

# Infectious Disease Emergencies in Returning Travelers

## Special Reference to Malaria, Dengue Fever, and Chikungunya

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### KEYWORDS

- Returning traveler • Dengue • Malaria • Chikungunya • Fever • Break bone fever
- *P knowlesi*

### KEY POINTS

- *Plasmodium falciparum* malaria in returning, nonimmune travelers can be a medical emergency.
- Dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) occurs mostly in secondary dengue infections and carries a high mortality rate if not diagnosed early and treated expeditiously.
- Detection of nonstructural protein (NS) 1 antigen in serum/blood can be a useful tool for early diagnosis (within the first week of fever) of dengue infection.
- Chikungunya is an essential differential diagnosis for dengue fever (DF) in travelers returning from endemic zones.
- Because no effective vaccine is available for the most common systemic infections in returning travelers, such as malaria, dengue, and chikungunya, pretravel advice, adequate prophylaxis, and prevention of mosquito bite remain the only effective tools in preventing these infections.

### INTRODUCTION

The twenty-first century has enabled people to crisscross the globe at an enormous speed, whether trade or curiosity about the planet takes them to various parts of the world. We live in a world of microbes, so likewise the various demographic diseases of the continents have caught up with the travelers going back to their destinations. An estimated more than 800 million travelers worldwide cross international

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boundaries each year.<sup>1</sup> Whether associated with tourism, humanitarian efforts, globalization of industry, or migrant work, studies suggest only a small number of travelers seek pretravel health advice. In addition, the composition of those traveling continues to become more diverse and medically complex, creating a vastly different perspective on travel-associated medical concerns, preparations, and required medical knowledge.<sup>2</sup> Recent establishment of collaborative sentinel surveillance networks created specifically to monitor disease trends among travelers offers new insight for evaluating travel health issues. These networks can help pretravel and post-travel patient management by providing complementary surveillance information, facilitating communication and collaboration between participating network sites, and enabling new analytical options for travel-related research. Annually, Americans make more than 300 million trips to other countries. An increasing number of these trips are to developing countries, and 30% to 60% of these travelers, estimated at more than 10 million people, become ill as a result of their travel.<sup>3,4</sup>

In a GeoSentinel Surveillance Network report on fever in returned travelers from different destinations spread across 6 continents during the period 1997 to 2006, febrile illness was reported in 28% of travelers as a chief complaint. The most common causes of fever were systemic illness (35%), diarrheal disease (15%), and respiratory illness (14%). Malaria was the most common cause of systemic febrile illness (21%), followed by dengue (6%). Other less common specific causes of systemic fever included enteric fever (2%) and rickettsioses (2%) (**Table 1**).<sup>5</sup>

Although fever in a returning traveler may be benign and due to a self-limiting infection, it must initially be considered a medical emergency. For arriving at a possible diagnosis of fever in returning traveler, a comprehensive history that details places of visit, duration, purpose, activities undertaken, and any medical exposure abroad or chemoprophylaxis taken along with physical examination is essential for initial work-up. Knowledge of incubation period (**Table 2**) and disease risk by geographic area helps in making a differential diagnosis.<sup>6</sup> Systemic febrile illness is most commonly noted in visitors traveling to sub-Saharan Africa and Southeast Asia.<sup>5,7</sup> In systemic febrile illness, malaria is most commonly reported among travelers from Oceania and sub-Saharan Africa and dengue predominates among travelers from Southeast Asia.<sup>5</sup> Acute diarrheal illness is more common in travelers from South Central Asia and dermatologic disorders are reported in a high proportion of travelers

**Table 1**  
Top 5 illnesses in returning travelers

Diagnosis	%
1. Systemic illnesses	35
Malaria	21
Malaria due to <i>P falciparum</i>	14
Malaria due to <i>P vivax</i>	6
Malaria due to other species	2
Dengue	6
<i>Salmonella enterica</i> serovar Typhi or Paratyphi infection	2
Rickettsia	2
2. Acute diarrhea	15
3. Respiratory illness	14
4. Genitourinary diseases	4
5. Gastrointestinal illnesses (other than diarrhea)	4

<b>Incubation Period</b>	<b>Diseases</b>
<7 Days	Common: malaria, traveler's diarrhea, dengue, enteric fever, respiratory tract infection Others: rickettsioses, leptospirosis, meningitis, yellow fever, arbovirus, meningococcal
7–21 Days	Common: malaria, enteric fever Others: rickettsioses, viral hepatitis, leptospirosis, HIV, Q fever, brucellosis, African trypanosomiasis
>21 Days	Common: malaria, enteric fever Others: tuberculosis, hepatitis B virus, bacterial endocarditis, HIV, Q fever, brucellosis, amebic liver disease, melioidosis

from sub-Saharan Africa and South Central Asia.<sup>7</sup> Based on this knowledge, comprehensive but judicious laboratory investigations should further help in confirmation of preliminary diagnosis in most of the cases.

There are several life-threatening illnesses that a traveler can acquire but this article discusses only malaria, dengue, and chikungunya, all 3 of which are caused by mosquito bites and, if left undetected or unsuspected, could be life threatening in travelers returning home. Because these diseases are not commonly seen in places far away from endemic areas, they are likely to be ignored or missed by a physician attending to a patient in an emergency department. Much of the illness encountered could be reduced, however, with adequate pretravel education and preparation.

## **MALARIA**

### **Introduction**

Malaria is caused by a protozoan parasite of the genus *Plasmodium* infecting red blood cells and is transmitted to humans by bite of a female anopheline mosquito. The 4 *Plasmodium* species that infect humans are *P falciparum*, *P vivax*, *P ovale*, and *P malariae*. Malaria is a life-threatening illness, caused by the asexual form of the parasitic protozoan *Plasmodium*. The clinical manifestations of malaria vary with geography, epidemiology, immunity, and age. It is an entirely preventable and treatable disease, provided that currently recommended interventions are properly implemented. The 2 most common species of malaria parasite that cause disease across the world are *P falciparum* and *P vivax*.<sup>8</sup> *P vivax* and *P ovale* have the ability to stay dormant or persist in the liver as hypnozoites. These hypnozoites can result in relapse of infection weeks to months after the primary infection. Recrudescence results from a failure to eliminate the parasites, which may occur within days or weeks. This could be due to either failure of the immune system or incomplete therapy, which commonly occurs in *P falciparum* but can happen in all the species of plasmodium.

### **Epidemiology**

An estimated 216 million clinical cases and 655,000 deaths due to malaria were reported in 2010, mostly in children aged less than 5 years living in sub-Saharan Africa.<sup>8</sup> It is estimated that approximately half of the world's population in 100 countries live in areas where malaria is transmitted.<sup>9</sup> Malaria is prevalent in regions of Africa, Asia, the Middle East, Eastern Europe, Central and South America, the Caribbean, and Oceania.<sup>9</sup> The major burden of malarial disease lies in Africa (81%) followed by Southeast Asia (13%) and the Eastern Mediterranean regions (5%).<sup>8</sup>

As for the geographic distribution of specific *Plasmodium* species, falciparum malaria predominates in sub-Saharan Africa and vivax malaria in the Indian subcontinent, Mexico, Central America, and China; both species occur in Southeast Asia and South America. *P. malariae* is prevalent at low levels in nearly all malaria endemic areas of the world, and *P. ovale* has limited distribution in Africa, New Guinea, and the Philippines.<sup>10</sup>

Malaria in developed and nonendemic countries is mostly imported. A malaria surveillance program in the United States in 2010 showed that among the total 1691 cases reported to Centers for Disease Control and Prevention (CDC), 1688 were classified as imported, 1 was transfusion related, and 2 were cryptic cases. Of these, *P. falciparum* was the leading cause of malaria (58.1%), followed by *P. vivax* (19.2%), *P. malariae* (2.1%), and *P. ovale* (1.9%). Of the total imported cases in the United States, 65% were acquired in Africa, 19% in Asia, 15% in the Americas, and 0.3% in Oceania.<sup>9</sup> Travelers who are visiting friends and relatives are at higher risk of malaria compared with other travelers, due to their longer stays, higher-risk destinations, inadequate use of chemoprophylaxis, fewer personal protection measures, and belief that they are already immune.<sup>5</sup>

### Clinical Features

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Patients remain asymptomatic from the time of the original mosquito bite until approximately a week later. The typical incubation period usually varies between 8 and 17 days for *P. falciparum*, *P. vivax*, and *P. ovale* and 18 to 40 days for *P. malariae*.<sup>11</sup> Therefore, febrile patients presenting within 7 days of entering an endemic area are unlikely to have malaria. The initial symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness, such as fever, headache, fatigue, muscle and joint pain, nausea, and vomiting. Fever is the common chief complaint in malaria and is present in 78% to 100% of patients.<sup>12</sup> Fever is often characterized by the classic malaria paroxysm of chills and rigors, followed by fever spikes, followed by profuse sweating and fatigue.<sup>13</sup> Paroxysms coincide with the synchronous rupture of blood schizonts and liberation of metabolic waste by-products into the bloodstream. Paroxysms can occur in 48-hour cycles (tertian malaria) in *P. falciparum*, *P. vivax*, and *P. ovale* infections and 72-hour cycles (quartan malaria) in *P. malariae*.<sup>13</sup> Although cyclic paroxysms are suggestive of malaria, they may not be discerned in all cases, especially in early stages of fever.<sup>11</sup> Uncomplicated malaria is defined as a symptomatic malaria characterized by the absence of clinical or laboratory signs of vital organ dysfunction and, therefore, suspected clinically mostly on the basis of fever or nonspecific symptoms. Physical findings may show enlarged spleen/liver, mild jaundice, and increased respiratory rate. Severe malaria or complicated malaria is generally defined as acute malaria with high levels of parasitemia (>5%) and/or major signs of organ dysfunction<sup>10</sup> (listed in **Box 1**). Physical findings may include pallor, petechiae, jaundice, hepatomegaly, and/or splenomegaly. Severe malaria is a life-threatening illness—a high case fatality rate, typically 10% to 20%, is seen in cases receiving treatment—and is fatal in the majority of untreated cases.<sup>10</sup>

