormalities include thrombocytopenia in 60–70% of cases (although rarely significant enough to result in bleeding in uncomplicated disease), mild-to-moderate anemia, elevated liver enzymes, mild coagulopathy, elevated blood urea nitrogen and creatinine [38, 39].

In general, obtaining blood cultures and a urine culture on admission is recommended, as invasive bacterial infections in malaria have been described. However, while the risk of concomitant bacteremia in malaria-endemic regions was shown to be of importance in children [40–42], in adult returning travelers it was found to be much less significant [43, 44].

Severe Malaria

According to the World Health Organization (WHO), severe malaria is defined by the presence of one or more of the following complications occurring in the absence of an alternative cause: impaired consciousness, severe physical deconditioning, two or more seizure episodes, acidosis, hypoglycemia, severe anemia, renal impairment, hyperbilirubinemia, pulmonary edema, significant bleeding, shock, and high parasite density [45••, 46••]. In the US, severe malaria was diagnosed in approximately 14% of malaria patients in 2017 [47]. Risk factors for severe malaria include residence in non-endemic areas, extremes of age, pregnancy, and immunocompromise [5, 6, 39]. Children are more likely to develop seizures, hepatosplenomegaly, and severe anemia, while adults are at a higher risk for acute renal failure and pulmonary edema [41, 46••]. *P. falciparum* is responsible for the majority of severe cases through rapid parasite biomass expansion, sequestration of infected erythrocytes, microvascular obstruction, endothelial activation, and subsequent end-organ damage [5, 6, 8, 11, 37]. It is generally accepted that *P. knowlesi* may cause severe disease through similar mechanisms, although cerebral malaria has not been reported to date [48]. Pathogenesis of severe malaria caused by *P. vivax* is poorly understood as this parasite does not tend to produce sequestration [5, 7, 49]. Several clinical syndromes comprise severe malaria.

Cerebral Malaria

Clinically defined as less than 11 points on Glasgow Coma Scale, cerebral malaria (CM) represents diffuse, symmetrical, potentially reversible encephalopathy caused by parasite sequestration in brain vasculature [50]. Parasites do not cross blood-brain barrier, although some degree of blood-brain barrier dysfunction may be present [51]. Brain edema is a common finding on imaging. If present, malarial retinopathy (retinal hemorrhages and patchy retinal whitening) increases diagnostic sensitivity and specificity of CM by 90% and 95%, respectively [52, 53]. Similar clinical presentations necessitate clinicians to rule out meningitis and meningoencephalitis when considering CM, and if lumbar puncture is performed, elevated opening pressure and nonspecific cerebrospinal fluid analysis are observed in CM. Neurological sequela in survivors is common and may include epilepsy, ataxia, hemiplegia, blindness, and long-term cognitive deficits [54].

Severe Anemia

Severe anemia is characterized by hemoglobin ≤ 5 g/dL in children and ≤ 7 g/dL in adults [45••]. Pathogenesis is multifactorial and is attributed to erythrocyte lysis, immune-medicated erythrocyte destruction in spleen, and bone marrow suppression due to inflammatory state. "Blackwater fever" is a phenomenon that includes massive intravascular hemolysis, hemoglobinuria, and renal failure in patients with repeated falciparum malaria and a history of quinine chemoprophylaxis that occurs more commonly in persons with G6PD deficiency [46••]. Transfusion threshold is not well established, however it is generally indicated in severe cases.

Acute Renal Failure

Acute renal failure in severe malaria is defined by creatinine > 3 mg/dL or blood urea nitrogen > 56 mg/dL [45••]. Severe malaria promotes renal damage by affecting different structures - glomeruli, tubules, and interstitial region. Parasitized red blood cells obstruct renal vasculature causing acute tubular necrosis. Hypovolemia and shock further contribute to pre-renal kidney injury. With complement activation, immune complex deposition can trigger glomerulonephritis. Interstitial nephritis has also been described. Worsening kidney function further exacerbates acidosis [55].

