

# Mosquito-borne Diseases

Michael A. Tolle, MD, MPH

Despite centuries of control efforts, mosquito-borne diseases are flourishing worldwide. With a disproportionate effect on children and adolescents, these conditions are responsible for substantial global morbidity and mortality. Malaria kills more than 1 million children annually, chiefly in sub-Saharan Africa. Dengue virus has expanded its range over the past several decades, following its principal vector, *Aedes aegypti*, back into regions from which it was eliminated in the mid-20th century and causing widespread epidemics of hemorrhagic fever. West Nile virus has become endemic throughout the Americas in the past 10 years, while chikungunya virus has emerged in the Indian Ocean basin and

mainland Asia to affect millions. Japanese encephalitis virus, too, has expanded its range in the Indian subcontinent and Australasia, mainly affecting young children. Filariasis, on the other hand, is on the retreat, the subject of a global eradication campaign. Efforts to limit the effect of mosquito-borne diseases in endemic areas face the twin challenges of controlling mosquito populations and delivering effective public health interventions. Travelers to areas endemic for mosquito-borne diseases require special advice on mosquito avoidance, immunizations, and malaria prophylaxis.

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"It is now agreed that there was no malaria in the Land of Saturn so long as the volcanoes in the Alban hills were active, because their gases purified the air and kept down the mosquitoes . . . ."

Fairfax Harrison, 1913.

[Footnote to translation of *Rerum rusticarum libri III* (Marcus Terentius Varro, 116 BC-27 BC)].

**S**ince ancient times, mosquitoes have been appreciated as the source of various ailments afflicting humans. Julius Caesar had the swamps around Rome drained in an attempt to control "Roman fever" (malaria), one of the early attempts, repeated throughout history, to control this determined scourge of mankind.<sup>1</sup> Over time, these attempts have met with variable success and continue to this day. Far from being controlled, in many regions of the world mosquito-borne diseases are flourishing, responsible for significant global morbidity and mortality, and disproportionately affecting children and adolescents.<sup>2-7</sup>

From the Department of Pediatrics, Baylor College of Medicine, Baylor International Pediatric AIDS Initiative, Houston, TX.

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Malaria, in particular, continues to impart a major disease burden on infants and young children in endemic regions.<sup>4,8-11</sup> There are 350 to 500 million cases of malaria annually, with at least 1 million deaths,<sup>11</sup> and 90% of mortality attributed to malaria is experienced by infants and young children, the vast majority in sub-Saharan Africa.<sup>11</sup> Vectored chiefly by *Ae. (Stegomyia) aegypti*, a species of mosquito that thrives in the human-modified peri-urban habitats of the developing tropical world, dengue virus has expanded its range considerably in recent years and is responsible for 50 to 100 million infections annually, with thousands of deaths, mostly from its severe form, dengue hemorrhagic fever.<sup>12</sup> As with malaria, most of its burden is borne by infants and children.<sup>6</sup> In the past decade, West Nile virus has emerged in the Americas, becoming endemic throughout the region<sup>13</sup>; chikungunya, a formerly obscure arbovirus endemic to East Africa, has emerged to cause millions of cases in the Indian Ocean basin and mainland south and southeast Asia<sup>14</sup>; and Japanese encephalitis virus has expanded its range in the Indian subcontinent and Australasia,<sup>15</sup> where it chiefly affects children less than age 10.<sup>16</sup> Due to coordinated control strategies, filariasis, a parasitic disease causing elephantiasis, has become less common and is the subject of a global eradication campaign directed by the World Health Organization (WHO).<sup>17</sup>

The objectives of this review are to consider the current state of these major mosquito-borne illnesses from a global perspective, with an emphasis on public health considerations and these diseases' impact on pediatric populations; to discuss the current state of mosquito control strategies; and to review aspects of travel medicine pertinent to mosquito-borne diseases.

## Mosquito Entomology

Comprising approximately 3500 species, mosquitoes are found beyond the tropical and subtropical regions of the world with which they are classically associated.<sup>1</sup> Particularly true for the chief genera which vector human disease-causing pathogens—*Anopheles* (malaria, filariasis), *Aedes* (yellow fever, dengue, chikungunya), and *Culex* (West Nile, Japanese encephalitis, filariasis)—mosquitoes are distributed globally, even in the Arctic.<sup>18</sup> Yet only a small fraction of the mosquito species on earth vector disease to humans.<sup>1</sup>

Most female mosquitoes take blood meals from vertebrates to obtain the necessary nutrition to produce their eggs,<sup>1,18</sup> injecting saliva (which may contain pathogens) into the host animal. While many mosquitoes are distinctly selective feeders, restricted to one or a few closely related species, some feed in a less restrictive manner, varying between mammals, birds, and reptiles.<sup>1</sup> Those which regularly feed on humans, and in which pathogens can complete an obligatory life cycle phase and multiply in the mosquito's salivary glands, can be important vectors of human diseases.<sup>18</sup>

Mosquitoes breed in water, occasionally depositing eggs directly on water, but generally using a variety of moist surfaces, tree holes, and containers.<sup>18</sup> Human activities, such as the production of a large amount of environmental debris that holds water pools (including disposable bottles and cans and discarded tires) and storage of water on or around living premises when reliable piped home water supplies are unavailable or unreliable, may markedly increase available mosquito-breeding sites and have been particularly implicated, as mentioned above, in the marked dissemination of *Ae. aegypti* (along with the dengue cases it very efficiently vectors) throughout most of the tropical world—including to areas from which both had been eradicated.<sup>19</sup>

Development time for larvae depends on specific environmental conditions (temperature, nutrient supply, degree of available light), with most tropical

mosquito larvae developing in approximately 1 week, while the larvae of many species endemic to temperate zones may overwinter.<sup>18</sup> The larval stage of mosquito development is a key target for many mosquito-control strategies, including larvicides, introduction of larval predators, and breeding habitat elimination, as is described in detail below.

### Vectorial Capacity

Once developed into adult mosquitoes, the ability of a mosquito species to vector human disease is influenced by several factors and is classically expressed by the concept of *vectorial capacity* (*C*)—a measure of transmission risk, the daily rate of future inoculations of humans arising from a currently infective human case (say, of malaria).<sup>1,3</sup> In the equation for vectorial capacity,  $C = ma^2p^n/\log_e p$ , where *m* is the mosquito density per human, *a* is the average number of bites per day for each mosquito, *p* is the probability of a mosquito surviving a given single day, *e* is the life expectancy of the female mosquito, and *n* is the extrinsic incubation period—the time the pathogen takes to develop in the mosquito before the mosquito becoming infective.<sup>1</sup>

Clearly, these variables, and thus transmission risk, are greatly affected by various and different factors.<sup>20</sup> Inversely related to temperature, *n* is tightly coupled to climactic conditions: *a* tends to be an intrinsic factor particular to each mosquito species (such as *Aedes albopictus* (chikungunya, dengue) being a typically aggressive feeder, or *Ae. aegypti* favoring humans as a food source), whereas human activities that promote or eliminate breeding sites can significantly modify *m*.<sup>1,3</sup>

## Malaria

While malaria can be transmitted by sharing of contaminated needles, organ transplantation, and blood transfusions, almost all malaria is transmitted by the bite of the female *Anopheles* mosquito.<sup>2</sup> Malaria is a protozoal infection of red blood cells and ranks as the most significant parasitic disease affecting humans.<sup>2</sup> Of the 172 known *Plasmodium* species, the vast majority typically are only capable of infecting birds, reptiles, and nonhuman mammals.<sup>21</sup> Four *Plasmodium* species (*falciparum*, *vivax*, *ovale*, *malariae*)

are known to commonly infect humans and cause clinical disease. Except for the recently described *Plasmodium knowlesi*<sup>22</sup> (discussed below), infections with other “nonhuman” *Plasmodium* are considered very rare.<sup>2</sup> The overwhelming majority of malaria infections worldwide are caused by *P. falciparum* and *P. vivax*,<sup>21</sup> with transmission taking place year-round in tropical, lowland endemic areas, and seasonal transmission taking place in more temperate zones or areas of higher altitude.<sup>2,23</sup>

Before the 20th century, malaria was found throughout most of the nonpolar world, including North America and northern Europe.<sup>1</sup> It has since been eradicated from most of the world outside the tropics, and malaria incidence in subtropical regions such as Mexico, the Middle East, North Africa, and China has been greatly reduced.<sup>1</sup> In much of the tropics, however, malaria remains a significant clinical problem, particularly in holoendemic regions of sub-Saharan Africa, where transmission is intense, and malaria is a major contributor to overall infant and child mortality.<sup>2,8,21,22,24,25</sup>

Malaria transmission has traditionally been considered restricted to certain temperature ranges (below 16°C, parasite development within the mosquito cannot take place<sup>1,2</sup>) and altitudes below 2000 m<sup>2</sup>. However, malaria distribution may be changing as a result of global climate change, with increased average temperatures in the East African highlands being cited as a possible explanation for the return of malaria transmission to highland areas >2000 m in recent years.<sup>23</sup>

*P. falciparum* causes the overwhelming majority of severe malaria cases and thus is the chief contributor to global malaria morbidity and mortality—a disease burden focused on infants and young children in hyper- and holoendemic regions where *P. falciparum* predominates, chiefly in sub-Saharan Africa where the vast majority of annual malaria deaths occur.<sup>8</sup> *P. vivax* (uncommon in sub-Saharan Africa and more common in south and southeast Asia, Oceania, and Central and South America) and *P. ovale* (most common in West Africa, rare beyond) have the ability to form a dormant hepatic form known as a hypnozoite that may cause disease, presenting months to years after initial infection.<sup>24</sup> *P. malariae* is a relatively rare form of malaria, responsible for perhaps 1% of cases worldwide, less common outside of Africa, and classically associated with a more mild course than, particularly, *P. falciparum*.<sup>24</sup> *P. knowlesi* is a malaria parasite of Old World primates<sup>22</sup> and human infection was thought to be rare

until recently, when a large series of human cases of *P. knowlesi* malaria were reported from Malaysian Borneo.<sup>22</sup> These cases had generally been originally misidentified as *P. malariae*, from which *P. knowlesi* is very difficult to differentiate microscopically.<sup>22</sup> Unlike *P. malariae*, *P. knowlesi* has been observed to commonly be life-threatening yet appears to be restricted to the range of its primary host, the long-tailed pig macaque, with most cases to date having been reported from Malaysia, Thailand, and Burma.<sup>22</sup>

### *Plasmodium Life Cycle*

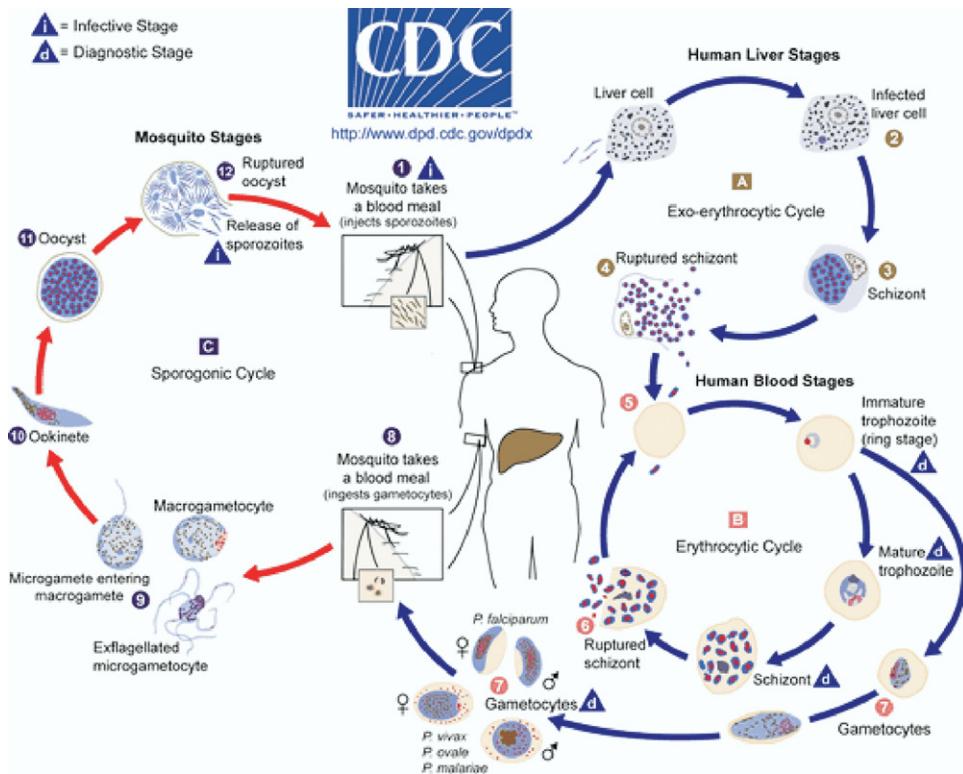
The life cycle of *Plasmodium* species can be seen in Figure 1. *Plasmodium* have both human and mosquito cycles.

