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Return to Travel in the Coronavirus Disease 2019 Pandemic Recovery Period and Implications for Imported Malaria: Reinforcing Prevention, Early Diagnosis, and Appropriate Treatment of Malaria

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Abstract

Return to international travel in the COVID-19 pandemic recovery period is expected to increase the number of patients with imported malaria in the United States (US). Malaria prevention in travelers and preparedness for timely diagnosis and appropriate treatment are key to minimize imported malaria morbidity and mortality. Intravenous artesunate (IVAS) is now available from commercial distributors in the US for the treatment of severe malaria. Hospitals and pharmacists should have a plan for malaria treatment, including stocking artemether-lumefantrine for uncomplicated malaria, and stocking or planning for rapid procurement of IVAS for the treatment of severe malaria.

Keywords

malaria; travel; artesunate; *Plasmodium falciparum* ; chemoprophylaxis

As the coronavirus disease 2019 (COVID-19) pandemic becomes less of a barrier to international travel, many United States (US) residents are pursuing their postponed trips to visit friends and relatives, planned vacations, or business travel. As COVID-19 restrictions continue to ease or disappear, rebounds in international travel up to and above pre–COVID-19 levels are expected to increase the importation of travel-associated infections including malaria, a rapidly progressive and potentially deadly yet preventable disease. Malaria prevention in travelers and preparedness for timely diagnosis and treatment are key to minimize imported malaria morbidity and mortality.

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As of September 2022, the volume of US passengers traveling abroad has returned to 2019 pre–COVID-19 levels [1] and, possibly, so too will the numbers of malaria cases imported into the US. After all, malaria case trends have been observed to follow international travel trends [2]. For example, after travel restrictions for the 2014–2015 West African Ebola outbreak were relaxed, the proportion of malaria cases imported into the US from impacted countries (Guinea, Liberia, and Sierra Leone) increased by 44% and 54% in 2016 and 2017 compared to 2015, respectively [3]. Compared to 2020 when travel restrictions were in full effect, the US Centers for Disease Control and Prevention (CDC) observed a 92% increase in the use of intravenous artesunate (IVAS) for treatment of severe malaria in the US in 2021 (unpublished data).

An important step in preventing imported malaria is for healthcare providers to prescribe and encourage patient adherence to a CDC-recommended malaria chemoprophylaxis regimen before, during, and after travel [4, 5]. During routine care, especially for patients who may travel internationally to visit friends and relatives, clinicians can ask patients about international travel plans and, if indicated, prescribe malaria chemoprophylaxis or refer patients to a travel medicine specialist [6]. Information on prevention of malaria in travelers can be found on the CDC website [4, 5].

The differential diagnosis of fever is broad in a patient recently returned from international travel. However, malaria is among the most common specific etiology of fever among returned travelers [7], and a timely diagnosis of this potentially deadly disease facilitates prompt treatment and optimizes outcomes. CDC has developed an algorithm for diagnosis and treatment of malaria in the US (Figure 1) that healthcare providers can use [8]. Malaria should be near the top of the differential diagnosis in a febrile patient who traveled to a malaria-endemic region even in the setting of COVID-19, seasonal respiratory viruses (eg, respiratory syncytial virus and influenza), and the recent Ebola outbreak in Uganda, as malaria can present as late as several months or more after exposure [9]. Microscopic examination of thick and thin blood smears to evaluate for parasites with results available immediately (ie, within a few hours) is the standard of care, even if a patient has a confirmed infection with severe acute respiratory syndrome coronavirus 2 or other febrile respiratory virus, as malarial coinfection is possible. If malaria blood smears cannot be performed with results available immediately, the rapid diagnostic test (RDT) can be used as an interim diagnostic measure while waiting for blood smear results. Polymerase chain reaction tests can confirm the *Plasmodium* species but are not useful for the initial diagnosis of malaria because the results are not available in time to inform acute management. Having malaria diagnostics available (blood smear or RDT followed by blood smear), especially in settings where patients with fever may present for care such as emergency departments, urgent care clinics, and primary care clinics, facilitates prompt diagnosis and treatment to give the patient the best chance at a good outcome. If malaria blood smear results or RDTs are not readily available, patients should be referred to a higher level of care for prompt evaluation for malaria. Malaria can quickly progress to severe illness and death if not rapidly diagnosed and appropriately treated.