The pathogenesis of clinical findings seen in severe malaria essentially involves sequestration of erythrocytes that contain mature forms of the parasite in the deep vascular beds of vital organs. This sequestration is promoted by several processes: the adherence of infected erythrocytes to endothelial cells, rosetting—the binding of infected erythrocytes to noninfected erythrocytes, reduced red cell deformability, and platelet-mediated clumping of infected erythrocytes.<sup>13</sup> This results in causing small infarcts, capillary leakage, and organ dysfunction, producing cerebral malaria, renal failure, hepatic dysfunction, or acute respiratory distress syndrome. Severe

**Box 1****Clinical features of severe malaria**

- Impaired consciousness/coma
- Prostration or sit up with assistance
- Failure to accept feed
- Multiple convulsions—more than 2 episodes in 24 h
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse/shock, systolic blood pressure <70 mm Hg in adults and <50 mm Hg in children
- Jaundice
- Hemoglobinuria
- Abnormal spontaneous bleeding
- Acute renal failure
- Pulmonary edema (radiologic)

anemia and thrombocytopenia that causes bleeding diathesis is produced by hemolysis, reduced cell deformity of parasitized and nonparasitized erythrocytes, increased splenic clearance, reduction of platelet survival, decreased platelet production, and increased splenic uptake of platelets.

Uncomplicated malaria is seen more often with *P vivax*, *P ovale*, and *P malariae*, whereas *P falciparum* is more commonly associated with severe malaria.<sup>9</sup> *P vivax* is usually considered benign but can be associated with debilitating illness with serious complications.<sup>14,15</sup> In a systematic review on clinical presentation of *P vivax*, a wide spectrum of clinical complications commonly associated with *P falciparum* were observed in *P vivax*, including severe anemia, thrombocytopenia, coagulation disorders, acute respiratory distress syndrome, acute renal failure, and jaundice.<sup>16</sup> *P ovale* and *P malariae* mainly present as uncomplicated malaria. *P ovale* presents with less severe course and usually tends to relapse less frequently compared with *P vivax*.<sup>11</sup> *P malariae* is often characterized by low parasitemia difficult to detect by microscopy.<sup>13</sup> Patients with *P malariae* infection may have a long latency period of many years before presenting with fevers, malaise, and splenomegaly.<sup>13</sup> Patients may experience a spontaneous recovery, or there may be series of recrudescence over many years (>50 years).<sup>11</sup> Chronic infection with *P malariae* may result in proteinuria and may be associated with nephrotic syndrome in young children living in endemic areas. Nephrotic syndrome is caused by immune complex-mediated glomerulonephritis. Nonimmune travelers are at high risk for progression to severe disease, especially if infected with *P falciparum*. For this reason, it is important to consider malaria in the differential diagnosis of all febrile patients with a history of travel to malaria endemic areas.

**Diagnosis of Malaria**

Clinicians should have high index of suspicion for malaria in travelers presenting with fever and history of travel to malaria endemic regions within the past 1 year and especially in the past 3 months. Apart from fever, patients usually present with nonspecific clinical features in uncomplicated malaria. If the diagnosis of falciparum malaria has been delayed, an apparently well-looking patient may rapidly deteriorate and present with jaundice, confusion, or seizures with high fatality rates. Therefore, accurate and

rapid laboratory diagnosis of malaria is essential for proper clinical management of patients. During work-up, malaria should not be ruled out in febrile patients who give history of prophylaxis, because approximately 10% of the travelers can develop *P falciparum* malaria, in spite of having taken effective chemoprophylaxis.<sup>17</sup> Chemoprophylaxis may result in delayed onset of symptoms and even obscure microscopic diagnosis.<sup>18</sup> Therefore, all chemoprophylaxis should be stopped while patients are investigated for malaria.

There are many diagnostic modalities available for diagnosis of malaria, but microscopy and rapid diagnostic tests (RDTs) are the most common diagnostic tools used to arrive at a specific diagnosis of malaria. In all suspected cases, blood examinations by microscopy and/or RDT should be submitted to the laboratory. All positive results ideally should be communicated to the treating physician within 4 hours of the sample reaching the laboratory for early initiation of therapy. Negative microscopy and RDT results should trigger contemplation of an alternative diagnosis, and empiric therapy for malaria should be withheld unless patients with a convincing exposure history demonstrate features of severe malaria.<sup>19</sup> In a scenario where the diagnosis of malaria is suspected but proficient laboratory services are unavailable, empiric treatment of *P falciparum* malaria should be instituted, pending referral of patient and/or specimen.<sup>12</sup>

### **Microscopy**

**Giemsa staining (thick and thin films)** Microscopy remains the gold standard for malarial diagnosis and also for endpoint assessment of outcome of therapy and drug trials. When malaria is suspected, both thick and thin Giemsa smear of blood should be prepared immediately. Diagnosis is made by detecting parasites in the thick smear because it concentrates the parasites 40-fold and adds to the sensitivity.<sup>13</sup> Thin smear subsequently helps in determining the malaria species and the level of parasitemia (the percentage of a patient's red blood cells that are infected with malaria parasites). Speciation helps in choosing the antimalarial therapy and parasite density can indicate disease severity, which needs to be monitored during and after treatment to ensure adequate resolution of the infection.<sup>12</sup> The detection threshold of Giemsa-stained thick blood film has been estimated at 20 to 50 parasites per microliter of blood (0.0004%–0.001% parasitemia).<sup>20</sup> This threshold of microscopy has shown to correspond to sensitivity of 68% to 92% for detection of malaria in field conditions.<sup>21</sup> Exclusion of malaria by microscopy requires 3 separate negative blood smears performed and read at 12-hour intervals over a 24-hour to 48-hour period.<sup>19</sup>

A major drawback of light microscopy is that the efficiency of the test depends on the type and quality of the smear, skill of the technician, parasite density, and time spent on examining the smear. In addition, mixed infections with *P malariae* or *P ovale* are often missed, because their densities are often low in comparison to that of *P falciparum*. These problems may occur more frequently in nonendemic areas where malaria microscopy is performed infrequently. Illustrating this point, a Canadian study reported a low sensitivity of microscopy (41%) for the diagnosis of malaria involving 100 patients.<sup>22</sup>

**Quantitative buffy coat** Quantitative buffy coat (QBC) is fluorescent microscopy based on the principle of concentrating the red blood cell-containing parasites within a narrow zone by centrifugation of blood in capillary tubes and staining of malarial parasite nucleic acid with acridine dyes. The sensitivity of QBC almost equals that of Giemsa-stained films.<sup>23</sup> The advantage of QBC is ease of interpretation and rapidity. Species identification and quantification are difficult, however, with this technique and, therefore, thick and thin blood film examination is still required. Moreover,

QBC requires expensive fluorescent microscope for interpretation of the result, which restricts its widespread use, especially in resource-poor countries.

**Antigen detection** RDTs detect malaria antigen in blood by immunochromatographic test with monoclonal antibodies directed against the target parasite antigen, which is impregnated on a test strip. The result is usually obtained in 5 to 20 minutes. Currently, different combinations of immunochromatographic tests are commercially available, targeting different genus specific or species-specific antigen for malaria diagnosis. Some of the commonly used antigens in RDTs are HRP-2 (*P falciparum* specific), aldolase (pan-specific), plasmodium lactate dehydrogenase (pLDH) (*P falciparum* specific), pLDH (*P vivax*- specific), and pLDH (panspecific).

RDTs based on different antigens have been shown to vary in their performance in field conditions. In a meta-analysis on diagnosing uncomplicated *P falciparum* malaria by RDTs, the overall sensitivity and specificity for histidine-rich protein 2 (HRP-2)-based RDTs were 95.0% and 95.2%, respectively, and for pLDH-based RDTs, 93.2% and 98.5%, respectively. HRP-2-based tests tended to be more sensitive but less specific than pLDH-based tests.<sup>24</sup> RDTs based on aldolase have shown inadequate detection thresholds, possibly because of the low concentrations of this target antigen in parasites.<sup>25</sup> Several RDTs are commercially available. Among these assays, BinaxNOW Malaria (Binax, Inc, Inverness Medical Professional Diagnostics, Scarborough, Maine) received US Food and Drug Administration (FDA) approval in 2007 for diagnosis of symptomatic malaria. This assay is based on the combination of detection of *P falciparum*-specific HRP-2 and pan-specific aldolase.

The BinaxNOW Malaria test has shown a superior sensitivity (97%) and negative predictive value (NPV) (99.6%) compared with microscopy (sensitivity 85% and NPV 99.6%).<sup>25</sup> Antigenemia level is associated with parasite density, so the apparent sensitivity of the BinaxNOW test may vary with differing levels of parasitemia. Its sensitivity varies in *P falciparum* and *P vivax* between 99% and 93% (for parasitemia in excess of 5000 parasites/ $\mu$ L) to 54% and 6% (for parasitemia of 0–100 parasites/ $\mu$ L of blood), with an overall specificity of 94% and 99%, respectively.<sup>26</sup> Because nonimmune travelers generally tend to have high parasitemia (10,000 parasites/ $\mu$ L),<sup>26</sup> the excellent sensitivity and NPV of RDTs, particularly for *P falciparum*, make it a valuable tool in making a rapid diagnosis of malaria in the ED.