Human infection with malaria is initiated when the female *Anopheles* injects into the human host saliva containing plasmodial sporozoites during feeding. Sporozoites enter the circulation and rapidly either enter hepatocytes or are cleared. Within hepatocytes, sporozoites reproduce asexually (known as schizony, forming hepatic schizonts). This stage is asymptomatic, reflects the primary incubation period, and lasts on average from 5 to 6 days for *P. falciparum* to 10 to 14 days for *P. vivax* to occasionally much longer (approximately 1 month, on average, for *P. malariae*).<sup>2</sup> At the completion of this stage, hepatic schizonts rupture and release plasmodial merozoites into the circulation. *P. vivax* and *P. ovale* hypnozoites may remain dormant for prolonged periods of time.<sup>2</sup> When these leave dormancy and enter schizony, they may cause the characteristic relapses associated with these plasmodial forms.<sup>2</sup>

A proportion of merozoites released into the circulation develop into male and female gametocytes. When taken up by female *Anopheles* in a blood meal, gametocytes develop into microgametes in the mosquito stomach, fuse to form a zygote, ultimately penetrating the mosquito stomach to form an oocyst. Within the oocyst, motile sporozoites develop, ultimately bursting the oocyst and migrating to the salivary glands, from which they will be injected into the next host at the mosquito’s next blood meal.<sup>2</sup>

### *Species-specific Virulence*

*P. falciparum*’s increased virulence as compared with other malarial forms is due to particular characteristics that differ from *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* produces many more merozoites per hepatocyte than other *Plasmodium* species, and, unlike *P. vivax* and *P. ovale*, which generally only



**FIG 1.** Life cycle of *Plasmodium*. (Reproduced with permission of the U.S. Centers for Disease Control (CDC-DPDx).) (Color version of figure is available online.)

invade reticulocytes, *P. falciparum* can invade red blood cells (RBCs) of all ages, rapidly increasing its systemic burden.<sup>2</sup> *P. falciparum* also produces a specific protein, *Plasmodium falciparum* erythrocyte membrane protein 1, which is associated with morphological changes in the RBC that promote cytoadherence to microvascular endothelium—a process responsible for the phenomenon of sequestration.<sup>2</sup> When *P. falciparum*-parasitized RBCs sequester from the circulation in the microvascular beds of vital organs, vital organ dysfunction takes place, reflected in the severe pathophysiology and clinical symptoms seen in falciparum malaria.<sup>2</sup>

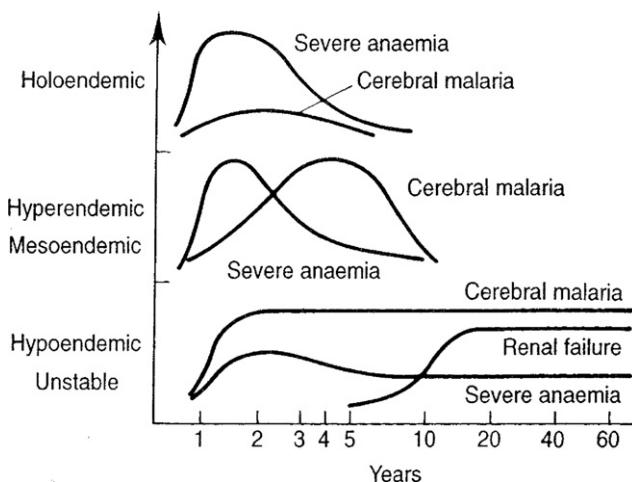
*P. falciparum* is not alone among *Plasmodium* species in exhibiting virulent features.<sup>22</sup> *P. knowlesi* has been observed to have the shortest erythrocytic cycle (24 hours, as compared with 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale*, and 72 hours for *P. malariae*) of all known human and nonhuman primate malarias, leading to potentially rapid increases in parasite load, with attendant risk of severe morbidity and mortality.<sup>22</sup>

## Clinical Epidemiology

Malaria endemicity varies widely on a global basis. Classically, endemicity is defined by the rate of enlarged spleens (or parasite rates on blood smears) in children between 2 and 9 years: hypoendemic: spleen rate or parasite rate 0 to 10%; mesoendemic: spleen or parasite rate 10 to 50%; hyperendemic: spleen or parasite rate 50 to 75%, adult spleen rate high; holoendemic: spleen or parasite rate over 75%, adult spleen rate low, parasite rates in infants (<1 year) high.<sup>2</sup>

Most of tropical Africa is either holoendemic or hyperendemic for *P. falciparum*, and people experience repeated infections throughout their lifetimes, with appreciable morbidity and mortality during childhood.<sup>2,3</sup> In holoendemic areas, the main clinical impact of *P. falciparum* is severe anemia in children ages 1 to 3; severe malaria is relatively infrequent in infants and older children, and cerebral malaria in children is rare.<sup>2,3</sup>

As malaria transmission becomes more variable or less intense, severe malaria may affect older children, and cerebral malaria becomes more common.<sup>2</sup> If children survive to older ages, immunity develops that



**FIG 2.** Relationship between malaria endemicity and clinical presentation in infants and children. (Reproduced with permission from White.<sup>2</sup>)

may control subsequent infections. Severe malaria is rare in adults; indeed, most adult infections are asymptomatic.<sup>2</sup> Where malaria transmission is low or strictly seasonal, early childhood immunity does not develop; symptomatic infection may occur at any age, and cerebral malaria becomes more common.<sup>1-3</sup> Figure 2 summarizes the relationship between malaria endemicity and clinical presentation in infants and children.

Nonimmune individuals (ie, travelers from developed countries) who contract malaria typically become quite ill.<sup>24</sup> *P. falciparum* may cause epidemics of severe malaria when nonimmune hosts migrate into a malarious area, such as is not uncommon in refugee movements.<sup>4,8</sup> Pregnancy increases susceptibility to malaria, and placental malaria is associated with poor perinatal outcomes.<sup>3,4,8</sup> Accordingly, intermittent antimalarial therapy in pregnancy is now standard practice in much of sub-Saharan Africa.<sup>25-28</sup>

Untreated, *P. falciparum* malaria is often severe, and cases of malaria imported from the tropics into developed countries where clinicians may be unfamiliar with malaria are frequently diagnosed after considerable delay, or misdiagnosed completely.<sup>24</sup> Malaria prophylaxis reduces the likelihood of contracting malaria but does not eliminate the possibility of contracting it, a subtlety not always appreciated by unfamiliar practitioners.<sup>29-31</sup>

### Clinical Presentation

*Falciparum* malaria typically develops from days to weeks after exposure, while *P. vivax* and *P. ovale* may develop significantly later, due to their ability to form

hepatic hypnozoites.<sup>24</sup> *P. malariae* has a long incubation period (mean, 30 days) and may have an indolent presentation, as well as exist chronically for years in some patients as an asymptomatic commensal organism.<sup>24</sup> *P. knowlesi* may present within several days of exposure but is geographically restricted.<sup>22</sup>

A history of having taken chemoprophylaxis for malaria does not rule out the development of malaria; malaria should always be considered and the diagnosis thoroughly explored in children and adolescents who have traveled in endemic regions within a year of onset of symptoms.<sup>24,32</sup> The diagnosis in this population may be more difficult, as symptoms may be less intense and blood smears for malaria more likely to be falsely negative.<sup>5</sup> As mentioned above, infants in holoendemic zones typically present with anemia, and severe malaria in children is more common outside holoendemic zones.<sup>2,8,24</sup>

Children and adolescents with malaria typically present with fever and may experience rigors, headache, muscle aches, nausea and vomiting, and considerable fatigue.<sup>24</sup> When malaria is not suspected, these symptoms may be mistaken for a nonspecific viral illness or other benign process.<sup>24</sup> Except with *P. falciparum*, rapid deterioration is uncommon.<sup>8,24</sup> Partially immune children may present with anemia, hepatosplenomegaly, or jaundice and may demonstrate parasitemia in the absence of symptoms; when symptomatic, their presentation may be considerably less dramatic than that of nonimmune children.<sup>24</sup>

Nonspecific laboratory abnormalities are common with malaria, including elevated liver enzymes, thrombocytopenia, and neutropenia. Hyponatremia and hypoglycemia, when present, are associated with a more severe clinical course.<sup>24</sup>

### Clinical Presentation of Severe Malaria

While nonfalciparum *Plasmodium* have traditionally been associated with nonsevere presentations, *P. vivax* and *P. knowlesi* may be associated with severe disease, including fatal outcome.<sup>3,22</sup> Recent work from Papua New Guinea shows similar rates of severe malaria associated with *P. vivax* and *P. falciparum*, with severe anemia and respiratory distress both seen commonly in severe *P. vivax* presentations.<sup>33,34</sup>

Yet, globally, the overwhelming majority of severe malaria cases are due to *P. falciparum*, for reasons discussed above.<sup>32</sup> Early symptoms include irritability, headache, and confusion.<sup>24</sup> In nonimmune children and adolescents, deterioration may be rapid.<sup>8,24,32</sup>

Seizures are common.<sup>8,24</sup> Particularly severe manifestations include decorticate or decerebrate posturing, nystagmus, and disconjugate gaze.<sup>8,24</sup> Cerebrospinal fluid (CSF) findings and neuroimaging studies typically give nonspecific findings, and it is important to exclude other serious causes of neurologic decompensation.<sup>24</sup>

In African and Thai children, cerebral malaria has been noted to be frequently accompanied by retinal findings, such as papilledema and retinal hemorrhage.<sup>35</sup> Such “malarial retinopathy” has been closely associated with cerebral malaria<sup>35,36</sup> and may help discriminate cerebral malaria from other similar severe neurological presentations,<sup>36</sup> particularly in endemic zones where asymptomatic parasitemia is common and its presence may be incidental to the true nature of the child’s illness.<sup>37</sup>

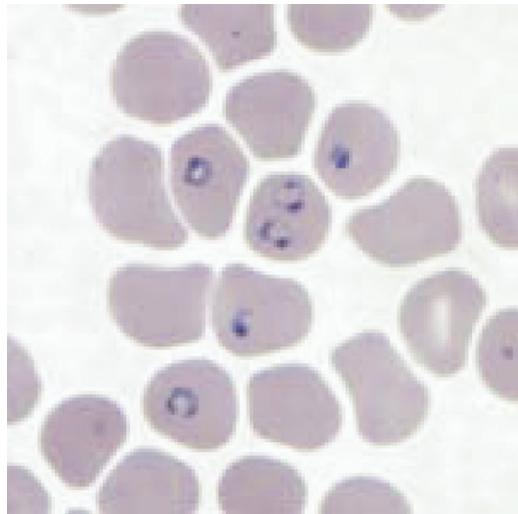
Other significant manifestations of severe malaria in children include hypoglycemia and respiratory distress.<sup>4,8,24</sup> *Plasmodium* suppress hepatic gluconeogenesis and induce insulin secretion from pancreatic islet cells; quinine, commonly used for severe malaria, may further increase insulin secretion, dramatically worsening hypoglycemia, and causing severe neurological damage.<sup>24</sup> In children, malaria-associated respiratory distress is generally due to severe acidosis.<sup>8,24</sup> Renal complications and shock related to malaria are uncommon in children.<sup>24</sup>

### Diagnosis

The proper management of malaria depends on the diagnosis being swift and reliable. In many malaria-endemic areas where diagnostics may be less available, clinical diagnosis of malaria is commonly employed.<sup>24,38,39</sup> This is frequently inaccurate, resulting in both an overdiagnosis of malaria, with concomitant inappropriate use of antimalarial drugs,<sup>38,40</sup> and a failure to diagnose and treat other life-threatening febrile illnesses.<sup>39</sup>

In returned travelers, appreciation of the risk of malaria based on travel history is of great importance.<sup>32</sup> As mentioned above, malaria should be considered in all children and adolescents who in the year before development of symptoms have traveled to a malaria-endemic region, regardless of a history of having taken malaria prophylaxis.<sup>32</sup> While *P. falciparum* generally has an incubation period of 10 to 20 days, incubation periods as short as 7 days have been reported.<sup>32</sup>

A variety of diagnostic tests exist for malaria. Historically, malaria has been diagnosed with blood



**FIG 3.** *P. falciparum* trophozoites in thin blood smears. (Courtesy of CDC-DPDx.) (Color version of figure is available online.)

smears; a minimum of three sets must be performed before malaria can be tentatively ruled out in an individual with a history of possible malaria exposure and clinical signs and symptoms potentially consistent with the disease.<sup>24</sup> Thick blood smears evaluate the presence or absence of parasites, while the particular *Plasmodium* species and its quantification may be determined on thin smears<sup>2</sup> (Fig 3); parasitemias of >5% of visible red blood cells are associated with severe malaria.<sup>4,8,32</sup> Blood smears may be more or less sensitive and/or specific depending on several factors, including the quality of smear preparation and the experience of the individual interpreting the smear.<sup>24</sup> Correct speciation may demand particular expertise<sup>32,41</sup>; with treatment and prognosis differing significantly in most locales between falciparum and nonfalciparum malaria,<sup>24,32</sup> misdiagnosis of *P. falciparum* as nonfalciparum can have serious consequences.