Other Complications

Other life-threatening complications include pulmonary edema, acidosis, hypoglycemia, hyperbilirubinemia, distributive shock, and high-grade parasitemia. Clinicians should also be aware of possible complications such as aspiration pneumonia, gram-negative sepsis, and splenic rupture. Malaria may follow a rapidly progressive course; therefore, timely diagnosis and management are crucial.

Recrudescence

Both *P. vivax* and *P. ovale* are known to form hypnozoites, quiescent forms in liver, that can re-emerge as blood-stage forms months or even years later if initial infection was inadequately treated. Recrudescence due *to P. falciparum* has also been described. This parasite does not produce dedicated dormant forms but infrequently escapes treatment through drug resistance and sequestration of parasite clones [56].

Diagnosis

Despite advances in technology in the past 20 years, microscopy (thick and thin smears) remains the gold standard for the diagnosis of malaria. Giemsa-stained thick smear is performed for identification of parasites as it examines lysed red blood cells. Thin smear allows for speciation and description of parasite stages. It is recommended to perform 2 smears of each type to increase diagnostic yield. If the initial set of smears is negative, they should be repeated 12 to 24 h apart until at least 3 sets are negative [57••]. Light microscopy is sufficient in diagnosing malaria for a parasite concentration above 5–10 parasites/μl, however, this method is interpreter-dependent [58]. Therefore, two major limitations arise with its use: availability of experienced laboratory personnel and sufficient parasite density. To aid in establishing prompt diagnosis, multiple RDTs have been developed. RDTs are designed to detect a falciparum-specific antigen and pan-malarial antigens including lactate dehydrogenase, aldolase, histidine-rich protein-2 (HRP-2), and others. Results are available within minutes [58, 59]. In the U.S., the only Food and Drug Administration-approved RDT is BinaxNOW Malaria (Binax, Inc., Abbott Diagnostics Scarborough, Scarborough, ME). This test detects two malarial antigens: HRP-2 (*P. falciparum*-specific) and aldolase (pan-malarial). Manufacturer-reported *P. falciparum* sensitivity was 95.3% and specificity was 94.2%. For *P. vivax*, *P. ovale,* and *P. malariae* sensitivity was significantly lower – 68.9%, 50%, and 43.8%, respectively [60]. Limitations of all RDTs include inability to detect mixed infections, inability to distinguish species of *Plasmodium*, and limited ability to monitor response to therapy. Although some studies demonstrated RDTs' superiority over microscopy [61], the consensus is to use both methods simultaneously [58]. Nonetheless, new RDTs are continuously being developed. As demonstrated in a recent meta-analysis, an ultrasensitive

RDT outperformed conventional RDTs in sensitivity, especially in asymptomatic patients in low-grade transmission areas [62]. This ultrasensitive RDT is not yet available in the United States. Serologic tests are not recommended for the diagnosis of malaria as they cannot distinguish between acute disease and prior exposure.

Treatment

General Treatment Considerations

When the diagnosis of malaria is confirmed, treatment should be initiated as soon as possible. Admission to the hospital is recommended for most malaria cases. With *P. falciparum* and *P. knowlesi* malaria, healthcare providers should be aware of possible rapid deterioration. When choosing a treatment regimen, several factors should be considered: plasmodium species, geographical area of disease acquisition, prior chemoprophylaxis, pregnancy status, and severity of the disease. Severe cases are treated with intravenous formulations while uncomplicated malaria can be treated with oral medications, if tolerated. In addition to clinical response monitoring, parasite density should be assessed via microscopy every 12–24 h. If unsuccessful chemoprophylaxis preceded the disease, a drug regimen different from the chemoprophylaxis regimen should be selected for treatment.