The limitation of the BinaxNOW Malaria test is its low sensitivity (60%) for detection of *P ovale* infection, probably due to its lower production of the aldolase and/or low parasite density.<sup>25,27</sup> This test also has limited use in quantifying the parasite load and monitoring the antimalarial treatment because HRP-2 can persist in blood after successful treatment,<sup>28</sup> although aldolase and pLDH fall rapidly after initiation of effective therapy but can subsequently become positive on appearance of gametocytes, because not all therapeutic regimens are gametocidal.<sup>26</sup> Moreover, false-negative reactions up to 40% have been noted in *P falciparum* in some parts of South America due to HRP-2 gene deletions.<sup>28</sup>

In conclusion, RDTs for malaria are rapid tests and are helpful in making a quick diagnosis of malaria in emergency departments, especially at odd hours when expert microscopic advice may not be available. RDTs are almost as sensitive as malaria microscopy for falciparum malaria but less sensitive for nonfalciparum malaria and cannot give additional information, such as parasite count and maturity. Therefore, RDT must be accompanied or followed by confirmatory blood smears for quantification of parasitemia and determination of the species.

**Serology** Detection of antibodies against malaria parasites, using either indirect immunofluorescence assay or ELISA, does not indicate current infection but rather

measures past exposure. Therefore, it has no role in diagnosis of acute infections. Serology may be used to screen donors to prevent transfusion-related malaria, however, and to confirm the diagnosis of malaria in recently treated cases in which the diagnosis could not be confirmed previously.<sup>29</sup>

**Molecular methods** Molecular technologies have been developed to improve the diagnosis of malaria by detecting specific parasite nucleic acid. The advantage of molecular methods is their exquisite sensitivity down to the level of 5 parasites/ $\mu$ L or 0.0001% parasitemia.<sup>30</sup>

Molecular methods are also useful in confirming *Plasmodium* species, when in doubt or when it is not possible by other methods. Real-time assays may also help in quantification of parasitemia.<sup>31</sup> Molecular methods, however, find limited use in routine diagnosis of acute cases because of high cost, need for specialized infrastructure, and longer turnaround time.

In addition to ordering the malaria-specific diagnostic tests, a baseline complete blood count and a chemistry panel should be requested. In the event of a positive malaria test, these additional tests aid in determining whether a patient has uncomplicated or severe manifestations of the malaria infection. Although nonspecific, fever accompanied by thrombocytopenia, a low white blood cell count, and signs of hemolysis, such as an elevated bilirubin level, are predictive clues to the presence of malaria.<sup>12</sup> Some of key laboratory findings in severe malaria<sup>10</sup> are listed in **Box 2**.

### Treatment

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The choice of treatment of malaria is guided by the infecting species of plasmodium, the probable drug susceptibility as determined by the region of acquisition of infection, the severity of infection, the clinical status of the person, and any previous use of antimalarials.

#### Uncomplicated malaria

Appropriately treated, uncomplicated malaria has a good prognosis, with a case fatality rate of approximately 0.1%.<sup>32</sup> Uncomplicated malaria caused by *P ovale*, *P vivax*, and *P malariae* can usually be managed with oral drugs on an outpatient basis, unless a patient has other comorbidities or is unable to take drugs orally. *P falciparum* infections in travelers can rapidly progress, however, to severe illness or death in as few as 1 to 2 days, due to little immunity against these infections. Therefore, all patients diagnosed with *P falciparum* or mixed infections or infections with unconfirmed species should be admitted to a hospital<sup>12</sup> and treated for multidrug-resistant *P falciparum* for at least 48 hours to ensure adequate response to therapy, regardless of how well they appear at presentation.

#### Box 2

##### Laboratory findings of severe malaria

- Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dL)
- Metabolic acidosis (plasma bicarbonate <15 mmol/L)
- Severe normocytic anemia (hemoglobin <7 g/dL)
- Hemoglobinuria
- Hyperparasitemia (>5%)
- Hyperlactatemia (lactate >5 mmol/L)
- Renal impairment (serum creatinine >265  $\mu$ mol/L)



Chloroquine is the treatment of choice for malaria, when it is sensitive, but emergence of resistance has been noted from various regions. Chloroquine resistance in *P vivax* is confined largely to Indonesia, Papua New Guinea, Timor-Leste, and other parts of Oceania.<sup>10</sup> Rare cases of chloroquine-resistant *P vivax* have also been documented in Myanmar, India, and Central and South America. *P ovale* and *P malariae* continue to remain sensitive to chloroquine throughout the world. Chloroquine resistance in *P falciparum* is prevalent throughout the world except for regions of Haiti, the Dominican Republic, most regions of the Middle East, and Central America west of the Panama Canal.<sup>33</sup> If chloroquine-resistant *P falciparum* is anticipated, then artemisinin combination therapy (ACT) is preferred for treatment of uncomplicated falciparum malaria.<sup>10</sup> ACT consists of an artemisinin derivative (artesunate, artemether, and artemotil) combined with a long-acting antimalarial (amodiaquine, lumefantrine, mefloquine, or sulfadoxine-pyrimethamine). Alternative treatment options for uncomplicated malaria by various plasmodium species are listed in **Table 3**.<sup>10,33</sup> Relapse has been reported in 25% of cases of vivax malaria when treated with chloroquine or other drugs,<sup>34</sup> because these antimalarials do not eliminate liver stages of parasite. Primaquine is required additionally for radical cure and to prevent relapse. Antimalarial drugs and their dosing are outlined in **Table 4**.<sup>32,33</sup>

### Severe malaria

Severe malaria is a medical emergency. After rapid clinical assessment and diagnosis of severe falciparum malaria, full doses of parenteral antimalarial treatment should be started without delay (see **Table 3**). There are 2 major classes of drugs available for parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives. Artesunate is recommended by the World Health Organization (WHO) in preference to quinidine for the treatment of severe malaria. Various randomized trials comparing artesunate and quinine have shown evidence of benefit with artesunate over quinine in adults and children.<sup>10,35</sup> Intravenous artesunate of reliable quality is not yet available in many countries; in these areas, quinine remains the treatment of choice. Artesunate was unavailable in the United States until 2007, when the Food and Drug Administration approved it as an investigational new drug for treatment of severe malaria. Parenteral quinine was replaced with quinidine for the treatment of severe falciparum malaria by the CDC, because quinidine was found more potent and effective in severe *P falciparum* infections. When intravenous therapy cannot be given immediately, options include intramuscular administration of quinine or an artemisinin or rectal administration of artesunate. Although the WHO has strongly recommended artesunate as the first line of therapy for severe malaria, CDC guidelines state that if both quinidine and artesunate can be obtained in similar time frames, the treating physician may choose either option. The CDC recommends artesunate in treatment of severe malaria if quinidine is unavailable, in patients with adverse effects or contraindications to quinidine, or in patients with a parasitemia greater than 10% of baseline at 48 hours after initiation of intravenous quinidine.

Management of patients with severe malaria also presents a broad array of clinical challenges given the complex pathophysiology of the infection involving multiple organ systems. **Box 3** outlines the intensive care management of severe malaria.<sup>10,12</sup>

### Treatment of malaria in pregnancy

Malaria in pregnancy is associated with high rate of maternal and perinatal mortality.<sup>12</sup> Pregnant women are more likely to develop severe *P falciparum* malaria than other adults because of physiologic immunosuppression that occurs during gestation and

<b>Table 3</b>		
<b>Guidelines for treatment of malaria</b>		
<b>Diagnosis</b>	<b>Chloroquine Sensitive/Resistance</b>	<b>Treatment</b>
<b>Uncomplicated malaria</b>		
<i>P. malariae</i>	All regions	Chloroquine phosphate or hydroxychloroquine
<i>P. vivax</i> or <i>P. ovale</i>	Sensitive region	Chloroquine phosphate or hydroxychloroquine plus primaquine phosphate
<i>P. vivax</i>	Resistant region	Atovaquone/proguanil or mefloquine or oral quinine sulfate plus doxycycline or tetracycline or clindamycin plus primaquine phosphate
<i>P. falciparum</i>	Sensitive region	Chloroquine phosphate or hydroxychloroquine
<i>P. falciparum</i> or species not yet identified	Resistant region	Artemether-lumefantrine or any ACT effective in region or atovaquone/proguanil or oral quinine sulfate plus doxycycline or tetracycline or clindamycin or mefloquine
<b>Severe malaria</b>		
Any species	All regions	Intravenous quinidine gluconate plus tetracycline, doxycycline, or clindamycin or intravenous artesunate <sup>a</sup> followed by one of the following: atovaquone/proguanil, doxycycline, clindamycin, or mefloquine
<b>Malaria during pregnancy</b>		
Uncomplicated malaria any species	Sensitive region	Chloroquine phosphate or hydroxychloroquine
<i>P. falciparum</i> / <i>P. vivax</i>	Resistant region	Quinine sulfate plus clindamycin or mefloquine
Severe malaria	Resistant region	Quinine sulfate plus clindamycin or artesunate plus clindamycin

If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of the treatment regimen. Use any one of the other options. If a patient cannot tolerate oral therapy, parenteral formulations of antimalarial drugs are recommended.

There is no evidence that there is clinical difference between currently available various ACTs.

Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, mefloquine is not recommended unless the other options cannot be used.

For *P. vivax* or *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* or *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

<sup>a</sup> Artesunate is an investigational new drug (contact CDC for information).

Data from Centers for Disease Control and Prevention (CDC). Treatment of malaria: guidelines for clinicians (United States). 2011. Available at: <http://www.cdc.gov/malaria/resources/pdf/treatmentable.pdf>. Accessed July 14, 2012; and World Health Organization. Guidelines for the treatment of malaria. 2nd edition. 2010. Available at: [http://whqlibdoc.who.int/publications/2010/9789241547925\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf). Accessed July 1, 2012.

the accumulation of erythrocytes infected with *P. falciparum* in the placenta through cytoadherence mechanisms. Complications, such as hypoglycemia and pulmonary edema, are more common than in nonpregnant individuals.<sup>19</sup> Prompt antimalarial therapy (**Table 3**) should be administered in addition to supportive care. For severe malaria, parenteral artesunate is preferred over quinine in the second and third trimesters because quinine is associated with recurrent hypoglycemia and artemisinins are

**Table 4**  
Doses of antimalarial drugs

Drug	Adult Dose	Pediatric Dose	Comments
Artesunate	2.4 mg/kg IV push at 0, 12, 24, and 48 h	2.4 mg/kg IV push at 0, 12, 24, and 48 h	
Atovaquone-proguanil	4 Adult tabs (each adult tab contains 250 mg atovaquone and 100 mg proguanil) PO as a single daily dose for 3 consecutive days	Dosage is based on weight. Each ped tab contains 62.5 mg atovaquone and 25 mg proguanil. Daily dose to be taken for 3 consecutive days: 5–8 kg: 2 ped tabs 9–10 kg: 3 ped tabs 11–20 kg: 1 adult tab 21–30 kg: 2 adult tabs 31–40 kg: 3 adult tabs ≥41 kg: 4 adult tabs	Not indicated for use in pregnant women
Artemether-lumefantrine	1 Tablet = 20 mg artemether and 120 mg lumefantrine A 3-d treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 h later, then 1 dose PO bid for the following 2 d.  5 To <15 kg: 1 tab per dose 15 To <25 kg: 2 tabs per dose 25 To <35 kg: 3 tabs per dose ≥35 kg: 4 tabs per dose		Lumefantrine absorption is enhanced by coadministration with fat, so should be taken after fatty meal. If patient vomits within 30 minutes of taking dose, then repeat the dose.
Chloroquine phosphate	600 mg Base (= 1 g salt) PO, then 300 mg base (= 500 mg salt) and 6, 24, and 48 h	10 mg Base/kg PO, then 5 mg base/kg at 6, 24, and 48 h	Use with caution in impaired liver functions because the drug is concentrated in liver.
Clindamycin, oral	20 mg Base/kg/d PO divided tid × 7 d	20 mg Base/kg/d PO divided tid × 7 d	
Clindamycin, parenteral	10 mg Base/kg IV followed by 5 mg base/kg IV q8h Switch to oral clindamycin as soon as patient is able to complete 7-d course	10 mg Base/kg IV followed by 5 mg base/kg IV q8h Switch to oral clindamycin as soon as patient is able to complete 7-d course	Safe in children and pregnant women

*(continued on next page)*

<b>Table 4 (continued)</b>			
<b>Drug</b>	<b>Adult Dose</b>	<b>Pediatric Dose</b>	<b>Comments</b>
Doxycycline	100 mg PO or IV bid × 7 d	2.2 mg/kg PO or IV bid × 7 d	Contraindicated in children <8 y, pregnant women
Mefloquine	750 mg Salt (= 684 mg base) PO followed by 500 mg salt (= 456 mg base) PO 6–12 h after the initial dose	15 mg Salt/kg (= 13.7 mg base/kg) PO followed by 10 mg salt/kg (= 9.1 mg base/kg) PO 6–12 h after the initial dose	Contraindicated in children with epilepsy, other seizure disorders, and persons allergic to mefloquine, with psychiatric disorders, or with cardiac conduction abnormalities
Primaquine phosphate	30 mg Base PO qd × 14 d	0.5 mg Base/kg PO qd × 14 d	Primaquine can cause hemolytic anemia in G6PD-deficient persons. G6PD screening must occur before starting treatment with primaquine. Primaquine should not be used during pregnancy and children less than 4 y old.
Quinidine gluconate	6.25 mg Base/kg (= 10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (= 0.02 mg salt/kg/min) continuous infusion for at least 24 h. Once parasite density is <1% and patient can take oral medication, complete treatment with oralquinine.	6.25 mg Base/kg (=10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (= 0.02 mg salt/kg/min) continuous infusion for at least 24 h. Once parasite density is <1% and patient can take oral medication, complete treatment with oralquinine.	Associated with cinchonism, tachycardia, prolongation of QRS and QTc intervals, flattening of T waves, hypotension, and hypoglycemia. Contraindicated in history of blackwater fever or thrombocytopenia purpura. Cardiac and glucose monitoring required during its administration.
Quinine sulfate (Qualaquin)	650 mg Salt (= 542 mg base) PO tid = 3 or 7 d (× 7 d if acquired in Southeast Asia)	10 mg Salt/kg = 8.3 mg base/kg) PO tid = 3 d (× 7 d if acquired in Southeast Asia)	Associated with cinchonism, sinus arrhythmia, ventricular tachycardia, atrioventricular block, and prolongation of QT intervals (these are rare compared with quinidine)
Tetracycline	250 mg PO qid × 7 d	25 mg/kg/d PO divided qid × 7 d	Contraindicated in children <8 y, pregnant women

*Abbreviations:* G6PD, Glucose-6-phosphate dehydrogenase; ped, pediatrics; tab, tablet.

*Data from* Mace KE, Lynch MF. Malaria. In: Bope E, Kellerman R, editors. *Conn's current therapy*. 1st edition. Saunders; 2012. p. 122–32; and Centers for Disease Control and Prevention (CDC). *Treatment of malaria: guidelines for clinicians*. 2011. Available at: <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>. Accessed July 14, 2012.

**Box 3****Intensive care management of severe malaria**

- Medication (diazepam or paraldehyde) for convulsions
- Management of fluid balance to optimize oxygen delivery and reduce acidosis
- Propping patients at angle of 45°; intubation or diuretics to manage acute pulmonary edema
- Careful monitoring and correction of hypoglycemia
- Dialysis for oliguric acute renal failure or control of electrolyte imbalance/acidosis
- Broad-spectrum antibiotics to manage shock or secondary bacterial infection
- Exchange transfusion considered if parasite density >10% or there is spontaneous bleeding

superior in reducing the risk of death due to severe malaria.<sup>10</sup> In the first trimester, however, risk of hypoglycemia is lower with quinine and there is greater uncertainty on the safety of artemisinins; therefore, both artesunate and quinine may be considered options until more data is available.<sup>10</sup>

**Prevention**

When visiting endemic regions, travelers should prevent mosquito bites by using adequate body covering clothing, bed nets, and repellents. Up to 50% DEET (chemical name, *N,N*-diethyl-*meta*-toluamide) is recommended as an effective repellent for all individuals over the age of 2 months, including pregnant women. The decision to use chemoprophylaxis depends on the benefit of chemoprophylaxis against the risk of possible adverse drug reactions. It is proposed that there is no need for chemoprophylaxis in areas where the annual incidence of malaria is below 10 cases per 1000 individuals.<sup>36</sup> Various regimens for chemoprophylaxis are outlined in **Table 5**.<sup>37</sup> For effective prophylaxis, all regimens should be taken before, during, and after travel to an area with malaria.<sup>37,38</sup>

**Table 5**  
**Chemoprophylaxis of malaria**

<b>Drug</b>	<b>Dose</b>	<b>Duration</b>
<b>Chloroquine-resistant regions</b>		
Atovaquone-proguanil	1 Tablet (250 atovaquone and 100 mg), daily	Begin 1–2 d before travel and for 7 d after leaving malarious areas
Mefloquine	250 mg, Once a week	Begin ≥2 wk before travel and for 4 wk after leaving malarious areas
Doxycycline	100 mg, Daily	Begin 1–2 d before travel and for 4 wk after leaving malarious areas
Primaquine	52.6 Salt, daily	Begin 1–2 d before travel and for 7 d after leaving malarious areas
<b>Chloroquine-sensitive regions</b>		
Chloroquine phosphate	500 mg (Salt), once a week	Begin 1–2 wk before travel and for 4 wk after leaving malarious areas

Data from Centers for Disease Control and Prevention (CDC). Chapter 3 Infectious diseases related to travel. In: Malaria. Available at: <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm>. Accessed August 4, 2012.

### **Vaccine**

The most important step in potential eradication of malaria is the development of an efficacious vaccine. This goal has remained elusive, partly because of the problems of selecting appropriate targets and the lack of reliable and predictive animal models for plasmodium. Because most of the morbidity and mortality (over 90%) due to malaria is caused by *P falciparum*, the primary focus has been on the development of an effective *P falciparum* vaccine. After failure of many candidate vaccines, the most promising candidate on the horizon is the RTS,S/AS01E vaccine, the only malaria vaccine in phase 3 evaluation. It is a pre-erythrocytic malaria vaccine that targets the circumsporozoite protein in combination with the adjuvant AS01. The hypothesized mode of action of this vaccine is to induce circulating antibodies to circumsporozoite that would prevent the load of sporozoites from reaching the liver and in addition stimulate T-cell response to promote the destruction of infected liver cells to further impede intracellular parasite development. This could lead to a significant decrease in infection in vaccines. It could also decrease load of parasites emerging from the liver with a subsequent impact on disease rate and severity. The clinical efficacy of this vaccine is predicted to be between 25% and 60% in different malaria endemic settings.<sup>39</sup> Depending on the full trial results expected in 2014, WHO recommendation for use may become available in 2015.