In many settings, rapid diagnostic tests (RDTs) based on the detection of species-specific histidine-rich proteins (HRPs) or lactate dehydrogenase exist which will readily both diagnose malaria and differentiate between falciparum and nonfalciparum infections.<sup>42,43</sup> These have been shown to have particular utility in resource-limited and rural settings where microscopy may not be available.<sup>43-45</sup> In field and clinical trials, several of these compared well with blood smear analysis in the detection of *P. falciparum*.<sup>42,43</sup> One recently reported randomized clinical trial demonstrated 95.4% sensitivity and 95.9% specificity in the detection of malaria using RDTs.<sup>43</sup>

Trial results notwithstanding, concerns have been raised about the performance of RDTs in general clinical practice.<sup>40,42,43</sup> In many resource-limited settings, nonclinicians (such as community health workers (CHWs)) are depended on to perform clinical tasks such as the evaluation of febrile children for the possibility of malaria.<sup>44</sup> Simple reliance on manufacturer's instructions included in the rapid test packages has been shown to be insufficient to ensure their proper use by CHWs.<sup>44</sup> However, with the combination of a pictorial "job aid" demonstrating how to properly use rapid malaria tests plus directed training, CHWs are able to demonstrate high performance in the accurate use of RDTs.<sup>44</sup>

RDTs and microscopy both suffer from diminished sensitivity at lower parasitemias,<sup>40</sup> and HRP-II-based RDTs may generate false-positive results when HRP-II persists in the circulation after parasite clearance, as is commonly the case.<sup>42,46</sup> Even more accurate than RDTs are molecular tests such as quantitative nucleic acid sequence-based amplification and polymerase chain reaction (PCR)<sup>45</sup>; detection levels below the accepted lower detection limit for microscopy of 20 parasites/ $\mu\text{L}$  have been noted.<sup>45</sup> Molecular diagnostics may be particularly useful where malaria incidence is low and false-negative microscopy or RDT results are more likely to be accepted as valid.<sup>45</sup> The chief drawback of molecular techniques is their infrastructure and technology requirement, a barrier to implementation in resource-limited settings.

### Malaria Treatment

*P. falciparum* infection in a nonimmune host is a medical emergency; accordingly, malaria cases should be treated without delay, and inpatient evaluation and treatment is recommended in such cases.<sup>24,32,41</sup> Children more than age 6 who have a history of malaria and reside, or have recently resided, in an area hyper- or holoendemic for malaria may be considered semi-immune<sup>24</sup>; they may be managed as outpatients if nontoxic-appearing and in a family context where outpatient evaluation and treatment is feasible.<sup>24</sup> In endemic regions, a substantial proportion of malaria cases are treated in village health centers, or otherwise outside a sophisticated medical environment, and such clear-cut options may be less available<sup>24,38</sup>; hence, in endemic regions, presumptive treatment of the febrile child for malaria is common practice.<sup>24,37,38</sup>

Historically, most malaria of all species were sensitive to drugs such as quinine and chloroquine.<sup>32</sup> Due

to the development of drug resistance, however, chloroquine-resistant *P. falciparum* is found in all malaria endemic regions except Hispaniola, Mexico, Central America west of the Panama Canal, and parts of China and the Middle East.<sup>31,32,41</sup> Multi-drug-resistant *P. falciparum* exists in Southeast Asia, particularly along the Thailand-Burma and Thailand-Cambodian borders, sub-Saharan Africa, and the Amazon and other tropical river basins in South America.<sup>31,32,41</sup> As well, around the globe high rates of *P. falciparum*-resistance to the commonly used combination treatment sulfadoxine-pyrimethamine (SP) have been seen<sup>32,41</sup>; the U.S. Centers for Disease Control and Prevention (CDC) no longer recommends SP as standby treatment for American travelers.<sup>32</sup> Chloroquine-resistant *P. vivax* is being seen with increasing frequency, primarily in Papua New Guinea and Indonesia, and some areas of the Middle East, South, and Southeast Asia have reported rates as high as 25%.<sup>32</sup>

In part due to regional differences in malarial drug resistance, malaria treatment varies by locale around the world. A variety of compounds have antimalarial efficacy and are approved for the treatment of malaria in one locale or another. Most countries, particularly in endemic regions, have specific national guidelines. The WHO has produced Malaria Treatment Guidelines<sup>4</sup> (including specific guidelines for the management of severe malaria<sup>8</sup>), and the U.S. and U.K. guidelines have been recently reviewed.<sup>32,41</sup>

The choice of specific antimalarial therapy depends on several determinations, including the severity of clinical presentation, the malarial species, the degree of parasitemia, the pattern of drug resistance in the area where malaria was contracted, the patient's ability to take oral medications, and the availability of medications.<sup>4,32,41</sup>

Even when malarial tests are negative, children with a history of malaria exposure and signs and symptoms consistent with malaria should be approached as if they have malaria until an alternative diagnosis is made.<sup>24</sup> Consequently, children with a positive malarial smear or other malarial test who are toxic-appearing should be investigated and empirically treated for other potential illness, including blood cultures and broad-spectrum parenteral antibiotics, until other, severe, life-threatening illness, such as Gram-negative sepsis, has been ruled out.<sup>24</sup>

**Treatment of Severe Falciparum Malaria.** Table 1 reviews manifestations of severe malaria.<sup>32</sup> Severe malaria should be treated, when possible, in an inpatient setting, preferably the intensive care unit, with

**TABLE 1.** Manifestations of severe malaria. In a patient with *Plasmodium* parasitemia and no other apparent cause for their symptoms, severe malaria is indicated by the presence of one or more of the following clinical or laboratory features<sup>4</sup>

Clinical manifestation:	Laboratory test:
- Prostration	- Severe anemia
- Impaired consciousness	- Acidosis
- Multiple convulsions	- Renal impairment
- Circulatory collapse	- Disseminated intravascular coagulation
- Respiratory distress (acidotic breathing)	- Hypoglycemia
- Pulmonary edema	- Hyperlactatemia
- Acute respiratory distress syndrome	- Parasitemia >5%
- Abnormal bleeding	
- Jaundice	
- Hemoglobinuria	

Adapted from WHO,<sup>4,8</sup> and Griffith et al.<sup>32</sup>

immediate initiation of effective parenteral treatment.<sup>8,32</sup> In the U.S., the only generally available parenteral drug is quinidine gluconate, given as a loading dose followed by continuous infusion; the loading dose may be omitted if the patient has recently received quinine or mefloquine.<sup>32</sup> Quinidine has the potential to induce fatal cardiac arrhythmias and so should be administered in the intensive care unit setting with telemetry and frequent monitoring of vital signs.<sup>32</sup> Electrolyte disturbances (hypomagnesemia, hypokalemia) and the receipt of other drugs that prolong the QT<sub>c</sub> interval increase the risk of adverse cardiac events with quinidine.<sup>32</sup>

In much of the world, artemisinins are used in the treatment of malaria<sup>4,8,32,41,47</sup>; intravenous and rectal suppository forms exist for use in severe malaria.<sup>8,47</sup> Artemisinins (including artesunate, artemether, dihydroartemisinin, and others) possess rapid action against all erythrocyte forms of plasmodium, including gametocytes, and typically yield brisk clinical improvement.<sup>47</sup> Artesunate has been shown in a large randomized trial in Asia to yield significant survival benefit over parenteral quinine (22% mortality with quinine; 15% with artesunate; 34.7% risk reduction) in the treatment of severe falciparum malaria,<sup>48</sup> and a Cochrane Review of randomized trials comparing intravenous quinine with artesunate (five intravenous artesunate, one intramuscular artesunate) showed a powerful reduction in risk of mortality (RR = 0.62), complications of treatment (hypoglycemia), and time to parasite clearance with artesunate over quinine.<sup>49</sup>

Previously unavailable in the U.S., since June 2007 intravenous artesunate has been available under an

**TABLE 2.** Poor prognostic features for children with severe malaria

Impaired level of consciousness
Respiratory distress
Hypoglycemia
Jaundice
Severe metabolic acidosis
Persisting lactic acidemia
Anemia (in the presence of impaired consciousness and/or respiratory distress)
• The combination of impaired level of consciousness and respiratory distress is a particularly poor prognostic feature

Adapted from Stauffer and Fischer<sup>24</sup>; Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. N Engl J Med 1995; 332:1399-404; Taylor TE, Borgstein A, Molyneux ME. Acid-base status in paediatric plasmodium falciparum malaria. Q J Med 1993;86:99-109; Krishna S, Waller DW, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. Trans R Soc Trop Med Hyg 1994;88:67-73.

investigational new-drug application that allows the investigational use of intravenous artesunate for the treatment of severe malaria or for uncomplicated malaria when parenteral therapy is required due to inability to take oral medications or parasitemia >5% or other signs of severe malaria are present.<sup>47</sup> Significant toxicity with artemisinins are uncommon and include elevated hepatic (subclinical hepatitis), hematologic effects (hemolysis, neutropenia, anemia), and, in one study, neurotoxicity (hearing loss associated with use of artemether-lumefantrine).<sup>47-50</sup>

For severe malaria, the WHO recommends intravenous artesunate as the treatment of choice in children and adolescents in areas of hypoendemic or unstable malaria.<sup>8</sup> In areas of higher endemicity, WHO feels data in children are limited and recommends artesunate, artemether, or quinine.<sup>8</sup> During pregnancy, WHO recommends either artesunate or quinine during the first trimester, and artesunate as initial therapy during the second and third trimesters.<sup>8</sup>

Mortality in untreated severe malaria may approach 100%.<sup>4</sup> Yet with careful, appropriate management, survival may be greatly enhanced.<sup>4</sup> While specific antimalarial treatment is critical, careful supportive care and management of severe malaria manifestations and complications are very important.<sup>4</sup> Table 2 lists poor prognostic features for children with severe malaria. Table 3 details supportive treatment, including management of dehydration, acidosis, and anemia—common causes of death in children with severe malaria.<sup>24,32</sup> When possible, severe malaria should be managed in concert with an experienced specialist. Additional assistance with suspected or confirmed malaria cases is available through the CDC Malaria Hotline: 770-488-7788.

**TABLE 3.** Adjunctive treatment for children with severe malaria

<b>Manifestation</b>	<b>Management (in addition to appropriate antimalarial treatment having been initiated)</b>
Coma (cerebral malaria)	Exclude other treatable causes of coma, including bacterial meningitis, hypoglycemia, etc. Maintain airway, intubating if necessary Avoid corticosteroids
Convulsions	Maintain airway Prompt treatment with intravenous or rectal diazepam
Hypoglycemia (blood glucose <40 mg/dL)	Correct hypoglycemia Maintain corrected blood glucose with glucose-containing infusion
Severe anemia (hemoglobin <5 g/dL or hematocrit <15%)	Transfuse with screened fresh whole blood
Acute pulmonary edema	Give oxygen and diuretic Stop intravenous fluids If necessary, intubate, add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxemia
Acute renal failure	Exclude prerenal causes Dialysis, if needed
Metabolic acidosis	Exclude or treat hypoglycemia, hypovolemia, and septicemia If severe, add hemofiltration or hemodialysis
Shock	Correct hemodynamic disturbances Suspect septicemia: Take cultures and give parenteral antimicrobials
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma, and platelets, if available) Give Vitamin K injection
Hyperpyrexia	Administer antipyretic drugs Administer other cooling measures, including fanning, sponging, cooling blanket

Adapted from WHO.<sup>4</sup>

While most adjunctive therapies, including the use of corticosteroids, have not been shown to be beneficial in severe malaria,<sup>4</sup> there is considerable interest in such therapies, particularly those that target the reversal of *P. falciparum* sequestration in vital organs.<sup>3</sup> Therapies that prevent the binding of infected cells to the endothelium; that target endothelial cell signaling pathways that promote sequestration; and that affect levels of nitrous oxide—production of which is decreased in children with severe malaria—are all under active ongoing investigation.<sup>3</sup>

### **Treatment of Uncomplicated Falciparum Malaria.**

A variety of approaches exist for the treatment of uncomplicated falciparum malaria (malaria without severe manifestations). These vary by area of malaria acquisition and age of the child. Chloroquine is the treatment of choice only for malaria acquired in chloroquine-sensitive areas; otherwise, the potential for chloroquine-resistance exists.<sup>32</sup> Due to combinations of antimalarials being more effective and less likely to induce drug-resistance than antimalarial monotherapies, the WHO recommends that uncomplicated falciparum malaria be treated with a combination of two or more antimalarials with different mechanisms of action.<sup>4</sup> The risk of developing resistance is a particular concern for the use of oral artemisinin monotherapies<sup>4</sup>; combinations of artemisinin drugs with other antimalarials are known as artemisinin-based combination therapies.<sup>4</sup> U.S. and WHO recommendations for the treatment of uncomplicated falciparum and nonfalciparum malaria are summarized in Table 4.