Uncomplicated Falciparum or Unknown Species Malaria Treatment

For uncomplicated *P. falciparum* malaria or unknown species malaria acquired in chloroquine-sensitive areas, chloroquine or hydroxychloroquine is recommended for children and adults by the CDC. If acquired in chloroquine-resistant area, an artemisinin-based combination therapy (ACT), atovaquone-proguanil, or quinine plus doxycycline or clindamycin is indicated [57••]. In contrary, the WHO recommends treatment of all uncomplicated malaria due to *P. falciparum* in adults, children including infants, pregnant women (second and third trimester) and breastfeeding women with ACT over chloroquine or hydroxychloroquine [45••]. Artemisinins as effective anti-malarial drugs were first derived from an herb in 1970s in China and since then they have gained widespread use [63]. Artemisinins are used in a two-drug combination to halt emerging resistance; they were proven to be safer and more effective than other regimens [64]. Artemether-lumefantrine, an ACT available in the U.S., is administered over a 3-day course in uncomplicated malaria and should be taken with food or fat containing drink (e.g., milk) to augment its absorption. Most common adverse events are mild and include headache, fever, and gastrointestinal disturbances. QT interval should be monitored for prolongation to avoid arrythmias [65]. ACT resistance has been increasingly reported, especially in Southeast Asia [66•, 67]. Atovaquone-proguanil is also an effective combination in treating uncomplicated falciparum malaria, although treatment failure as high as 10% was reported in some studies [68]. Treatment duration is 3 days and the most common side effects include gastrointestinal disturbances and transaminitis. Mefloquine is an alternative treatment in falciparum malaria acquired in areas with chloroquine resistance. Treatment with mefloquine is of last resort if other agents are unavailable due to multiple undesired neuropsychiatric effects [69, 70•, 71].

Uncomplicated Non-falciparum Malaria Treatment

In uncomplicated malaria caused by *P. malariae* or *P. knowlesi,* either chloroquine or hydroxychloroquine is sufficient as no resistance have been reported. Both drugs are administered in 4 doses: at 0, 6, 24, 48 h. Severe adverse reactions are rare. These medications can also be used against *P. vivax* or *P. ovale* malaria acquired in areas without chloroquine resistance. For *P. vivax* acquired in chloroquine-resistant area, an ACT, atovaquone-proguanil, quinine plus doxycycline (preferred) or clindamycin, or mefloquine is recommended.

Most malarial drugs are effective against the erythrocytic stage of the parasite. To prevent relapses due to dormant liver hypnozoites in vivax and ovale malaria, an additional agent should be used. Primaquine can be added to any regimen, while tafenoquine can only be used in combination with chloroquine. Both medications are known to cause severe hemolytic anemia in persons with G6PD deficiency, thus testing should be obtained promptly as soon as vivax and ovale malaria is confirmed [45••, 57••].

Severe Malaria Treatment

Intravenous (IV) artesunate is the treatment of choice in severe malaria as it is significantly more effective than IV quinine [72]. Treatment should be initiated as soon as possible and if not available, oral artemether-lumefantrine should be given. This regimen is preferred due to the fast onset of action, and other options include atovaquone-proguanil, quinine, and mefloquine. Once available, IV artesunate should replace oral therapy for the first 24 h. If parasite density decreases to $\leq 1\%$ and the patient can tolerate medications orally, an oral treatment, with artemether-lumefantrine preferred, should replace IV artesunate to complete a full course. Otherwise, IV artesunate should be continued for up to 7 days; parasitemia and ability to tolerate oral medications should be assessed daily. This regimen is safe and effective in adults, children, and pregnant women in the second and third trimesters. Administration in the first trimester was associated with teratogenic effects in animal

models. Insufficient clinical data exist to establish safety in the first trimester of pregnancy in humans, however, the risks of untreated severe malaria in pregnant women should be compared to the hypothetical harm of the drug [73•]. Additionally, clinicians should be aware of cases of post-artemisinin hemolytic anemia occurring more than 7 days after the treatment, therefore patients should be followed weekly for up to 4 weeks after the treatment [57••, 74].