### **Zoonotic malaria**

Recently, a fifth malarial species, known as *P knowlesi*, has been reported from forested regions of Southeast Asia. *P knowlesi* was originally believed restricted to macaques in Southeast Asia but now have been shown to cause naturally acquired human infections.<sup>40</sup> Significantly, *P knowlesi* infections are known to result in severe malaria and are commonly associated with complications, such as respiratory distress, acute renal failure, and shock, with high mortality. In a 2-year case series from Sabah, Malaysia, severe malaria was seen in 39% of the patients with *P knowlesi* infections at a tertiary care referral hospital. Severe malaria was also associated with high parasite (2%–4%) count and case fatality rate of 27%, comparable to that of *P falciparum*. *P knowlesi* may have been underreported previously because it is indistinguishable from *P malariae* on blood smear examination and needs molecular methods for definite diagnosis.<sup>41</sup> Because *P malariae* infections are associated with low parasitemia, *P malariae* parasitemia on microscopy should arouse suspicion for *P knowlesi* and treatment should be given for severe *P knowlesi*, if molecular tools are not available for confirmation of diagnosis.

Chloroquine is recommended by the CDC for treatment of *P knowlesi* infections, whereas WHO<sup>10</sup> malaria treatment guideline has not given any recommendations for the same. Recently, in a 2-year retrospective case study of 56 patients in Malaysia, the group receiving artemether-lumefantrine had faster parasite clearance compared with other regimens. Also, a lower case fatality rate (17%) was noted with intravenous artesunate than for those who received quinine (31%) for *P knowlesi*. Therefore, oral artemether-lumefantrine for uncomplicated knowlesi malaria and intravenous artesunate therapy for severe knowlesi malaria was more efficacious in this particular study.<sup>42</sup>

### **DENGUE FEVER**

DF is one of the most significant arboviral diseases in terms of mortality and morbidity, affecting the tropical and subtropical regions of the world. According to a WHO estimate, its incidence has increased by a factor of 30 over the past 50 years.<sup>43</sup>

Dengue virus (DENV) belongs to the genus *Flavivirus* of the family *Flaviviridae*. It is an enveloped, single-stranded, positive-sense RNA virus. The genome is approximately

11 kilobases long and encodes for 3 structural proteins and 7 NSs. NS1 is a highly conserved glycoprotein that seems to be essential for virus viability but has no established biologic activity.<sup>44</sup> Unusually for a viral glycoprotein, NS1 is produced in both membrane-associated and secreted forms.

DF is caused by any of 4 closely related viruses or serotypes: dengue 1–4. Infection with one serotype does not protect against the others, and sequential infections with heterologous DENV strains put people at greater risk for DHF and DSS.<sup>45</sup>

### ***Epidemiology and Transmission of the Dengue Virus***

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Dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *A albopictus*, found throughout the world. Symptoms of infection usually begin 4 to 7 days after a mosquito bite and typically last 3 to 10 days. In order for transmission to occur, the mosquito must feed on a person during the 5-day period when viral burden in the blood is high; this period usually begins a little before a person becomes symptomatic. After entering the mosquito through the blood meal, the virus requires an additional 8 to 12 days before it can be transmitted to another human. The mosquito remains infected for the remainder of its life, which may be days or a few weeks.

In rare cases, dengue can be transmitted by organ transplants or blood transfusions from infected donors, and there is evidence of vertical transmission.<sup>46</sup> But in the vast majority of infections, a mosquito bite is responsible.

In many parts of the tropics and subtropics, dengue is endemic, that is, it occurs every year, usually during a season when *Aedes* mosquito populations are high, often when rainfall is optimal for breeding. These areas are at periodic risk for epidemic dengue, when large numbers of people become infected during a short period. Dengue epidemics require a concurrence of large number of vector mosquitoes, a large number of people with no immunity to 1 of the 4 virus types (DENV 1, DENV 2, DENV 3, and DENV 4), and the opportunity for contact.

The 4 DENVs originated in monkeys and independently jumped to humans in Africa or Southeast Asia between 100 and 800 years ago. Dengue remained a minor, geographically restricted disease until the middle of the twentieth century. The disruption of World War II—in particular the coincidental transport of *Aedes* mosquitoes around the world in cargo—is thought to have played a crucial role in the dissemination of this virus. DHF was first documented in the 1950s during epidemics in the Philippines and Thailand. It was not until 1981 that large number of DHF cases began to appear in the Caribbean and Latin America, where highly effective *Aedes* control programs had been in place until the early 1970s.

Today approximately 2.5 billion people, or 40% of the world's population, live in areas with risk of dengue transmission. Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean.<sup>43</sup> Estimates suggest that annually 100 million cases of DF and half a million cases of DHF occur in the world, with a case fatality in Asian countries of 0.5% to 3.5%. The first epidemic of DHF in Southeast Asia occurred in 1954 in Manila, Philippines. The incidence of DHF has increased dramatically since 1950. However, in recent years since 1980, the incidence of DHF has increased approximately 5 times.

Most of the dengue infections (89%) among US residents occur in returning travelers from endemic areas. Travel to the Caribbean (43%); Mexico, Central America, or South America (34%); and Asia and the Pacific (21%) are the leading regions for imported dengue infection in United States.<sup>47</sup> Because contact between *Aedes* and people is infrequent in the continental United States, these imported cases rarely result in secondary transmission. DF epidemics have occurred occasionally in the continental United States since the end of World War II. The last reported continental

dengue outbreak was in south Texas in 2005.<sup>48</sup> Most dengue cases in US citizens occur in inhabitants of Puerto Rico, the US Virgin Islands, Samoa, and Guam, which are endemic for the virus. The most recent island-wide epidemic occurred in 2007, when more than 10,000 cases were diagnosed.<sup>49</sup>

### ***Clinical Presentation***

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Patients usually presents with a history of high-grade fever, rash, and severe headache for 2 days associated with body aches. Rash first appears on the trunk and spreads to the limbs. Patients subsequently may develop altered sensorium.

The symptoms of dengue infection usually start after 3 to 7 days of mosquito bite but may extend up to 14 days. So DF should be considered in all febrile travelers who give a brief history of travel to a dengue endemic area within the past 2 weeks.<sup>49</sup> DENV infections present with wide variety of clinical manifestations, ranging from asymptomatic infection to mild febrile illness to severe disease.<sup>50</sup>

The majority (75%) of DENV infections are asymptomatic or may present as undifferentiated febrile illness, often only with a maculopapular rash. Classic DF is an acute febrile illness with headaches noted in 63%, musculoskeletal pain in 52%, and rash in 34% of cases.<sup>51</sup> The onset is sudden with high fever, severe headache (especially in the retro-orbital area), and intense arthralgia, myalgia, and deep bone pain. Therefore, DF is also often called "break bone fever."<sup>52,53</sup> After 3 to 4 days of fever, an indistinct macular rash can develop, sparing the palms and soles. As the rash fades or desquamates in 1 to 5 days,<sup>45</sup> localized clusters of petechiae on the extensor surfaces of the limbs may remain (**Fig. 1**). Moderate leukopenia and thrombocytopenia can be seen in 47% of patients and are useful diagnostic features.<sup>54-56</sup> Raised lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase levels may be seen in more than half of the cases.<sup>45</sup> Hemorrhagic manifestations are uncommon in DF but in rare cases can be life threatening. The main bleeding sites, apart from petechiae in skin, may present as epistaxis and less commonly as gastrointestinal bleeding. Case fatality rate of DF is less than 1% and recovery from DF is usually uneventful.<sup>57</sup> Sometimes, convalescence may be prolonged as generalized weakness, lasting several weeks, especially in adults.

DHF and DSS are the serious and life-threatening manifestations of dengue. DHF/DHS is an acute immunopathologic disease that is usually seen in secondary infection, in approximately 90% of cases, after exposure to heterologous DENV serotype. DHF may occur after primary infection in infants due to prior presence of maternal anti-dengue antibodies.<sup>45</sup>

The case definition of DHF includes 4 features: fever, a positive tourniquet test, thrombocytopenia ( $<100 \times 10^9/L$ ), and hemoconcentration ( $>20\%$  above normal level).<sup>57</sup> DHF is characterized by sudden onset of fever, which usually lasts for 2 to 7 days and is followed by a fall in temperature to normal or subnormal levels. A maculopapular rash similar to that seen in DF is also seen in many patients. The period of defervescence is the critical stage in DHF<sup>58</sup> and coincides with severe thrombocytopenia and elevation of aminotransferases.<sup>59</sup> Plasma leakage due to increased vascular permeability<sup>60</sup> begins during this stage and can be a life-threatening feature. Plasma leakage is manifested as tachycardia, hypotension, pleural effusions, ascites, pericardial effusion, hemoconcentration, and hypoproteinemia. Tender hepatomegaly is observed in almost all patients and splenomegaly may be seen in some.