With respect to the treatment of uncomplicated falciparum malaria, several important points bear mentioning. While atovaquone-proguanil (*Malarone*) has gained in popularity over recent years, and is the current drug-of-choice for presumptive treatment of malaria in travelers,<sup>32</sup> failure of atovaquone-proguanil in the treatment of *P. falciparum* in Africa has been noted, although rarely.<sup>32</sup> Tetracyclines are, of course, not recommended for use in children less than age 8, and, when used, tetracyclines or clindamycin must be used with a more rapid-acting drug such as quinine, and not as monotherapy.<sup>32</sup> Mefloquine resistance is common in many areas of southeast Asia, including the border areas of Thailand with Burma and Cambodia, eastern Burma, the Laos-Burma border, the Burma-China border, and southern Vietnam.<sup>32</sup> Accordingly, mefloquine should not be used for treatment of *P. falciparum* from these areas.<sup>4,32,41</sup> *Coartem* (artemether + lumefantrine), while a common malaria treatment outside of the U.S., should not be used in children younger than age 12.<sup>41</sup>

**Treatment of Nonfalciparum Malaria.** Nonfalciparum malaria is generally uncomplicated. Exceptions exist, particularly in Southeast Asia, where, as previously described, severe malaria due to *P. vivax* or *P. knowlesi* is occasionally seen<sup>22,33,34</sup>; severe nonfalciparum malaria may be managed in a similar fashion to severe falciparum malaria, with admission to hospital, parenteral antimalarials, and close observation for treatment response and the development of complications.<sup>4,8</sup>

**TABLE 4.** Recommendations for the treatment of uncomplicated malaria<sup>a</sup>

<b>U.S. recommendations (for <i>P. falciparum</i>, <i>P. vivax</i>, <i>P. ovale</i>, and <i>P. malariae</i>)</b>	<b>WHO recommendations</b>
<i>P. falciparum</i> or species not yet identified	
Acquired in chloroquine-sensitive area:	The treatment of choice for uncomplicated malaria due to <i>P. falciparum</i> is a combination of two or more antimalarials with different mechanisms of action
- Chloroquine <sup>b</sup>	- Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated malaria due to <i>P. falciparum</i>
- Second-line treatment: Hydroxychloroquine <sup>b</sup>	- The following ACTs are currently recommended:
Acquired in chloroquine-resistant area:	-Artemether-lumefantrine (Co-artem) -Artesunate plus amodiaquine -Artesunate plus mefloquine -Artesunate plus sulfadoxine-pyrimethamine
- Oral quinine plus: Tetracycline <sup>c</sup> or Doxycycline <sup>c</sup> or Clindamycin; or Atovaquone-Proguanil; or Mefloquine (if the above not available)	The choice of ACT in a country or region will depend on the degree of resistance to the nonartemisinin drug in the combination:
For either:	In areas of multi-drug-resistance, such as Southeast Asia: Artesunate plus mefloquine Artemether-lumefantrine
- Admit to hospital	In Africa: Artemether-lumefantrine Artesunate plus amodiaquine Artesunate plus sulfadoxine-pyrimethamine
- Daily monitoring of symptoms	The artemisinin derivative components of the combination must be given for a minimum of 3 days for optimal effect
- Daily repeat of blood smears until smears negative, or if discharged prior to negative smear, repeat smear at Day 7 of therapy	- Artemether-lumefantrine (Co-artem) should be used with a six-dose regimen <sup>c</sup> - Amodiaquine plus sulfadoxine-pyrimethamine (SP) may be considered as an option in situations where ACTs are not available
<i>P. vivax</i> or <i>P. ovale</i> acquired outside Papua New Guinea or Indonesia	Therapy for chloroquine-sensitive <i>P. vivax</i> similar to U.S. recommendations:
Chloroquine <sup>b</sup> (second-line treatment: Hydroxychloroquine <sup>b</sup> )	Chloroquine followed by Primaquine (if not severely G6PD-deficient) Also may use Amodiaquine, and, where ACT adopted for first-line treatment for <i>P. falciparum</i> malaria, it may be used for <i>P. vivax</i> , followed by Primaquine
If not G6PD-deficient, anti-relapse therapy with Primaquine	<i>P. ovale</i> may be treated with Chloroquine, followed by Primaquine
If G6PD-deficient, avoid Primaquine and advise regarding possible recurrence	
<i>P. vivax</i> acquired in Papua New Guinea or Indonesia	Evidence that the following options may be effective against Chloroquine-resistant <i>P. vivax</i> :
Atovaquone-proguanil	-Amodiaquine -Mefloquine plus Quinine -Artemisinin derivatives expected to be highly effective
Alternatives: Quinine plus Tetracycline <sup>c</sup> or Doxycycline <sup>c</sup> or Mefloquine	
If not G6PD-deficient, anti-relapse therapy with Primaquine	
If G6PD-deficient, avoid Primaquine and advise regarding possible recurrence	
<i>P. malariae</i>	Chloroquine
Chloroquine <sup>b</sup> (second-line treatment: Hydroxychloroquine <sup>b</sup> )	

Adapted from WHO,<sup>4</sup> and Griffith et al.<sup>32</sup><sup>a</sup>Details of specific doses and durations of therapy available at [http://www.cdc.gov/malaria/features/updated\\_treatment\\_guidelines.htm](http://www.cdc.gov/malaria/features/updated_treatment_guidelines.htm) and <http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf>, respectively.<sup>b</sup>If chloroquine or hydroxychloroquine cannot be used, may use options for chloroquine-resistant *P. falciparum*.<sup>c</sup>Contraindicated in children younger than 8 years of age and in pregnant women.

Uncomplicated nonfalciparum malaria is generally managed with chloroquine.<sup>32,41</sup> As previously mentioned, chloroquine-resistant *P. vivax* is seen with increasing frequency in Papua New Guinea and parts of Indonesia.<sup>32</sup> Treatment options for chloroquine-resistant *P. Vivax* include atovaquone-proguanil, mefloquine, or quinine plus tetracycline or doxycycline, with atovaquone-proguanil generally preferred.<sup>32</sup>

Quinine plus clindamycin does not have data supporting its use for initial treatment of *P. vivax*, yet high-dose (2.5 mg/kg base over 3 days) primaquine has demonstrated 85% efficacy against chloroquine-resistant *P. vivax*.<sup>32</sup>

It is important to deliver “terminal prophylaxis” with primaquine after the treatment of *P. vivax* or *P. ovale* infection, as both of these plasmodial species have the

potential to form relapse-associated hypnozoites.<sup>2,24,32</sup> CDC advises 0.5 mg/kg of primaquine base daily, to a maximum of 30 mg daily, for a period of 14 days for terminal prophylaxis, including for patients who have taken atovaquone-proguanil for malaria prophylaxis<sup>32</sup>; while active against liver-stage parasites (ie, “causal”), atovaquone-proguanil does not eradicate hypnozoites.<sup>32</sup> As primaquine may cause severe intravascular hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, G6PD deficiency must be screened for before the use of primaquine.<sup>32</sup>

## Malaria Prevention

The approach to malaria prevention varies by setting. In endemic, resource-limited areas, priority has been given to broad public health approaches, including the use of insecticide-treated bed nets (ITNs) and curtains, intermittent preventative therapy (IPT), and vector control along with prompt case detection and treatment, while for travelers from nonendemic areas who visit malarial regions, personal protective approaches including avoidance of mosquito bites and use of chemoprophylaxis are generally employed. Malaria vaccines hold great interest, with substantial advances having been realized in the last few years. As well, *Anopheles* control plays an important role in malaria prevention.

**Insecticide-treated Bed Nets (ITNs).** ITNs are made by treating bed netting with pyrethroid insecticides that have very low human toxicity and persistent residual activity against mosquitoes.<sup>51</sup> The ITN functions as a “baited trap,” where mosquitoes are attracted to the individual sleeping under the net and killed.<sup>51</sup> ITNs, therefore, have both a personal and a community protective effect and exert a level of control on adult *Anopheles* populations where they are used at high uptake.<sup>51,52</sup>

In sub-Saharan African regions with stable malaria transmission, use of an ITN has been shown to reduce malaria incidence, morbidity, and mortality in both children and adults.<sup>53</sup> ITNs have been identified as a priority intervention in the promotion of child survival, with estimates that the lives of more than 600,000 children less than age 5 could be saved annually were ITNs to achieve 80% usage in high burden settings.<sup>9</sup> Accordingly, ITNs have a prominent role in organized efforts to control malaria, including major campaigns such as Roll Back Malaria (RBM).<sup>51</sup>

Routine availability of ITNs through clinics as well as local and regional mass distribution campaigns increase rates of ITN coverage, as do health care provider and counselor recommendation and reinforcement that fam-

ilies use available ITNs.<sup>54</sup> In Kenya, where ITNs are chiefly distributed (either free or at low subsidized rates) to women and children under age 5, ITN coverage for children less than age 5 has increased from 7% in 2004 to 67% in 2006<sup>10</sup>; this improved level of ITN coverage has been associated with a 44% reduction in child malaria deaths.<sup>10</sup> Reasons for nonuse vary but in some areas include diversion to economic uses such as fishing and drying fish.<sup>55</sup>

ITNs are also associated with a reduction of malaria in pregnancy<sup>56</sup> that yields important benefits for both mother and infant.<sup>56,57</sup>

**Malaria Control in Pregnancy.** Pregnancy increases a woman’s susceptibility to malaria.<sup>56</sup> As a result of complications including stillbirth, intrauterine growth restriction, and preterm birth, up to 200,000 infant deaths annually are caused by malaria (chiefly *P. falciparum*) associated with pregnancy.<sup>57</sup> As compared with noninfection, active placental infection with *P. falciparum* at delivery is associated with low birth weight and with a twofold greater risk of malaria during the first 30 months of a child’s life.<sup>57</sup> Human immunodeficiency virus (HIV)-infected mothers have higher malarial parasite densities and rates of perinatal complications than HIV-uninfected women.<sup>58</sup> As well, HIV-infected mothers have higher rates of placental malaria,<sup>58</sup> which carries a significantly increased risk of mother-to-child HIV transmission.<sup>59</sup> Maternal morbidity from pregnancy-associated malaria is chiefly due to severe anemia.<sup>57</sup>

For areas of stable malaria transmission, the WHO recommends a three-part approach to malaria control in pregnancy, including case detection and treatment, ITNs, and intermittent preventive treatment (intermittent preventive treatment during pregnancy—IPTp).<sup>56</sup> As mentioned above, in Africa, use of ITNs as compared with nonuse of bed nets is associated with significant increases in mean birth weight and reductions in miscarriages and stillbirths in the first few pregnancies (as malaria-specific immunity is developing) and reduced placental parasitemia in all pregnancies.<sup>56</sup> In Thailand, use of ITNs, as compared with the use of untreated nets, is associated with reductions in anemia and fetal loss in all pregnancies, but not with reductions in clinical malaria or low birth weight.<sup>56</sup>

IPT involves the administration of a complete therapeutic course of an antimalarial treatment at set times to members of an at-risk population; in this respect, it differs from chemoprophylaxis. For areas of medium or high malaria transmission, WHO recommends IPTp with SP on at least two occasions after the first

trimester.<sup>25</sup> In Africa, SP is the most commonly used pharmaceutical for IPTp.<sup>60</sup> A two-dose SP regimen given at the beginning of the second and third trimesters in Malawi was associated with a 70% reduction in placental malaria as compared with chloroquine treatment followed by weekly chloroquine prophylaxis for at least 45 days before delivery.<sup>61</sup> IPT with SP has subsequently been shown to be beneficial in reducing the risk of low birth weight and improving maternal hematologic indices,<sup>62</sup> and IPT is generally considered safe (fatal adverse reactions to SP of 0.11/100,000 SP exposures in surveillance data from Malawi<sup>63</sup>).

Based on data from an area of Kenya with high malaria transmission, it has been suggested that for HIV-infected mothers, monthly SP may be superior to the two-dose Malawi regimen.<sup>26</sup> This was recently evaluated in a randomized trial in a mesoendemic region of Zambia. In this trial, monthly SP during pregnancy was not shown more efficacious than the two-dose regimen for the prevention of adverse birth outcomes, placental malaria, or maternal anemia<sup>27</sup>; this difference from the Kenyan data may be due to differences in intensity of malaria transmission between the two areas.<sup>27</sup>

Given the safety, simplicity, and effectiveness of IPTp with SP as a public health measure directed at maternal-child health in malaria-endemic regions, concerns have been raised over the threat posed to the strategy by increasing levels of resistance to SP in Africa and Southeast Asia.<sup>28</sup> While multiple antimalarials, including chloroquine, mefloquine, amodiaquine, proguanil, and atovaquone-proguanil, have been evaluated for use during pregnancy (as both treatment and prophylaxis), there is little information on alternative approaches to IPTp versus SP.<sup>28</sup> IPTp clinical trials comparing SP versus mefloquine, SP alone versus SP plus azithromycin, and SP alone versus SP plus artesunate are currently underway in Benin, Tanzania, and Malawi, respectively.<sup>28</sup>

**IPT for Prevention of Malaria in Children.** Given the substantial toll taken by malaria on African children, and the limited effectiveness and coverage of ITNs, other preventive approaches are required. Population-level antimalarial chemoprophylaxis has been proven effective in reducing malaria morbidity and mortality in children<sup>64</sup> but has been difficult to broadly employ due to obstacles to implementation and concerns regarding the development of drug resistance and impairment of the naturally acquired immunity critical for healthy survival in areas of high malarial burden.<sup>65</sup>

IPT has been shown to have a variety of benefits when administered to children in malarious areas of varying transmission intensity.<sup>62,65-68</sup> In Senegal, where malaria transmission is highly seasonal, IPT with one dose of artesunate plus one dose of SP on three occasions during transmission season has been shown highly effective in the prevention of malaria and to improve child nutritional status.<sup>62,66</sup> SP plus amodiaquine has also been evaluated on the same seasonal schedule in Senegal and shown to be highly effective, while reserving artemisinins (for which development of drug resistance is a concern) for the treatment of acute malaria.<sup>65</sup>

IPT has also proven beneficial for children in areas of high perennial transmission.<sup>67</sup> A trial in Western Kenya evaluated the effect on SP delivered at 4-month intervals as compared with placebo. Children who received IPT with SP had significantly lower levels of anemia and improvements in tests of sustained attention, suggesting IPT could be a valuable addition to school health programs.<sup>67</sup>

When given to infants on the regular routine immunization schedule (an approach known as intermittent preventive treatment for malaria in infants with SP—IPTi-SP) in areas of high malaria transmission, IPT has yielded substantial benefits.<sup>68</sup> An expert committee of the U.S. Institute of Medicine reviewed published trials and unpublished pooled analyses of WHO, UNICEF, and the IPTi Consortium (a group of 17 malaria research organizations) and reports that IPTi-SP decreases the incidence of clinical episodes of malaria by 20 to 30%; that IPTi-SP may decrease infant hospital admissions for both malaria and nonmalaria diagnoses; and that protection against clinical malaria remained substantial for approximately 35 days after the SP dose and suggests that IPTi-SP may be implemented within the routine expanded program of immunization in areas of high malaria burden and low SP resistance.<sup>69</sup>