All patients meeting the criteria for severe malaria should be admitted to an intensive care unit regardless of the causative plasmodium species. Antipyretics can be administered in pediatric patients to prevent seizures, otherwise no clear benefit has been established. IV fluids should be administered with caution to prevent pulmonary edema. Glucose should be monitored every 4 h with dextrose solutions added as maintenance fluids if indicated. Benzodiazepines are preferred for treatment of malaria-associated seizures, however, oversedation should be avoided [39, 45••, 74]. Whole blood transfusion was associated with improved survival in children with cerebral malaria, however, such benefit in adults is unclear [75]. Limited evidence suggests restrictive broad-spectrum antibiotic strategy in returning travelers diagnosed with malaria as incidence of bacterial co-infections was much lower than in the population of endemic regions [43, 76].

The following treatments were found to be harmful or of unknown benefit and therefore should be avoided: antiepileptics, mannitol, exchange transfusion, high-dose corticosteroids, albumin, and N-acetyl cysteine [45••, 77–79].

Prevention

Vector control measures include the use of repellents, insecticide-treated bed nets, indoor residual spraying, larval control, and avoidance of outdoor activities from dusk to dawn. All travelers to endemic areas should be timely started on chemoprophylaxis prior to departure. Malarial chemoprophylaxis functions by targeting the liver schizont, blood schizont, or hypnozoite stages. The choice of the regimen depends on the destination, duration of travel, planned activities, comorbidities, allergies, pregnancy status, cost, and the time left to endemic country entry, as some agents should be started weeks prior [80]. Acceptable chemoprophylaxis options include doxycycline, atovaquone-proguanil, chloroquine, hydroxychloroquine, mefloquine, primaquine, and tafenoquine. The CDC Yellow Book provides extensive guidance on the use of malarial chemoprophylaxis [2•].

Vaccine development is challenged by the complexity of plasmodium life cycle and ongoing mutations in key proteins of the parasite. The first and currently the only malaria vaccine approved by the WHO in 2021 for use in areas with moderate-to-high transmission in children is RTS,S/AS01, a pre-erythrocytic recombinant protein vaccine [45••]. Its development dates back to the 1980s and the results of a phase 3 clinical trial published in 2015 demonstrated 36% efficacy at 48 months follow-up in 5–17 months old children who received 4 doses [81•]. However, the effect was shown to wane over the years, leading to rebound malaria cases [82, 83]. Nevertheless, it is currently being trialed in Ghana, Kenya, and Malawi as a part of the Malaria Vaccine Implementation Programme. More vaccine candidates are underway, some of which are approaching late-stage clinical evaluation: R21/Matrix M vaccine targeting PfCSP protein, Rh5 blood-stage vaccine, attenuated whole sporozoite vaccine, and vaccine targeting sexual-stage antigens [84, 85]. Novel technologies such as DNA and mRNA-based vaccines are also being explored.

Conclusions

Global malaria burden has decreased since the 2000s owing to local surveillance programs, robust vector control measures, new rapid diagnostic tests, and highly active artemisinin-based therapy. However, more recently, malaria elimination has plateaued and an increase in cases was seen during the COVID-19 pandemic. In addition to the socioeconomic challenges disrupting local efforts in containing this parasitic disease, emerging drug resistance presents a substantial threat to malaria control.

In non-endemic countries such as the U.S., a high index of clinical suspicion in conjunction with complete history taking is needed for the diagnosis of malaria to be considered. Clinicians should familiarize themselves with the diagnostic and treatment options available at their practice locations. All travelers to endemic areas should be counseled to seek expert consultation prior to travel. Although the first malaria vaccine was approved by the WHO in 2021, it is only recommended for use in areas of endemicity in children of certain ages. There are currently no vaccines available for travelers. With novel technologies used in vaccine development, more vaccine candidates are underway.

Declarations

Conflict of Interest Anastasia S. Weiland declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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