Hemorrhagic manifestations usually occur once the fever has settled.<sup>61</sup> The cause of hemorrhage is thrombocytopenia and associated platelet dysfunction or disseminated intravascular coagulation seen in DHF.<sup>57</sup> In DHF, bleeding may occur from any site and does not correlate with the platelet counts.<sup>61</sup> Spontaneous petechiae





**Fig. 1.** Rash of DF. (Reproduced from Wattal C, Gupta PS, Datta S. Dengue fever and encephalitis. In: Khardori NM, Wattal C, editors. Emergencies in infectious disease. From head to toe. Delhi [India]: Byword Books Private Limited; 2010. p. 41–8.)

or ecchymoses may be noted in approximately one-half of patients with DHF and manifest as positive tourniquet test, easy bruising, and bleeding at a venipuncture site. Gastrointestinal bleeding (15%–30%), metorrhagia (40%), and epistaxis (10%) are also seen in some cases.<sup>62</sup> Convalescence in DHF is usually short and uneventful with overall case fatality of 1% to 5%.<sup>45</sup>

The term, DSS, is used when shock is present along with the 4 criteria.<sup>57</sup> DSS is characterized by rapid weak pulse with narrowing of pulse pressure (ie, the difference between the systolic and diastolic pressures) less than or equal to 20 mm Hg or signs of poor capillary perfusion (cold extremities, delayed capillary refill, or rapid pulse rate).<sup>57</sup> Severe abdominal pain, persistent lethargy, and change from fever to hypothermia on days 2 through 7 are usually the warning signs for impending DSS.<sup>63</sup> Other complications associated with DSS are liver failure, disseminated intravascular coagulation, encephalopathy, myocarditis, acute renal failure, and hemolytic uraemic syndrome.<sup>61,64</sup> Patients presenting with DSS are a medical emergency, because they may deteriorate rapidly and die within 12 to 24 hours.<sup>57</sup> Early diagnosis and aggressive treatment are critical in the outcome of DSS, because a high mortality rate of 25% to 50% associated with it can be reduced to 0.5% to 1.0% with appropriate treatment.<sup>45</sup>

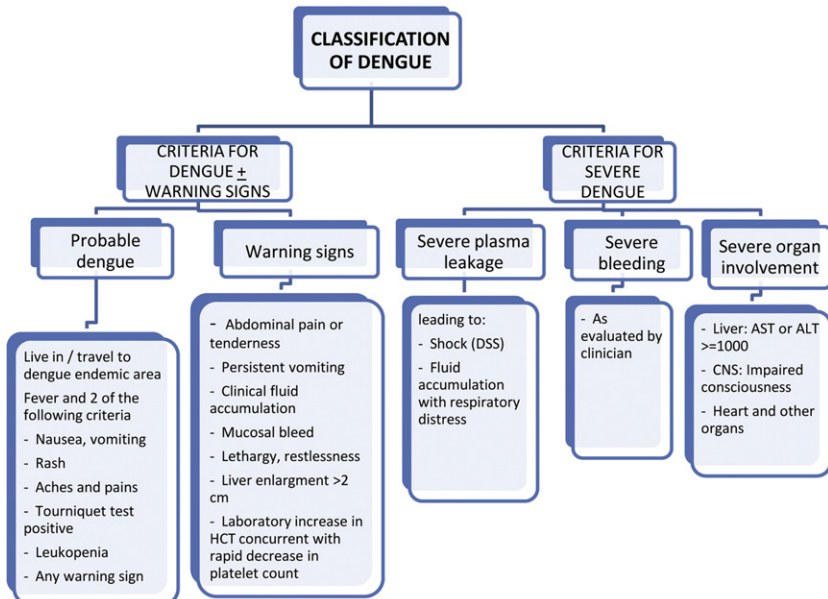
These criteria for classification of dengue, especially that of DHF/DSS, in the past have resulted in diagnostic dilemmas. There were difficulties in applying the criteria for DHF in a clinical situation, together with reports of missing of severe cases, because they did not fulfill the strict criteria of DHF. For these reasons, the WHO published a revised set of guidelines to help in arriving at more specific diagnosis and disease classification of dengue for case management.<sup>60</sup> According to this revised classification, dengue has been divided into 2 broad categories—dengue (with or without warning signs) and severe dengue (summarized in Fig. 2). These revised guidelines of WHO are currently being evaluated for performance in practical settings.

### Differential Diagnosis

The following are usually the alternate diagnoses:

1. Other hemorrhagic arboviral disease
2. Chickengunya viral infections
3. Meningitis
4. Measles
5. Typhoid fever

Evaluating patients who present with fever and rash can be challenging because the differential diagnosis is extensive and includes minor and life-threatening illnesses. For patients presenting with fever and rash, 4 concerns must be addressed immediately: first, whether the patient is well enough to provide a history or whether cardiorespiratory support is urgently required; second, if the nature of the rash requires patient isolation; third, whether skin lesions require urgent institution of antimicrobial therapy, as in meningococcal rash; and finally, consideration must be given to the possibility that the patient has an exotic disease acquired during travel.



**Fig. 2.** Dengue classification for diagnosis and assessing levels severity. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS: central nervous system; HCT: hematocrit.

Key points in arriving at a presumptive diagnosis include determination of the primary types of skin lesions present, the distribution and progression of the rash, and the timing of the onset of the rash relative to the onset of fever and other signs of systemic illness.

The differential diagnosis of the rash in DF is provided in **Table 6**.<sup>64</sup>

### Diagnosis

In view of the high mortality rate in untreated complicated dengue cases<sup>45</sup> and to reduce the disease burden, it is imperative to have a rapid and accurate diagnosis of dengue infection.

History of travel to dengue endemic area in the past 2 weeks in a febrile traveler is the first clue towards a diagnosis of DF. A complete blood cell count at the first visit and thorough physical examination for signs of deranged hemodynamic status, plasma leakages, and hemorrhages should alert a clinician to possible diagnosis of dengue and its complications. A rapid decrease in platelet count associated with a rising hematocrit compared with the baseline is suggestive of progress to the plasma leakage/critical phase of disease and a requirement for hospitalization. In all suspected cases of dengue infection, tests for specific diagnosis of dengue should be performed to confirm its diagnosis.

The major diagnostic methods currently available are based on detection of the virus, antibodies, antigens, or a combination of these techniques.

Diagnosis of dengue infection can be established by testing acute-phase serum samples during the first 5 days of symptoms. This detection coincides with the febrile phase of illness and detection of viremia. Convalescent-phase serum (more than 5 days of symptoms) is usually associated with defervescence and the detection of IgM/IgG antidengue antibodies.

Rash	Causative Organisms
Maculopapular rash	Viral illness (DF, measles, rubella, cocksackie, echo, cytomegalo, hepatitis B virus, hepatitis C virus, herpes simplex virus, West Nile fever, human parvovirus B19) Bacteria (chronic meningococemia, bacterial endocarditis, secondary syphilis, staphylococcal scalded skin syndrome, staphylococcal toxic shock syndrome, <i>Mycoplasma pneumoniae</i> , salmonella)
Nodular lesions	Bacteria (nocardia, atypical mycobacteria, pseudomonal sepsis) Fungi (candidal sepsis, blastomycosis, histoplasmosis, coccidioidomycosis, sporotrichosis)
Diffuse erythema	Scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome
Vesiculobullous eruptions	Varicella, disseminated herpes simplex virus, echo, cocksackie, poxvirus
Petechial and purpuric eruptions	Bacteria ( <i>Neisseria meningitidis</i> , rickettsiae, listeria, staphylococci) Viruses (viral hemorrhagic fevers—dengue cocksackie A9, echovirus 9, cytomegalovirus, Epstein-Barr virus)

Reproduced from Wattal C, Gupta PS, Datta S. Dengue fever and encephalitis. In: Khardori NM, Wattal C, editors. Emergencies in infectious disease. From head to toe. Delhi [India]: Byword Books Private Limited; 2010. p. 41–8.

### ***Virus detection***

Acute infection with DENV is confirmed when the virus is isolated from serum or autopsy tissue specimens or the specific DENV genome is identified by reverse transcription–polymerase chain reaction from serum or plasma, cerebrospinal fluid, or autopsy tissue specimens during an acute febrile illness.

**Cell culture** Owing to the availability of freely circulating viable virus particles in the blood for the initial 5 days after onset of the disease, virus isolation by cell culture and subsequent detection by immunofluorescence is the gold standard for diagnosis of DENV infection in the acute phase.<sup>65</sup> But due to its low sensitivity, laborious procedure, and time consumption (a minimum incubation period of 7 days is required), it has gradually been replaced by PCR.<sup>66,67</sup>

**Molecular methods** Molecular methods have become a primary tool to detect virus early in the course of illness because PCR can detect DENV in the blood (serum) from patients approximately in the first 5 days of the appearance of symptoms, when antibodies are usually not detectable. A positive PCR result is a definite proof of current infection and usually confirms the infecting serotype as well. A negative result, however, is interpreted as indeterminate. Current tests are between 80% and 90% sensitive and more than 95% specific.<sup>68</sup> Currently, several PCR tests, such as 1-step, real-time PCR (RT-PCR) or nested RT-PCR, are used to detect the viral genome in acute-phase serum. Several RT-PCR assays have been developed and automated, but none of these tests is commercially available yet. RT-PCR developed by CDC, called CDC DENV-1-4 Real-Time RT-PCR Assay, diagnoses dengue within the first 7 days after symptoms of the illness appear, which is when most people are likely to see a health care professional. The test can identify all the 4 serotypes. The CDC has developed this assay using the Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument, used also for influenza testing.

The requirement of a highly trained staff and the need for sophisticated equipment as well as the cost involved associated with molecular methods have limited their application as a routine diagnostic assay.