**Malaria Vaccine.** With estimates of 3 billion persons living in areas at risk for malaria, there is great interest in a malaria vaccine, one of the developing world's most significant medical needs.<sup>70</sup> Increased global funding for malaria vaccine development and the coordinated efforts of programs such as the Gates Foundation-funded Malaria Vaccine Initiative have yielded several candidate vaccines focused on particular malarial stages and currently at various phases of development<sup>71-73</sup>; to date, the vaccine farthest along in development is the preerythrocytic vaccine (vaccines

which aim to prevent malaria infection<sup>72</sup>), RTS,S/AS02A (known as RTS,S).<sup>70</sup>

RTS,S is based on antigenic components (“sub-units”) of the *P. falciparum* circumsporozoite protein,<sup>71</sup> conjugated to an adjuvant, and has shown safety and partly protective efficacy in multiple human trials during its development.<sup>74-77</sup> In adults in The Gambia, RTS,S efficacy was 71% at 9 weeks after last vaccination but dropped to 0% in the following 6 weeks.<sup>74</sup> In a trial in Mozambican children aged 1 to 4 years, RTS,S was noted to delay first infection (efficacy for delay of first infections in the first 6 months follow-up was 45%), yet most children had at least one malaria infection (83% in RTS,S arm versus 93% in the control arm).<sup>75</sup> In a separate study of Mozambican children of the same age followed for clinical episodes of malaria, 25% in the vaccine group had at least one episode, as compared with 34% in the control group: a 26% difference.<sup>76</sup> Severe malaria was even less common (49% lower rate) in the RTS,S group.<sup>76</sup> Recently published results of an RTS,S trial in Mozambican infants have also been encouraging, with the vaccine shown to be safe and immunogenic, as well as efficacious; 23.7% of infants in the vaccine group and 50.0% in the control group had at least one malaria infection, a difference of 52.6%.<sup>77</sup>

Other pre-erythrocytic vaccines in development include those that utilize different subunits of *P. falciparum* circumsporozoite protein, as well as DNA and live recombinant vaccines.<sup>72,73</sup> Erythrocytic stage vaccines, which are designed to protect against severe malaria, but not infection, are also in development.<sup>78</sup> The furthest along in development of these is based on *P. falciparum* merozoite surface proteins (MSP-1 and MSP-2) and *P. falciparum* ring-stage infected-erythrocyte surface antigen combined with an adjuvant.<sup>78</sup> In a phase I/IIb trial in children ages 5 to 9 in Papua New Guinea, vaccinated children experienced parasite densities 62% lower than controls; further studies are ongoing.<sup>78</sup> Transmission-blocking vaccines are also in development.<sup>72</sup> Designed to induce antibodies against sexual stage gametocytes, they are aimed at protecting communities from malaria transmission.<sup>72</sup>

The complete public health impact of a partially effective malaria vaccine such as RTS,S is unclear.<sup>79</sup> Some models suggest that partially effective vaccines may have a substantial impact on malaria morbidity and mortality in the first years of life, with little effect on community-wide malaria transmission, and there are concerns that over time, severe malaria may, in fact, increase in older

**TABLE 5.** Objectives of the Roll Back Malaria (RBM) initiative

(Launched by WHO in 1998, endorsing the four main objectives of the Global Malaria Control Strategy, adopted by the Ministerial Conference in Amsterdam in 1992.) The RBM goal is to reduce the global malaria burden by half by 2010 as compared with 2000
1. To provide early diagnosis and prompt treatment of malaria
2. To plan and implement selective and sustainable preventive measures, including vector control
3. To detect early, contain, or prevent epidemics
4. To strengthen local capabilities in basic and applied research to permit and promote the regular assessment of a country's malaria situation, in particular, the ecological, social, and economic determinants of the disease

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children who develop less immunity to blood stage parasites during their early childhood.<sup>70</sup>

### Anopheles Control

Given the need for coordinated global action against malaria, the RBM Initiative was initiated by WHO in 1998. With a goal to reduce the global malaria burden by half by 2010 (as compared with 2000), RBM has four main objectives, as outlined in Table 5. A key notion in RBM is vector control.<sup>51</sup>

Given that vector density is a key variable in the equation for a vector's capacity to transmit infections, vector reduction seems an obvious and important part of the control of any vector-transmitted disease; indeed, in the case of malaria, vector control is generally considered the most effective measure in the disease's prevention.<sup>51</sup> While novel methods of *Anopheles* control utilizing transgenic mosquitoes (in which *Plasmodium* cannot develop) and the release of irradiated sterile males are in development,<sup>80,81</sup> the proven efficacy of more ancient methods is instructive. Historical campaigns targeted toward elimination or control of *Anopheles* (and *Ae. aegypti*) as a means of malaria (and yellow fever) control have met, at times, with great success.<sup>1,82,83</sup> The landmark, military-style U.S. campaign directed at enabling the construction of the Panama Canal yielded a remarkable reduction in malaria incidence, along with the eradication of yellow fever, by utilizing a comprehensive strategy of altering mosquito habitat by drainage and landfill, and the use of insecticidal oils in ponds and swamps.<sup>1,84</sup>

While effective, these types of methods are costly and complicated, and, since the advent of dichloro-diphenyl-trichloroethane (DDT) in the 1940s, control of malaria vectors has focused on the use of insecticides applied in

the home—the site where most infections occur.<sup>1</sup> As described above, ITNs exert a level of control on adult *Anopheles* populations in communities that utilize them at high levels of uptake. So does indoor residual spraying (IRS), which involves the application of long-acting insecticides on the walls and roofs of all domestic shelters—human and animal—in a given area, to kill the mosquitoes that rest on these surfaces.<sup>52</sup> IRS reduces malaria transmission by reducing both overall *Anopheles* density and the lifespan of surviving *Anopheles* such that they do not live long enough to transmit malaria.<sup>52</sup> IRS works better against some *Anopheles* species than others; *An. gambiae*, which both rests and delivers bites indoors, is well-controlled by IRS, while *An. arabensis*, which is less likely to rest indoors, is less well-controlled.<sup>52</sup>

Between 1955 and 1969, the Malaria Eradication Programme, based on IRS using DDT and organized by the WHO, yielded significant reductions in malaria burden in southern Africa, Asia, and Latin America and contributed to the eradication of malaria from Europe and several countries in Asia and the Caribbean.<sup>52</sup> DDT is long-acting and requires no more than one or two treatments annually, augmenting its operational feasibility.<sup>51</sup> In much of sub-Saharan Africa, however, IRS was not implemented at large-scale. Yet malaria eradication projects in numerous sub-Saharan African countries between 1950 and 1980 showed that even in areas of stable malaria transmission, *Anopheles* numbers and, accordingly, malaria, could be controlled by IRS, although transmission could not be interrupted in most cases.<sup>52</sup>

Today, in most areas with substantial malaria burden, IRS is a key feature in malaria control programs, and its effectiveness depends on several factors, including uptake within targeted communities—rates of >80% of shelters sprayed are typically required for malaria transmission to be controlled.<sup>52</sup> Insecticide resistance is also of major importance. Exposure to pesticides applies strong selective pressure on *Anopheles* populations.<sup>85</sup> Pyrethroid resistance is of critical concern, as such insecticides are the mainstays of *Anopheles* control (given the cessation of DDT use over safety concerns), and pyrethroid resistance may reduce the efficacy of ITNs (which are treated with pyrethroids such as permethrin and deltamethrin) and IRS utilizing pyrethroids.<sup>85</sup>

Indeed, in some malaria-endemic countries, the replacement of DDT with pyrethroid insecticides has been accompanied by the reappearance of *Anopheles* vectors previously eliminated.<sup>86</sup> Accordingly, while

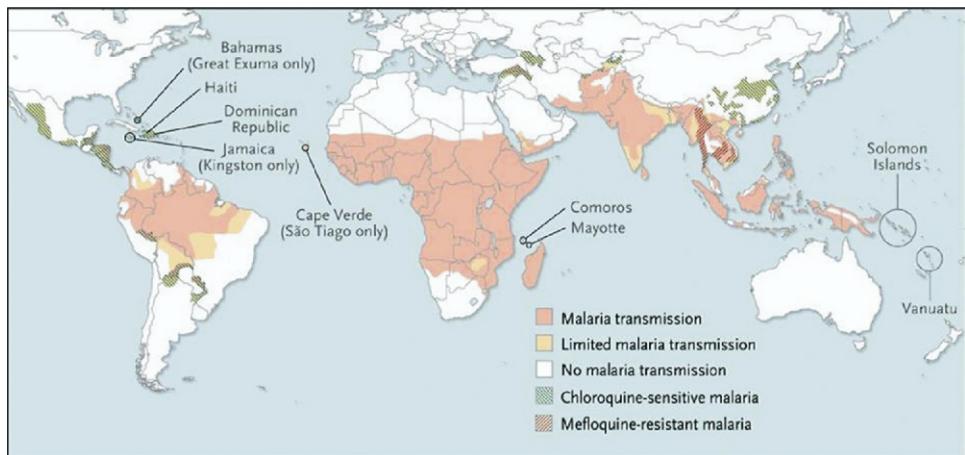
not without controversy, the WHO recommends DDT for IRS under certain circumstances and has recently published a statement outlining such scenarios.<sup>86</sup>

Control of larval production also has a role in some settings for *Anopheles* control, particularly when mosquito breeding takes place in semi-permanent sites that can be readily identified and either eliminated or treated with an antilarval measure, such as larvicidal bacteria, larvivorous fish, or application of an antilarval oil.<sup>51</sup> Given the breeding habits of many *Anopheles* species, larval control plays less of a role in malaria control than it does in the control of *Ae. aegypti*-vectored infections such as yellow fever and dengue.<sup>51,52,87</sup> As will be described below, *Ae. aegypti*'s close association with human habitation and its preference for breeding in discrete, readily identifiable, human-made water containers make its control much more approachable with antilarval methods.<sup>87,88</sup>

### Malaria Prevention in Travelers

Figure 4 details malaria's global range, as well as the typical patterns of resistance seen in a particular area.

While antimalarials taken as chemoprophylaxis are a very important part of prevention of malaria in travelers, nonpharmaceutical interventions, too, have a role in this regard. As *Anopheles* most frequently bite from dusk through evening and night, travelers should, when possible, avoid mosquito contact during such times. Scheduling children's activities accordingly is helpful as is consideration of the seasonality of travel in areas where malaria transmission is not year-round; wet seasons may be associated with periods of higher malaria transmission.<sup>30</sup> Sleeping under a bed net is essential when nights will be spent in buildings with open windows or doors. As mentioned above, the efficacy of bed nets is enhanced by treating them with permethrin, and clothes, too, can be similarly treated to improve their ability to protect against mosquito bites (0.5% permethrin soaked or sprayed on, allowed to dry for 6 hours before use<sup>30</sup>). Insect repellents containing *N,N*-diethyl-*m*-toluamide (DEET), the most effective mosquito repellent able to be placed on skin,<sup>89</sup> should be used when skin will be exposed to mosquitoes. While the effectiveness of DEET lasts longer at higher concentrations, the American Academy of Pediatrics recommends that with infants and children DEET be used at no more than 30% concentration, and that DEET not be used on children less than age 2 months.<sup>90</sup> Care should be taken not to apply DEET to the hands or around the eyes or mouths of



**FIG 4.** Areas where malaria is endemic (Reproduced with permission.<sup>31</sup> ©2008 Massachusetts Medical Society. All rights reserved.) (Color version of figure is available online.)

young children.<sup>90</sup> When necessary, DEET may be used during pregnancy.<sup>89</sup>

Once inoculated by an infective mosquito, sporozoites briskly leave the circulation and enter hepatocytes, where they develop before returning to the circulation to initiate the symptom-producing erythrocytic phase of malaria infection, as detailed above. So-called causal drugs, such as atovaquone-proguanil and primaquine, eliminate *Plasmodium* in the hepatic phase, while other commonly used chemoprophylactic agents, such as chloroquine, mefloquine, and doxycycline, have their effect in the circulation by maintaining a concentration sufficient to inhibit the infection of RBCs<sup>31</sup>; in addition to its effect in the hepatic stage, atovaquone-proguanil also affects the blood stage and has utility as an option for the treatment of clinical malaria.<sup>32</sup> Atovaquone-proguanil, chloroquine, mefloquine, and doxycycline are all recommended as options for malaria chemoprophylaxis by WHO and CDC.<sup>29-31</sup> All have been shown to have >95% efficacy in preventing *P. falciparum* malaria,<sup>31</sup> although efficacy in many travelers may be lower, and it is important for both travelers and health care providers alike to remember that no chemoprophylactic regimen is 100% effective.