Once malaria has been diagnosed, the distinction between uncomplicated versus severe malaria is based on clinical findings and laboratory results. This clinical classification

is important for the appropriate treatment of malaria. CDC recommends artemether-lumefantrine (Coartem), an oral drug, as the first-line treatment for uncomplicated malaria due to *Plasmodium falciparum* or an unknown species. In the US, severe malaria is defined as a patient with confirmed malaria and any of the following clinical findings or laboratory results: impaired consciousness/coma, hemoglobin <7 g/dL, acute kidney injury, acute respiratory distress syndrome, circulatory collapse/shock, acidosis, jaundice (with other signs of severe malaria), disseminated intravascular coagulation, and/or parasite density ≥5% [8]. Patients with severe malaria should be treated promptly and aggressively with IVAS, regardless of the *Plasmodium* species identified on the blood smear [10]. If IVAS cannot be started at the time of diagnosis, an oral antimalarial, preferably artemether-lumefantrine (Coartem), can be started as a temporizing agent until IVAS can be initiated.

As of 30 September 2022, CDC no longer provides IVAS for the treatment of severe malaria in the US, as there is a US Food and Drug Administration–approved and commercially available product from major pharmaceutical distributors. If a hospital does not have IVAS in stock, they can call the drug manufacturer for assistance to rapidly procure the drug (1–855-5AMIVAS or 1–855-526–4827). The CDC website also has detailed instructions on how to obtain IVAS [10]. Since patients with malaria can present anywhere, hospitals should have a plan to stock or emergently procure IVAS or to rapidly transfer patients with severe malaria to a hospital where IVAS is stocked, taking into consideration the historical incidence of malaria cases at their institution. For example, some hospitals that manage malaria cases regularly have chosen to stock IVAS, whereas other hospitals that rarely admit patients with malaria have put into place emergency procurement plans. Some hospitals have put agreements into place with other hospitals in their system or area to ensure IVAS stock is shared between institutions. If IVAS is not emergently available, having a plan to rapidly transfer patients to a hospital with IVAS can decrease delays in providing appropriate and lifesaving treatment.

Last, cost considerations highlight that preparedness for timely malaria diagnosis and treatment may be important, but prevention is paramount. The cost of treating a patient with severe malaria can be substantial, with average hospital costs of US$26,000, not including the cost of IVAS [11]. Appropriate chemoprophylaxis is estimated to reduce the risk of contracting malaria by more than 95%, and chemoprophylaxis can cost as little as US$1.00 per day for doxycycline for travelers [6]. Prevention of malaria with chemoprophylaxis and mosquito-avoidant measures (eg, mosquito repellant, insecticide-treated bed nets, protective clothing) is ultimately the most cost-effective, impactful tool to stem the incoming tide of imported malaria cases.

Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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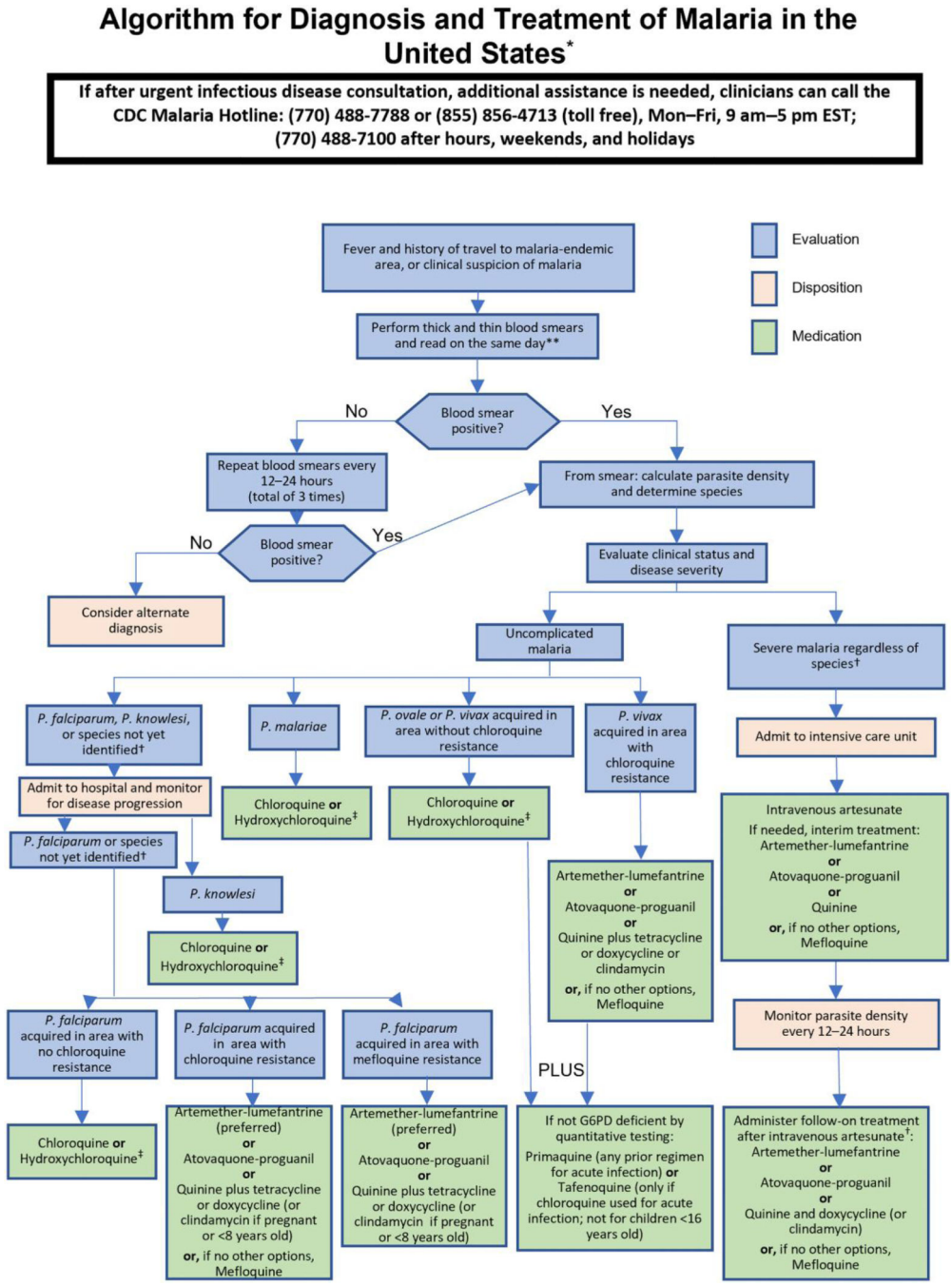

Figure 1.

Algorithm for diagnosis and treatment of malaria in the United States. *Treatment for special populations (children and pregnant women) can be found in the Centers for Disease Control and Prevention (CDC) treatment guidelines and treatment table. **If rapid diagnostic test (RDT) is performed, smear should also be performed with results available as soon as possible. A positive RDT can inform initial treatment decisions while a blood smear is in process. †If species is later identified as *Plasmodium vivax* or *Plasmodium ovale*, add primaquine if not G6PD deficient by quantitative testing. Tafenoquine can only

be used if concurrently given with chloroquine or hydroxychloroquine. ‡Drug options for chloroquine-resistant *Plasmodium falciparum* may be used.