### ***Serology***

The acquired immune response after a DENV infection consists of the production of IgM and IgG antibodies directed against primarily the virus envelope proteins. A primary dengue infection is characterized by a slow and low titer antibody response. IgM antibodies first appear on days 3 to 5 of illness, peak in approximately 2 weeks, and then decline to undetectable levels in 2 to 3 months.<sup>60,69,70</sup> It is estimated that 80% of all dengue cases have detectable IgM antibody by day 5 of illness, 93% to 99% by days 6 to 10 days of illness, and subsequently may remain detectable for several months.<sup>60,68</sup>

Antidengue IgG is detectable at low titers at the end of the first week of illness, which slowly increases and is detectable for several months thereafter.<sup>60</sup> In contrast, during a secondary infection, the kinetics of the IgM response is more variable. Although IgM levels may also peak at approximately 2 weeks, their levels are significantly lower in secondary dengue infections. Therefore, some antidengue IgM false-negative reactions are observed during secondary infections.<sup>60</sup> IgG antibodies in secondary dengue infection appear early, before, or simultaneously with IgM and rise dramatically over the proceeding 2 weeks. The IgG antibodies may persist for up to 10 months or a lifetime. These IgG antibodies are nonspecific and react broadly with many flaviviruses, including West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus (JEV), and yellow fever virus (YFV).<sup>50,60</sup>

**IgM ELISA (MAC-ELISA)** The IgM antibody capture ELISA (MAC-ELISA) is based on capturing human IgM antibodies on a microtiter plate using antihuman-IgM antibody followed by the addition of dengue viral antigen (DENV 1–4). The antigens used for this assay are derived from the envelope protein of the virus. This test is most commonly used in diagnostic laboratories because of its automation and high sensitivity and specificity (90% and 98%, respectively) when used in convalescent-phase sera.<sup>66</sup> High specificity of MAC-ELISA is due to its detection of non-cross-reacting anti-dengue IgM antibodies with other flaviviruses. The major limitation of MAC-ELISA is that it is often not useful in early diagnosis of acute dengue because IgM antibodies appear after 5 to 10 days in primary and 4 to 5 days in secondary infections.<sup>44</sup> MAC-ELISA is more sensitive in detecting primary than secondary infections,<sup>71</sup> and it may be negative in up to 30% of secondary infections.<sup>69,72</sup>

**IgG ELISA** IgG ELISA used for the detection of a past dengue infection uses the same viral antigens as the MAC-ELISA. This assay correlates with the hemagglutination assay previously used. In general IgG ELISA lacks specificity within the flavivirus serocomplex groups and, therefore, is less specific than IgM ELISA.<sup>50,60</sup> It can also make interpretation difficult in assessing dengue infection in travelers previously immunized with JEV and YFV vaccines. In a study of DF among Israeli travelers to Thailand, IgG tests showed false-positive results in 11% to 17% and 15% to 14% of healthy individuals vaccinated against JEV and YFV, respectively.<sup>73</sup>

**Interpretation of serology assays** A single positive MAC-ELISA indicates a probable recent dengue infection.<sup>66,68</sup> This is because IgM antibodies for dengue may remain elevated for 2 to 3 months after the illness and, therefore, cannot differentiate between acute and recent dengue infections.<sup>60</sup> A single positive IgG test is unreliable because of its cross-reactivity with other flaviviruses. Therefore, to confirm diagnosis of acute dengue, paired serum samples are required to demonstrate seroconversion of IgG/IgM antibody or rising titer ( $\geq 4$ -fold) of IgG antidengue antibodies (**Table 7**).<sup>57,66</sup> The optimal time interval for collecting paired sera is 7 to 10 days. Paired serum samples can also be useful in differentiating primary and secondary dengue infections. Samples with a negative IgG in the acute phase and a positive IgG in the convalescent phase of the infection are considered primary dengue infections,<sup>68</sup> whereas samples with a positive IgG in the acute phase and a 4-fold rise in IgG titer in the convalescent phase are considered secondary dengue infection. Ratio of IgM and IgG antibodies in a single serum sample can also be used to differentiate primary from secondary infection ( $\geq 1.2$  for primary and  $\leq 1.2$  for secondary dengue infections).<sup>66</sup>

<b>Diagnosis of Dengue</b>	<b>Serology Results</b>
Highly suggestive	Positive IgM in single serum sample Positive IgG in a single sample with an HI titer of $\geq 1280$
Confirmed diagnosis	IgM seroconversion in paired sera IgG seroconversion in paired sera or $\geq 4$ -fold IgG titer in paired sera
Primary infection	Negative IgG in the acute-phase serum and a positive IgG in the convalescent-phase serum Ratio of IgM and IgG in single serum sample $\geq 1.2$
Secondary infection	Positive IgG in the acute-phase serum and a 4-fold rise in IgG titer in the convalescent-phase serum sample Ratio of IgM and IgG in single serum sample $\leq 1.2$

In a study among 1035 febrile returning travelers, the diagnostic value of IgG and IgM testing on single serum sample, had high false-positivity rate (42.5%) with positive predictive value of 50%.<sup>74</sup> But, combinations of thrombocytopenia or both leukopenia and thrombocytopenia and positive ELISA results greatly improved the positive predictive value value of the test to 88.5% and 90.5%, respectively.

### **Antigen (NS1) detection**

The NS1 of the dengue viral genome has been shown a useful tool for the diagnosis of acute dengue infections. NS1 antigen can be detected as early as the first day after the onset of fever up to day 9, once the clinical phase of the disease is over.<sup>75</sup> Dengue NS1 antigen has been detected in high concentrations in the sera of DENV-infected patients during the early phase of the disease.<sup>44</sup> NS1 Ag levels are similar in both the primary and secondary dengue infection (range 0.01–2 µg/mL).<sup>75,76</sup>

ELISA-based NS1 antigen assay is commercially available and many investigators have evaluated its sensitivity and specificity. In a study at the authors' center,<sup>77</sup> for early diagnosis of dengue infection, acute-phase serum and convalescent-phase serum were investigated using IgM capture ELISA and NS1. The positivity rate of NS1 in acute-phase sera was 71.4% whereas IgM capture ELISA remained 6.4%. During convalescence period, NS1 sensitivity fell to 28.6% whereas IgM capture ELISA improved to 93.6%. Higher detection rate by NS1 Ag in acute area and by IgM in convalescent sera has been observed by other investigators also.<sup>78,79</sup> This is because of early appearance and waning of NS1 compared with IgM.<sup>75</sup> The specificity of NS1 assay was 100%.<sup>77</sup> Due to its highly conserved region, NS1 Ag circulates uniformly in all serotypes of DENV and does not cross-react with other flaviviruses, rendering it highly specific for dengue infection. This results in its higher specificity of 98% to 100%.<sup>80</sup>

Therefore, NS1 assay complements the shortcomings of serology and is useful in early detection (within first 5 days) and provides specific diagnosis of dengue infection without the requirement of paired sera. The method using simple equipment and large number of samples can be processed at a time. Its cost-effectiveness in comparison to the cell culture and molecular methods makes it the test of choice in resource poor settings. At the authors' center, both MAC-ELISA and NS1 assay are used on a single serum sample to improve the diagnostic algorithm for dengue infection.

### **Treatment**

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Management of dengue infections is mainly symptomatic and with antipyretics (aspirin should be avoided to avert development of Reye syndrome) and fluid resuscitation is the mainstay of treatment. Intensive supportive care of patients with suspected DHF-DSS is lifesaving. Blood component transfusions, especially platelets, are used only for risk of bleeding rather than a certain level of thrombocytopenia.

Prevention by way of use of mosquito nets and repellents is effective. Mosquito breeding sites can be eliminated by avoiding stagnant water bodies. Other antimosquito measures are discussed later.

## **CHIKUNGUNYA FEVER**

### **Introduction**

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Chikungunya fever (CHIKF) is a viral illness caused by an RNA virus that belongs to the *Alphavirus* genus in the family *Togaviridae* and is transmitted by the *Aedes* mosquitoes. The name is derived from the Makonde dialect, which means, *that which bends up*, referring to the posture of an affected patient acquired due to excruciating pain in the joints. Chikungunya virus (CHIKV) is geographically distributed in Africa, Southeast

Asia, and India.<sup>81</sup> CHIKV is believed to have originated in Africa where it is maintained in nature by a sylvatic cycle involving wild primates and forest-dwelling mosquitoes, such as *A furcifer*, *A luteocephalus*, or *A taylori*. It was subsequently introduced in Asia where it is transmitted from human to human mainly by *A aegypti* and, to a lesser extent, by *A albopictus* through an urban transmission cycle.<sup>81</sup> CHIKV has been divided into 3 genotypes based on phylogenetic studies. These genotypes, based on the gene sequences of an envelope protein (E1), are Asian, East/Central/South African, and West African.<sup>82–84</sup> Unlike DF, CHIKF results in greater and prolonged morbidity than mortality.