#### Advice for Travelers—Malaria Prophylaxis

In deciding which prophylactic agent to offer a traveler, it is important to consider both the likelihood of malaria exposure and, importantly, the pattern of drug resistance of *Plasmodium* sp

in the area being traveled to (Fig 4). For travelers to areas where chloroquine-resistant malaria has not been reported (detailed above), chloroquine is the first choice for malaria chemoprophylaxis.<sup>91,92</sup> In areas where chloroquine-resistant *P. falciparum* is seen, atovaquone-proguanil, mefloquine, or doxycycline should be used; mefloquine-resistant *P. falciparum* is seen in some areas of Southeast Asia, obviating, of course, its use there.<sup>91,92</sup> For pharmokinetic reasons, atovaquone-proguanil and doxycycline are dosed daily, while chloroquine and mefloquine are dosed weekly.<sup>91,92</sup> Due to its causal effect, atovaquone-proguanil need only be continued for 1 week after return from a malarial area; chloroquine, mefloquine, and doxycycline must be continued for 4 weeks after the final malaria exposure.<sup>91,92</sup>

Primaquine has utility as a choice for primary prophylaxis, particularly in areas where chloroquine-resistant *P. vivax* is seen, particularly Papua New Guinea and parts of Indonesia.<sup>32</sup> Its use obviates the need for a subsequent course of primaquine as antirelapse therapy, as described above, but its contraindication in persons with G6PD deficiency (due to its tendency to induce hemolysis) and the need to test for G6PD before its use have restricted its widespread use in primary malaria chemoprophylaxis.<sup>31</sup>

Children may generally take the same chemoprophylaxis as their adult traveling companions.<sup>30,31</sup> Exceptions to this include the recommendation

that doxycycline not be used in children less than age 8, and a difficulty in some settings of accessing formulations of chloroquine and mefloquine suitable for small children (ie, liquid formulations), given the lack of pediatric-sized tablets for these two medications.<sup>31</sup> Chloroquine is approved for all ages of children, while mefloquine is approved for children  $\geq 5$  kg and may be used off-label, when required, in children  $< 5$  kg.<sup>91,92</sup> Atovaquone-proguanil has the advantage of being available in a [1/4] size pediatric tablet, is approved for use in children  $\geq 11$  kg,<sup>30</sup> and has been safely used in Africa in children as small as 5 kg.<sup>93</sup> As well, atovaquone-proguanil is the CDC-recommended choice for standby emergency treatment of malaria, when clinical malaria is possible and proper medical services are unable to be accessed in a timely manner.<sup>32</sup>

While both WHO and CDC recommend that pregnant women avoid travel to malaria-endemic areas, malaria chemoprophylaxis options, although limited, do exist for such travelers.<sup>31,91,92</sup> Doxycycline, atovaquone-proguanil, and primaquine are not recommended in pregnancy, but chloroquine may be used by pregnant travelers to areas where *P. falciparum* is chloroquine-sensitive.<sup>31</sup> Mefloquine may be used for travel to chloroquine-resistant areas, although data on its use in the first trimester are limited, so a delay in travel until later in pregnancy is generally advised.<sup>91,92</sup>

## Yellow Fever

In severe yellow fever (YF) cases, patients develop jaundice. Yellow in Latin is *flavus*, hence the name of the virus, as well as of the family (*Flaviviridae*) and genus (*Flavivirus*) of which YF is the prototype species.<sup>94</sup> Mostly arthropod-borne (thus known as arboviruses), there are more than 70 additional related but distinct viruses in the family *Flaviviridae*, including several others discussed in this review: dengue viruses, Japanese encephalitis virus, and West Nile virus.<sup>15</sup>

YF virus is a small, single-stranded RNA virus with an envelope containing a single glycoprotein with specific antigenic determinants<sup>95</sup>; as will be discussed below, this well-conserved antigenic simplicity greatly

aided the development of a very effective vaccine against YF.

Despite the availability of an effective vaccine, YF virus continues to be responsible for a significant disease burden. As many as 600 million persons live in areas of Africa and the Americas endemic for YF (Fig 5), and case reports of YF likely grossly underestimate the true number of YF cases; estimates in some years are as many as 200,000 YF cases, with 30,000 deaths annually, and 90% of the burden in Africa.<sup>15</sup> Unpredictable and explosive urban outbreaks are chiefly seen in West Africa.<sup>96</sup> For unclear reasons, despite the ability of *Ae. aegypti* from various regions of Asia to transmit YF virus experimentally to monkeys,<sup>95</sup> and the widespread presence of *A. aegypti* in the Middle East, Asia, and the Pacific, YF does not occur in these regions.<sup>15,94</sup>

### History of Yellow Fever, and Its Control, in the Americas

YF virus has its origins in Africa and was introduced to the Americas as early as the 15th century, most likely by infected mosquitoes, including *Ae. aegypti*, breeding in water containers on ships trafficking slaves.<sup>94,97</sup> The first epidemic documented to be YF occurred in the Yucatan in 1648, and over the next 250 years outbreaks took place broadly across the tropical Americas and coastal North America and Europe<sup>83</sup>; some outbreaks involved considerable mortality, including as many as 20,000 deaths each in Barcelona (1821) and the lower Mississippi Valley (1878).<sup>82,94</sup>

During these times, YF, with its tendency to cause devastating disease with high mortality rates, was understandably the source of great fear, particularly as its etiology and mode of transmission were unknown<sup>82</sup>; early beliefs included the theory of “contagion” of North American ports by some element from the West Indies, to be defended against by quarantining arriving ships.<sup>82</sup> By the late 19th century it had become well accepted that YF was not directly communicable person-to-person,<sup>82</sup> and in 1881, Dr. Carlos Finlay, a Cuban physician, suggested YF was not only transmitted by mosquitoes, but by a specific mosquito—*Ae. Aegypti*.<sup>83</sup> After YF took the life of 13 soldiers for every 1 killed in combat during the American military campaign in Cuba in the late 1890s,<sup>82</sup> experiments that proved the “mos-



**FIG 5.** Yellow fever endemic zones. (Reproduced with permission of the U.S. CDC.) (Color version of figure is available online.)

quito hypothesis” were performed in Cuba by Walter Reed and colleagues, who concluded the “spread of yellow fever can be most effectually-

controlled by measures directed to the destruction of mosquitoes.”<sup>98</sup>

Subsequent efforts at mosquito control targeting *Ae. aegypti* proved very successful, and urban YF was eliminated from Havana, Panama (allowing the construction of the Canal), and Rio de Janeiro, and subsequently from much of the Americas<sup>82,83,95</sup>; in 1925, only three cases of YF were reported in the Western Hemisphere.<sup>82</sup>

YF may well have been eradicated in the Western Hemisphere were *Ae. aegypti* its only vector; it is not. Now known to be a zoonosis, YF virus is maintained in nature in a sylvatic (jungle) cycle in which *Ae. aegypti* do not participate.<sup>15,82,94</sup>

In Africa, *Ae. africanus* serves as the principal vector for a sylvatic cycle (also known as forest or jungle cycles) of YF transmitted between lower primates, which generally remain asymptomatic; species such as lemurs, genets, and many others can also become infected and infect mosquitoes and may be involved in the transmission cycle.<sup>94</sup> When people become infected in the forest, they may transport YF to populated areas where an urban cycle vectored by *Ae. aegypti* may develop; these urban cycles can generate large outbreaks with substantial morbidity and mortality.<sup>94</sup> An intermediate (or savannah) cycle has also been noted in some regions of Africa, where YF is vectored by multiple non-*Ae. aegypti* species, and many YF outbreaks have their origins.<sup>94</sup>

While the YF zone in Africa encompasses most of its tropical area, there appear to be differences in regional epidemiology.<sup>96</sup> There are seven genotypes of YF virus, which may vary in transmissibility and are regionally distributed.<sup>94,96</sup> In East and Central Africa, epidemics are few and have tended to occur during periods of civil unrest (such as in Ethiopia from 1960-1962, and the 2003 and 2005 outbreaks in Sudan) and in unvaccinated persons<sup>96</sup>; these may be associated with large population movements into areas with endemic sylvatic YF.<sup>94</sup> For unclear reasons, which could include poor adaptation of the East African YF virus genotype to local *Ae. aegypti* populations, *Ae. aegypti*-vectored urban YF has yet to be seen in East Africa.<sup>96</sup>

This contrasts with West Africa, where West Africa genotypes I and II are prevalent, and epidemic YF, including large urban YF outbreaks vectored by *Ae.*

*aegypti*, is historically more common, occurring during stable socio-political times and without mass movements of people.<sup>94,96</sup>

In the Americas, sylvatic cycles of YF transmission are maintained chiefly by *Haemagogus* sp. mosquitoes, and human infections are sporadic, typically occurring when unimmunized persons (such as forest workers or migrant farmers clearing forest for farming) enter forested areas containing *Haemagogus*.<sup>94</sup> Most activity is found in the Amazon, Orinoco, and Araguaia river basins of South America, but sylvatic transmission has been reported as far afield as the island of Trinidad (never in Tobago) and Panama east of the Canal.<sup>94</sup> Human infections peak during the rainy season (typically December to May) when *Hamagogus* populations are the highest.<sup>94</sup> Unlike African primates, New World primates are susceptible to YF virus,<sup>15</sup> and the discovery of dead monkeys may herald local sylvatic YF activity.<sup>94</sup>

As discussed above, with the elimination of *Ae. aegypti* in the early 20th century, urban YF was eliminated from the Americas.<sup>83</sup> Although reinfestation with *Ae. aegypti* has taken place virtually throughout the region,<sup>64</sup> with the exception of a small urban outbreak in Santa Cruz, Bolivia, in 1999,<sup>99</sup> urban YF has not been seen in the Americas since 1954.<sup>99</sup> An outbreak in 2008 in Paraguay was initially feared to be *Ae. aegypti*-vectored but was later shown to be sylvatic in nature.<sup>100</sup>

### Clinical Yellow Fever Illness: Presentation, Course, Diagnostics, and Management

Clinically, YF has an incubation period of 3 to 6 days,<sup>15,101</sup> and severe cases classically have been noted to pass through three distinct phases: infection, remission, and intoxication.<sup>102</sup> Most YF infections, however, are inapparent or mild, particularly in endemic areas, where high levels of immunity develop among indigenous persons.<sup>15,101</sup> Mild YF is an acute febrile illness of short duration (often <48 hours), characterized by fever, headache, myalgias, and other mild constitutional symptoms.<sup>101</sup> Proteinuria may be present, as may be Faget's sign (bradycardia in relation to temperature)—a characteristic finding in YF (and other tropical illnesses, including typhoid).<sup>101</sup> More substantial cases may last several days before the patient's uneventful recovery.<sup>101</sup>

In severe cases, a period of remission lasting up to 24 hours may occur, with a marked diminishment of

fever and an apparent improvement in clinical status.<sup>15</sup> This, however, is followed by the intoxication phase (which may also occur in severe YF from the onset of disease, without a mild phase or period of remission), in which severe and widespread cellular necrosis takes place in the liver, and variable pathologic effects are seen in other organs, manifested as jaundice, myocardial and renal dysfunction, and, ultimately, hepatic failure, encephalopathy, and hemorrhage, including characteristic hematemesis, as well as bleeding from other mucosal surfaces, including the gastrointestinal and genitourinary tracts.<sup>15,101,102</sup> Laboratory tests typically show a leukopenia and thrombocytopenia, elevated liver enzymes, and abnormalities on clotting tests.<sup>15,101</sup>

YF is classically a clinical diagnosis, with a history of residence or travel in endemic areas within the incubation period, particularly if unimmunized, making the diagnosis more likely. Particularly in poor endemic areas, access to advanced diagnostics is limited.

On liver biopsy, a mid-zonal coagulative necrosis with sparing of periportal hepatocytes and minimal inflammation is seen, and viral antigen may be demonstrated within hepatocytes.<sup>101</sup> Serological diagnosis may be obtained by demonstration of IgM by enzyme-linked immunosorbent assay (ELISA) during the acute phase of the illness, or by standard techniques showing a rise in titer between paired acute and convalescent samples.<sup>101</sup> Virologic techniques to identify YF have relied on PCR techniques specific to YF virus, and multiplex reverse transcription (RT)-PCR assays have been developed that under laboratory conditions can diagnose and differentiate multiple flaviviruses from each other (including YF, Japanese encephalitis virus (JEV), West Nile virus (WNV), St. Louis encephalitis, and the four Dengue serotypes).<sup>103</sup> Novel molecular diagnostic methods are under investigation, including the use of mass spectrometry in developing a platform for universal identification and genotyping of flaviviruses.<sup>104</sup> These methods are being investigated for use with miniature mass spectrometers currently under development that could allow such assays to be utilized in rural and remote areas and in rapid responses to outbreaks of apparent flaviviral disease.<sup>104</sup>

While novel treatment methods, including pharmacotherapeutics, for flaviviral illness are under investigation,<sup>105</sup> there currently is no specific therapy for YF or any other flaviviral illness.<sup>101</sup> Much

like for dengue hemorrhagic fever (discussed below) and other similar hemorrhagic fevers, care is supportive and should include intensive care, where available.<sup>6,101</sup> Severe YF may carry a case fatality rate as high as 50%.<sup>101</sup>

### YF Control

Given YF's virulent nature and the lack of specific options for clinical case management, control of YF has been given high priority as a public health intervention in endemic zones.<sup>106</sup>

*Ae. aegypti* control is critical to control of YF; as was shown more than 100 years ago, elimination of *Ae. aegypti* results in complete control of urban cycles of YF transmission.<sup>83</sup> *Ae. aegypti* elimination also controls dengue viruses,<sup>107</sup> which infect *Ae. aegypti* very efficiently,<sup>94</sup> and for which *Ae. aegypti* is the principal (and by far most important) vector.<sup>108</sup>