### **Epidemiology**

The disease was documented first time in the form of an outbreak in Tanzania.<sup>85</sup> After the initial identification of CHIKV, sporadic outbreaks continued to occur in Central and Southern Africa, but little activity was reported after the mid-1980s.<sup>86</sup> In 2004, however, an outbreak originating on the coast of Kenya subsequently spread for the first time outside the continental Africa to Comoros and La Réunion. From the spring of 2004 to the summer of 2006, an estimated 500,000 had occurred in La Réunion.<sup>87</sup> This rapid spread of this outbreak was attributed to a mutation of alanine at position 226 with valine (E1-A226V) in CHICKV,<sup>88</sup> which enabled an increase in infectivity to a second vector, *A albopictus*, compared with its infectivity of *A aegypti*.<sup>89</sup> *A albopictus* has wider distribution in temperate regions, making it possible for the spread CHIKV to European regions.<sup>86,87,89</sup> In the following 2 years, CHICKV spread to several other Indian Ocean islands and other parts of the world. The epidemic also spread from the Indian Ocean islands to India, where large outbreaks occurred in 2006.<sup>87</sup> The outbreak in India continued into 2010, resulting in millions of cases<sup>90</sup> with new cases appearing in areas that had not been affected early. The persistence of cases of infection in India is presumably attributable to a vast number of immunologically naive people who help sustain viral transmission.<sup>91</sup> The disease is now reported from almost 40 countries from various WHO regions, including Southeast Asia.<sup>92</sup> The first outbreak of CHIKF in Europe was reported from Italy.<sup>93</sup> In 2010, imported cases also were identified in Taiwan, France, and the United States. These cases were due to the infected viremic travelers returning from Indonesia, La Réunion, and India, respectively. Between 2006 and 2010, 106 laboratory-confirmed or probable cases of CHIKV were detected among travelers returning to the United States compared with only 3 cases reported between 1995 and 2005.<sup>87</sup>

### **Clinical Symptoms**

The incubation period for CHIKV after the bite of *Aedes* mosquito is 3 to 7 days (range 1–12 days).<sup>87</sup> Not all individuals infected with virus develop symptoms and it is estimated that 3% to 28% of infections are asymptomatic.<sup>87</sup>

CHIKV can manifest as acute, subacute, or chronic disease.<sup>87</sup> In the acute stage, a case is suspected when a patient presents with acute onset of fever greater than 38.5°C (101.3°F) and severe arthralgia or arthritis not explained by other medical conditions or by a patient who has resided in or visited epidemic or endemic areas within 2 weeks before the onset of symptoms. The fever can be continuous or intermittent; defervescence is not associated with worsening of symptoms,<sup>87</sup> in contrast to dengue infections. The fever typically last from several days up to 2 weeks.<sup>87,92</sup> Shortly after the onset of fever, the majority of infected persons develop severe, often debilitating, and migrating polyarthralgias.<sup>91,92</sup> The joint pains are usually symmetric and occur most commonly in wrists, elbows, fingers, knees, and ankles but can also affect more proximal joints.<sup>91</sup> The joint pain may show saddleback patterns and tends to be worse in the

morning and relieved by mild exercise.<sup>92</sup> Swelling of joints due to tenosynovitis can be seen in some cases. Arthralgias are often incapacitating due to pain, tenderness, swelling, and stiffness.<sup>87</sup> The lower extremity arthralgia can be severely disabling, resulting in a slow, broad-based, halting gait, which can persist for months.<sup>91</sup>

Transient maculopapular rash usually occurs 2 to 5 days after onset of fever in approximately 50% of patients.<sup>87,92</sup> It is typically maculopapular, involving the trunk and extremities but can also include palms, soles, and face.<sup>87</sup> Other skin lesions recognized during recent outbreaks include vesiculobullous lesions with desquamation, aphthous-like ulcers, and vasculitic lesions.<sup>94,95</sup> Common features in patients presenting with CHICKF are given in **Box 4**.

There has also been infrequent documentation of hemorrhagic manifestations, including hematemesis and melena due to CHIKV infection in Southeast Asia, although some of these cases also exhibited concomitant rising titers of dengue antibodies.<sup>96,97</sup> Other infrequent signs and symptoms reported include headache, retro-orbital pain, nausea, vomiting, meningeal syndrome, conjunctivitis, uveitis, retinitis, and acute encephalopathy.<sup>91,92,98</sup> The acute phase of CHIKF usually lasts for 3 to 10 days.<sup>87</sup>

Subacute CHIK disease is most common 2 to 3 months after infection and is characterized by reappearance of distal polyarthritis after improvement and development of transient vascular disorders (such as Raynaud syndrome).<sup>87</sup> In addition to physical symptoms, the majority of patients complain of depressive symptoms, general fatigue, and weakness.<sup>87</sup>

Chronic CHIK disease is persistence of arthralgias for more than 3 months. It may be associated with destructive arthropathy/arthritis resembling rheumatoid or psoriatic arthritis, in some cases.<sup>87</sup> It is estimated that 80% to 93%, 57%, and 47% of patients with CHIKV infection complain of persistent symptoms after 3 months, 15 months, and even 2 years, respectively.<sup>99,100</sup>

Risk factors for protracted disease are older age (>45 years), pre-existing joint disorders, and more severe acute disease.<sup>99,101</sup>

Pregnant women with CHIKV infections do not have different clinical outcomes.<sup>91</sup> During pregnancy CHIKV infections do not seem to result in transmission of the virus to the fetus but in up to 49% of cases vertical transmission can occur if pregnant woman is viremic at the time of delivery.<sup>102</sup> Intrapartum transmission resulting in neonatal complications, including neurologic disease, hemorrhage, and myocardial disease, has been reported.<sup>91</sup>

Clinical and epidemiologic similarities of infection due to CHIKV, DENV, and *Plasmodium* can make the differential diagnosis difficult in a febrile traveler. Few differentiating features may give clinicians an early clue to the possible diagnosis. In chickengunya infection, fever occurs early in the course of the illness and is of shorter duration than with dengue. A terminal maculopapular rash, conjunctival injection, myalgia, and arthralgia or arthritis is seen more often with chikungunya. DF is

#### Box 4

##### Common features seen in CHIKF

###### Common

Fever (76%–100%), polyarthralgia (71%–100%), backache (34%–50%), headache (7%–74%)

###### Infrequent

Rash (28%–77%), stomatitis (25%), oral ulcers (15%), hyperpigmentation (20%), exfoliative dermatitis (5%)



suggested by severe backpain with features of bleeding and plasma leakage like purpura, malena, and shock. Periodicity of fever and alteration of consciousness/seizures should prompt a diagnosis of malaria. Confirmation by laboratory diagnosis is essential to arrive at a specific diagnosis.

### **Diagnosis**

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Infections with CHIKV are diagnosed in the laboratory by virus isolation RT-PCR, and serology.<sup>87,91</sup>

#### **Virus isolation**

Virus isolation being the gold standard, is possible from acute serum specimens ( $\leq 8$  days)<sup>87,91</sup> by inoculating into a susceptible cell line or suckling mouse. CHIKV produces typical cytopathic effects within 3 days after inoculation in a variety of cell lines. The cytopathic effects must be confirmed by CHIKV specific antiserum and the results can take 1 to 2 weeks.<sup>103</sup> Virus isolation must only be performed in biosafety level 3 laboratories to reduce the risk of viral transmission.<sup>87</sup> Virus isolation, although the gold standard, is infrequently used for the diagnosis of CHIKV infection due to time-consuming laborious procedure and risk of laboratory transmission.

#### **RT-PCR**

RT-PCR is currently the most sensitive and rapid method for detecting CHIKV mRNA<sup>87</sup> and, therefore, more commonly used for the diagnosis and confirmation of CHIKV infection. RT-PCR can detect CHIKV from sera within first week of infection.<sup>104,105</sup> Real-time PCR demonstrates high sensitivity of less than 1 plaque-forming unit or 50 genome copies and results can be available from within 1 to 2 days.

#### **Serologic tests**

For serologic diagnosis, an acute-phase serum must be collected immediately after clinical onset and a convalescent-phase sera after 10 to 14 days after the onset of the disease. Serologic diagnosis can be made by demonstration of a 4-fold increase in CHIK IgG antibody in acute and convalescent sera. Getting paired sera is, however, usually not practical. Alternatively, the demonstration of IgM antibodies (MAC-ELISA) specific for CHIKV in acute-phase sera is used when paired sera cannot be obtained. Results of MAC-ELISA can be available within 2 to 3 days. Cross-reaction with other flavivirus antibodies, such as o'nyong-nyong and Semliki Forest, occurs in the MAC-ELISA; however, the latter viruses are rare in Southeast Asia but if further confirmation is required, it can be done by neutralization tests and hemagglutination inhibition assay.<sup>103</sup>

### **Treatment**

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There is no specific antiviral therapy available for CHIKV and treatment is mostly supportive, bed rest, fluids, and symptomatic treatment of fever and pain.<sup>87,92</sup> Paracetamol is the drug of choice with use of other analgesics, if paracetamol does not provide relief. Aspirin is preferably avoided for fear of gastrointestinal and other side effects, such as Reye syndrome. Nonsteroidal anti-inflammatory drugs, narcotics (eg, morphine) or short-term corticosteroids may be tried for recalcitrant pains, after evaluating the risk-benefit of these treatments.

### **Prevention**

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Because currently there is no vaccine available for CHIKV, protection against the mosquito remains the best way to prevent infection. The best way to control mosquito-borne disease is an integrated approach that includes antilarval and

antiadult methods and protection against mosquito bites. In antilarval methods, source reduction where the mosquitoes lay eggs should be eliminated, such as flower vases, discarded tires, and water storage tanks for air coolers. Chemical larvicides include use of fenthion, chlorpyrifos, whereas biologic larvicides, such as *Gambusia affinis* fish, can be used in stagnant ponds or sewage oxidation ponds. Antiadult measures include spraying or fogging of insecticides, such as Pyrethrum, or residual spray, such as DDT, Lindane, and Malathion. Protection against mosquito bites includes use of mosquito nets, mosquito repellent, such as DEET and adequate body covering by light clothing. Individuals acutely infected with CHIKV can also contribute to the spread of the disease through infected vectors<sup>87</sup>; therefore, they are also advised to take mosquito protection measures.

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