As sylvatic YF cannot be eliminated,<sup>15,94</sup> vaccination has been critical to YF control in endemic zones.<sup>15,94,95,97</sup> Many regions of the world, however, including the southeast U.S.,<sup>108</sup> contain vectors (such as *Ae. aegypti*) capable of transmitting YF and thus are susceptible to emergence of YF should the virus be introduced by travelers.<sup>107,108</sup> As well, recent concerns over the safety of the YF vaccine have raised questions over vaccination policies.<sup>106,108-111</sup>

### Yellow Fever Vaccine

In the 1930s, two live-attenuated YF vaccines were developed from serial passage of human-derived YF virus in tissue lines: the French neurotropic vaccine (FNV) from passage in mouse brain and the 17D vaccine from chicken embryo tissue.<sup>95</sup>

FNV was administered en masse to nearly 40 million people in French West Africa between 1939 and 1952 and was associated with a marked fall in YF incidence in the region.<sup>95</sup> FNV, however, was associated with large numbers of encephalitis cases in children, and after 1961 was no longer recommended for children less than 10 years of age.<sup>95</sup> Its manufacture was discontinued in 1980.<sup>95</sup>

The 17D vaccine, however, has remained in continuous use since its development in 1936.<sup>108</sup> Over 400 million doses have been given, and generation of long-lasting immunity in recipients is the rule.<sup>108</sup> Although International Health Regulations requiring YF immunization subscribed to by many countries in endemic zones demarcate the need for a YF vaccine booster every 10 years,<sup>106</sup> multiple studies have demonstrated retention of

neutralizing antibodies in considerable percentages of previously immunized persons for far longer than 10 years<sup>95</sup>; in one study, 81% of U.S. World War II veterans (none of whom had traveled to a YF endemic area since 1948) previously vaccinated with 17D between 1940 and 1945 showed neutralizing antibody persistence when assessed 30 years later (1975-1976).<sup>112</sup>

YF remains a major public health threat in endemic countries, particularly in Africa where the majority of disease burden is seen and the threat of outbreaks is the greatest. In outbreaks of YF in endemic zones, those too young to have been immunized during previous epidemics are more vulnerable to infection.<sup>94,106</sup> As well, severe manifestations of YF may be more common in infants and younger children than in older adolescents and adults.<sup>5</sup>

Accordingly, for endemic countries of Africa, the WHO recommends incorporation of YF vaccine into routine infant and child immunization schedules, to be given at the time of measles vaccine between 9 and 12 months of age.<sup>106</sup> All told, 32 of the 44 countries endemic for YF have either partial or national expanded programs of immunization with YF vaccine,<sup>94</sup> although coverage in many is less than 50%.<sup>106</sup>

Surveillance is very important in the detection of YF outbreaks, for which emergency vaccination campaigns are implemented; the largest mass vaccination campaign to date took place in southern Mali in April 2008, when 6000 health care providers and 2000 volunteers vaccinated 6 million persons at risk.<sup>113</sup> Mass vaccination is also mobilized in the Americas after sylvatic outbreaks affecting primates—so-called “monkey die-offs.”<sup>114</sup> While YF vaccine is typically given to those ages 9 months and older, during emergency vaccination campaigns the inoculation may be given as young as 6 months of age.<sup>5</sup>

### Advice for Travelers—Yellow Fever

Many countries require a YF vaccination certificate, dated no less than 10 days and no more than 10 years before entry, for those travelers arriving from areas experiencing YF outbreaks, while some require the certificate from all those arriving from any endemic country.<sup>106</sup> Some countries, principally in endemic West and Central Africa, require certificates from all arriving travelers, including those from countries where there is no risk of YF.<sup>106</sup> Waiver letters stating medical contraindication to

vaccination are accepted in some, but not all, countries requiring YF vaccination.<sup>5</sup>

Contraindications to YF vaccine include immunosuppression, age younger than 6 months, and allergy to eggs.<sup>5,111</sup> HIV infection is not a strict contraindication to YF vaccination,<sup>5</sup> although symptomatic individuals or those with CD4 counts <200 cells/mm<sup>3</sup> (or CD4% less than 25% for children <5 years) should not receive YF vaccine (or other live vaccines, such as MMR or Varicella).<sup>5,111</sup> YF vaccine should be avoided in pregnancy, unless the traveler will be at an unavoidable high risk of YF exposure.<sup>5,111</sup>

With only a low rate (2-5%) of mild reactions (including headache and myalgias), the 17D vaccine has historically been considered very safe.<sup>108</sup> Rare cases of encephalitis have been reported in infants less than 9 months of age,<sup>95</sup> hence, its contraindication in infants younger than 6 months of age, and lack of general recommendation for those ages 6 to 8 months.<sup>5,95,111</sup>

The safety of YF vaccine, however, has been called into question in recent years following reports of acute viscerotropic disease (YF-associated viscerotropic disease) first recognized in 2001.<sup>108</sup> This presents 2 to 5 days after receipt of an individual's first YF vaccine as a febrile illness with multi-organ failure, is clinically indistinguishable from naturally acquired YF disease, and has a 60% case fatality rate.<sup>108</sup> Although acute viscerotropic disease is very rare, with an overall incidence of approximately 0.3 to 0.4 per 100,000 vaccinated persons,<sup>109,110</sup> the risk from some vaccine lots may be higher.<sup>115</sup> During a YF vaccination campaign in southern Peru in October 2007, the rate of acute viscerotropic disease was nearly 20-fold higher—7.9 per 100,000—in recipients of one particular 17D lot, while no viscerotropic disease was seen in individuals in the same area inoculated with a different 17D lot.<sup>115</sup> Newer approaches to YF vaccine production are under development using cell culture systems, including use of a full-length cDNA clone of 17D-204 virus, and may reduce the risk of selection of more virulent subpopulations potentially associated with current production methods.<sup>109</sup>

The risk of acute viscerotropic disease is higher in individuals older than 60 years of age and

those with thymus disorders,<sup>108-110</sup> and genetic factors may play a role in susceptibility.<sup>108</sup> The risk in infants and children appears to be much lower, with estimates based on data from Brazil's extensive experience with YF immunization, including routine child immunization, indicating a risk of around 1 case per 10 million doses.<sup>111</sup>

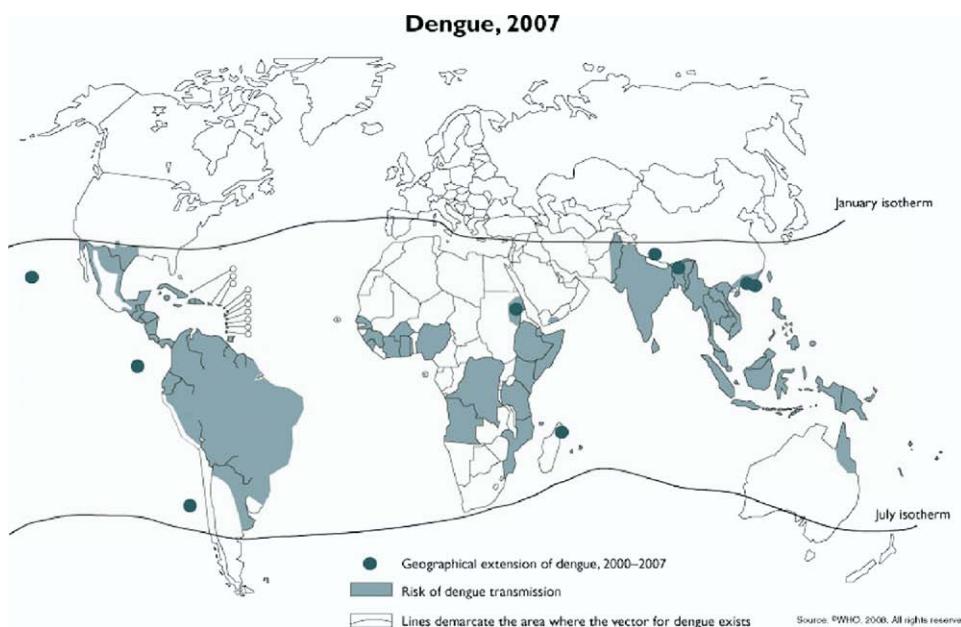
Neurotropic disease may also be seen after YF vaccination.<sup>108-110</sup> This, too, is very rare, occurring at approximately 0.4 per 100,000 vaccinations, and includes multiple presentations; most notably, post vaccine encephalitis and autoimmune involvement of the central and peripheral nervous systems, including Guillain-Barre syndrome, may be seen.<sup>110</sup>

These risks have made decisions regarding YF vaccination more complicated. Based on reported cases of YF in unvaccinated travelers, particularly for older travelers, the incidence of severe vaccine-associated adverse events may be greater than the risk of acquiring YF if unvaccinated.<sup>108</sup>

However, great risk exists for unvaccinated individuals who travel to areas of active transmission. When and where YF transmission is actively and currently taking place is very difficult to know with certainty. Poor surveillance data, immune local populations, and under-recognition of YF cases in endemic zones may generate "epidemiologic silence" in a given region, making extremely accurate individual risk assessment nearly impossible.<sup>108,110</sup> Physicians giving advice to travelers to YF endemic regions must remain up-to-date on current YF activity, such as reported by WHO and CDC, and carefully scrutinize travelers' itineraries to best determine approximate risk of YF exposure, balancing the need for YF immunization with care in not prescribing vaccination for individuals not at risk of YF exposure.

## Dengue

The dengue viruses share an ancient common ancestry with YF, having sylvatic origins and being maintained in nature in enzootic forest cycles involving lower primates as primary hosts.<sup>116</sup> All continue to exist enzootically, YF as described above, and dengue, similarly, in forested areas of tropical West Africa and



**FIG 6.** Areas endemic for dengue. (Reproduced with permission of the WHO.) (Color version of figure is available online.)

Asia.<sup>116</sup> Urban cycles of both viruses can occur, with transmission vectored primarily from and to humans by *Ae. aegypti*, highly adapted to characteristics of modern human habitation.<sup>116</sup> Over time, YF has maintained genetic stability and, accordingly, its sylvatic nature<sup>94</sup>; while dramatic, urban YF is uncommon. In contrast, the dengue viruses have experienced marked genetic variation,<sup>94</sup> allowing complete adaptation to *Ae. aegypti* and maintenance via human-mosquito-human cycles in population centers throughout the tropics.<sup>94,116</sup> With the worldwide failure of *Ae. aegypti*-control, dengue has become a major global health problem, with an impact focused on pediatric and adolescent populations.<sup>117</sup>

As much as half the world's population lives in dengue endemic regions (Fig 6), where between 50 to 100 million infections occur.<sup>12,117</sup> While most dengue infections are asymptomatic or cause a self-limited febrile syndrome, as many as 500,000 cases of severe dengue infection annually occur: dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS). In southeast Asia, where dengue is hyperendemic, more than 90% of DHF/DSS cases are in children less than age 15 years, and between 5 to 10% are in infants.<sup>117</sup> In less endemic regions of Asia, dengue outbreaks and cases of severe dengue occur in patients of all ages.<sup>6</sup> In the Americas, adults are more likely to experience severe dengue,<sup>6</sup> although this may be

changing.<sup>118</sup> A shift in age patterns for DHF has been noted recently in Brazil, which traditionally accounts for the largest dengue burden in the Americas; the fraction of DHF cases aged <15 years has risen from <10% in 1998 to >50% in 2007.<sup>118</sup>

As such, over the past 30 years, dengue has become a major cause of morbidity and mortality in children throughout the tropics. In many dengue endemic regions, dengue outbreaks generate considerable public attention. The disease is greatly feared by the general public, generating much anxiety for caregivers of febrile children, and placing significant pressure on already overburdened pediatric care systems during epidemics.<sup>6,119</sup>

In many countries, dengue is one of the leading causes of pediatric hospitalization.<sup>6</sup> While this is particularly true for southern and Southeast Asia, where the burden of dengue has historically been the greatest, the Americas have seen a tremendous surge in dengue activity in the 2000s.<sup>6,120</sup> Many countries in the region share the example of El Salvador, where, after having no reported dengue cases until 1980, there were more than 16,000 confirmed cases in 2000,<sup>120</sup> and the pediatric services of many district hospitals were filled beyond capacity at the height of the outbreak. In 2008, more than 1 million dengue cases were reported in the region,<sup>121</sup> and some evidence suggests that with all four dengue serotypes now

circulating in the region, the Americas may be en route to becoming a hyperendemic region for dengue similar to Southeast Asia, with continuing cycles of progressively more severe dengue and DHF epidemics.<sup>120,121</sup>

### Clinical Picture

Dengue infection begins with the bite of an infected mosquito. Approximately 3 to 4 days later (dengue has an incubation period of 3-14 days), the host develops detectable viremia, followed in approximately 24 hours by the sudden onset of fever. In young children, uncomplicated dengue often presents as an undifferentiated febrile illness.<sup>15</sup> In the “classic” form of primary infection, seen in older children and adults,<sup>6,15</sup> viremia and fever continue for 3 to 7 days, during which time the symptoms of classic dengue may be noted: myalgias and arthralgias (hence the historical characterization of dengue as “break bone fever”<sup>122</sup>), headache, retro-orbital pain, nausea, vomiting, and backache.<sup>6,15</sup> A maculopapular rash and lymphadenopathy may be noted, and thrombocytopenia and leucopenia are common laboratory findings.<sup>6,15</sup> Minor bleeding manifestations may be noted.<sup>123</sup> Viremia may be of shorter duration in secondary dengue infections,<sup>12</sup> and, particularly in adolescents and adults, prolonged fatigue and subsequent depression may follow resolution of constitutional symptoms.<sup>15,123</sup>

### Severe Dengue

In most patients, defervescence marks start of clinical recovery; classic dengue fever is generally self-limiting.<sup>123</sup> Some patients, however, progress to severe dengue. The pathologic hallmark of severe dengue is plasma leakage secondary to increased vascular permeability, which typically occurs around the time of defervescence.<sup>6,12,123</sup>

The WHO case definitions of dengue fever and DHF/DSS are shown in Table 6, and for DHF the WHO has defined four categories of severity (I-IV).<sup>6</sup> Grade I is defined as fever, constitutional signs and symptoms, and a positive tourniquet test. Spontaneous bleeding marks passage to Grade II. Grades III and IV characterize DSS, with Grade III being defined as circulatory failure without notable shock (rapid, weak pulse; narrow pulse pressure or hypotension; cold, clammy skin, restless) and Grade IV being profound shock without detectable blood pressure or pulse.<sup>6</sup>

The case fatality rate for DSS is high, making a diagnosis of severe dengue of great clinical importance. Careful early management reduces mortality

**TABLE 6.** WHO case definitions: dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS)

#### Dengue fever

Probable DF is an acute febrile illness with *two or more* of the following manifestations:

- Headache
- Rash
- Myalgia
- Arthralgia
- Retro-orbital pain
- Hemorrhagic manifestations
- Leukopenia; and:
  - Supportive serology; or
  - Occurrence at the same location and time as other confirmed cases of dengue

Confirmed DF is a case confirmed by laboratory criteria (isolation of the dengue virus, demonstration of dengue genomic sequence or dengue virus antigen, or fourfold or greater change in antibody titers)

#### Dengue hemorrhagic fever

To fulfill the WHO case definition for DHF, *all* of the following must be present:

- Fever or history of acute fever, lasting 2-7 days
- Bleeding (hemorrhagic tendencies), evidenced by at least one of the following:
  - Positive tourniquet test
  - Petechiae, ecchymosis, or purpura
  - Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations
  - Hematemesis or melena
- Thrombocytopenia ( $100,000$  platelets/ $\text{mm}^3$  or less)
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - A rise in hematocrit = or  $>20\%$  above average for age, sex, and population
  - A drop in hematocrit following volume-replacement treatment = or  $>20\%$  of baseline
  - Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia

#### Dengue shock syndrome

To fulfill the WHO case definition for DSS, *all* four criteria for DHF listed above must be present, *plus* evidence of circulatory failure manifested as:

- Rapid and weak pulse
- Narrow pulse pressure ( $<20$  mmHg)
- Hypotension for age (defined as systolic pressure  $<80$  mmHg for children  $<5$  years of age, or  $<90$  mmHg for children age  $5$  years and older)
- Cold, clammy skin and restlessness

Adapted from the World Health Organization. Dengue, dengue haemorrhagic fever and dengue shock syndrome in the context of the integrated management of childhood illness (2005).

from shock<sup>6,124</sup>; indeed, it is shock, not hemorrhage, as suggested by the term DHF, that is the gravest danger to the individual infected with dengue.<sup>6</sup>

To this effect, the usefulness of the WHO classification scheme has recently been called into question.<sup>125</sup> Studies in endemic regions have found the WHO case classifications difficult to apply,<sup>126</sup> even by clinicians experienced in dengue.<sup>126</sup> As well, in clin-

ical practice, the scheme may suffer from low sensitivity and specificity for severe dengue,<sup>125,127,128</sup> as evidenced by a large pediatric study in a highly endemic region of southern Vietnam that showed mucosal bleeding to be present at equal rates in children with both dengue fever and DHF; poor differentiation between dengue fever and DHF by the presence of tourniquet test results, thrombocytopenia, and petechiae; and 18% of children with shock failing to fulfill all four criteria necessary for a diagnosis of DHF.<sup>127</sup> Similar findings have been noted in adults in Nicaragua.<sup>128</sup>

It has been suggested that rather than concentrating diagnostic efforts on a tightly defined classification scheme, detection of vascular permeability as manifested by capillary leakage and stratifying patients as to the risk of developing DSS should take priority.<sup>6,12,127</sup> Radiograph and ultrasound evaluations of the chest and abdomen can detect accumulating fluid,<sup>127</sup> and thickening of the gallbladder wall, in particular, has been shown to predict development of vascular permeability in children with dengue.<sup>129</sup>

Although ultrasonographic signs of plasma leakage are detectable before changes in hematocrit,<sup>130</sup> such investigations are not universally available in resource-limited settings. Where this is the case, evaluation of hemoconcentration via serial hematocrit is a useful measure of capillary leak.<sup>127</sup> In the large Vietnamese pediatric study mentioned above, 94% of the patients with shock had hematocrits more than 20% above the local population mean hematocrit (the WHO definition of hemoconcentration), and past work in the same region has shown that such an elevated hematocrit on presentation with suspected dengue illness is almost always associated with shock.<sup>127</sup> Other studies of predictive markers for developing DSS have associated younger age, altered sensorium, significant alterations in laboratory bleeding parameters (such as PTT), and, as will be discussed below, secondary dengue infection, along with the parameters mentioned above, with a tendency to develop DSS and, accordingly, require early and aggressive management.<sup>131,132</sup>

It has been suggested that the severity of dengue infection in a host may be determined to some degree by the individual's genetic background.<sup>133,134</sup> It has been epidemiologically noted that severe dengue is rare in Africa and Haiti, and less common in Cuba and elsewhere in the Americas in individuals of African descent.<sup>133</sup> Recent work from Colombia, where DHF

is more common in mestizos as compared with Colombians of African descent, has shown differences in cytokine levels between the two groups.<sup>133</sup> Molecular studies lend additional support to a genetic basis for susceptibility, as specific polymorphisms in the genes encoding for transporters associated with antigen processing appear to confer susceptibility to both DHF and DSS, particularly for primary infection,<sup>135,136</sup> while expression of human leukocyte antigen-DR4 may be associated with protection against the development of severe dengue.<sup>134</sup>

### *Pathogenesis and Epidemiology*

There are four dengue virus serotypes (DEN-1, DEN-2, DEN-3, DEN-4).<sup>12</sup> During infection, homologous antibodies to a particular type are produced, generating type-specific immunity.<sup>6</sup> However, the individual remains susceptible to infection with other (heterologous) dengue serotypes.<sup>6</sup> During subsequent infection with a different serotype, the preexisting heterologous antibodies are unable to neutralize the new serotype, instead forming circulating nonneutralizing antibody-virus complexes.<sup>6,137</sup> Fc receptors on mononuclear cells bind these circulating complexes, serving to enhance dengue virus uptake and replication in macrophages, leading to higher viral loads than in primary infections, the release of vasoactive mediators, and, sometimes, rapid occurrence of hemorrhage and vascular permeability.<sup>6,137</sup>

This process, called *antibody-dependent enhancement*, is believed to play a pivotal role in the development of severe dengue (DHF/DSS), as noted in Cuba in 1981 during a DEN-2 epidemic in which more than 10,000 cases of DHF/DSS were seen.<sup>138</sup> Four years prior, when DEN-1 had circulated in Cuba, only mild disease was noted despite 44% of the population having serologic evidence of infection.<sup>12</sup> In 1981, the death rate was almost 15-fold higher in children ages 3 to 14 than in young adults aged 15 to 39, with the highest death rates seen in children ages 3 and 4 with secondary DEN-2 infections.<sup>139</sup> When DEN-3 circulated in Havana in 2001, some 20 years after the DEN-2 epidemic, DHF cases were only seen in adults, ie, children in 2001 were too young to have any preexisting antibodies to dengue.<sup>140</sup>

Such disease patterns appear to be typical for dengue infections; indeed, when populations without preexisting dengue antibodies are exposed to dengue, typically only classic dengue fever is seen, and generally just in adults.<sup>12</sup>

Antibody-dependent enhancement also likely underlies the propensity of infants, unlike older children and adults, to develop severe dengue with the first dengue infection.<sup>12</sup> In endemic Southeast Asia, where all four dengue serotypes circulate, infants have been noted to develop DHF with first dengue infection, with peak incidence between 6 and 9 months.<sup>141</sup> This time period correlates with waning of neutralizing antibody fractions received from the infant's mother for a particular strain, while passively transferred heterotypic antibodies persist at levels sufficient to enhance dengue infection to DHF.<sup>12,141</sup>

All told, even with secondary infection, progression to severe dengue is uncommon, occurring at rates of 2 to 4%.<sup>142</sup> Immunologic factors other than antibody-dependent enhancement likely play a role in the etiology of severe dengue, including T-cell responses and the effects and interactions of specific cytokines<sup>137</sup>; the exact nature of these factors is unclear and the subject of much debate.<sup>12</sup> While quite uncommon, beyond infancy severe dengue is occasionally seen with primary infection<sup>137</sup>; it has been suggested that some dengue strains are more virulent than others, with such highly virulent strains first noted in Southeast Asia.<sup>12</sup>

### Diagnosis

The presence of fever and variable constitutional symptoms noted in dengue fever carry, particularly in endemic tropical zones, a broad initial differential diagnosis, including malaria, and other viral (influenza, measles, rubella, other arboviral infections including chikungunya, YF, and JEV) and bacterial diseases (typhoid, leptospirosis, sepsis, meningococcemia, rickettsial disease). The WHO has provided a case definition for probable dengue fever as an acute febrile illness with two or more of the following: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, leukopenia; and either supportive serology or occurrence at the same location and time as other confirmed cases of dengue.<sup>6</sup>

Given dengue fever's acute and uncomfortable nature, most patients present for medical attention during the first few days of infection, when accurate serological diagnosis (with IgM ELISA) is not possible<sup>12,143</sup>; IgM is generally undetectable until after defervescence, making necessary comparison of paired samples and delaying confirmation of diagnosis.<sup>6,12</sup> False-positive results are common in many settings,<sup>144</sup> particularly in regions highly endemic for other flavi-

viruses (whose antigens cross-react in serological tests), such as Southeast Asia,<sup>16,103</sup> and accuracy and sensitivity are lower when antidengue IgM is assessed via dried blood spots on filter paper.<sup>12</sup> IgG is not produced until at least day 8 of primary infection<sup>143</sup>; its absence in samples collected between day 0 and day 8 marks a case as a primary dengue infection, while simultaneous detection of IgM and IgG suggests a secondary infection.<sup>143</sup>

To accurately diagnose dengue fever in the febrile period, tests utilizing viral antigen, viral isolation, or molecular techniques (PCR) must be used.<sup>12</sup> A variety of rapid tests incorporating these technologies are under development, including mass cataloging and multiplex RT-PCR, as described above for YF.<sup>103,104</sup> While intriguing, these utilize complex, expensive technology, unlikely to be widely available in the field in endemic settings in the near future.

Dengue viruses contain seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5).<sup>143</sup> NS1 is highly conserved across the four dengue serotypes and can be detected in serum throughout the febrile phase of the illness.<sup>143</sup> Tests based on detection of NS1 have been developed and marketed.<sup>12,143</sup> The Platelia Dengue NS1 Ag test (Bio-Rad, Richmond, CA), based on NS1 antigen-capture ELISA, was evaluated in South America and Southeast Asia; its sensitivities were 88.7 and 93.4%, respectively, with 100% specificities in both regions.<sup>145,146</sup> Recently, two new commercially available NS1 antigen tests were evaluated on acute serum samples in French Guiana and compared with Platelia.<sup>143</sup> The Dengue NS1 Ag STRIP (Bio-Rad), the first RDT available for dengue detection, showed sensitivity of 81.5% after 15 minutes and 82.4% after 30 minutes, with specificity of 100%, while the pan-E Dengue Early ELISA (Panbio, Brisbane, Queensland, Australia) demonstrated sensitivity of only 60.4% and specificity of 97.9%.<sup>143</sup>

The success of the RDT in this study holds promise, as the need for rapid tests based on antigens from pathogens is well-recognized, for dengue, as well as for a host of other tropical illnesses whose burdens are most marked in resource-limited settings.<sup>147</sup> Availability of this sort of simple-to-use RDT, with its minimal technology requirement (only serum separation), could prove a major advance to routine clinical practice in dengue endemic areas, allowing confirmation of suspected dengue without requiring the service of a reference laboratory.<sup>143</sup>

## Management

While generally quite uncomfortable for the affected individual, dengue fever is a self-limited illness and may be managed with antipyretics, analgesics, and general supportive care. While hematologic indices (hematocrit and platelets) should be followed, admission to hospital is not necessary, and the individual typically recovers spontaneously in a reasonably short period of time.<sup>6</sup>

Severe dengue, on the other hand, is a medical emergency, requiring intensive inpatient management, and carries, even with treatment, case fatality rates generally on the order of 1 to 5%,<sup>148</sup> with rates in excess of 15% in some outbreaks.<sup>149</sup> Particularly in children, severe hemorrhage is rare and almost always associated with marked shock,<sup>12</sup> the typical cause of death in severe dengue.<sup>6,117,150</sup> Prognosis in severe dengue depends chiefly on the early recognition and treatment of shock; indeed, aggressive but careful management may reduce mortality substantially.<sup>6,150</sup> Shock in dengue is not due to cardiac dysfunction but rather to intravascular volume loss through plasma leakage.<sup>12</sup> As shock progresses, pulse pressure narrows, and, if not aggressively treated, complete cardiovascular compromise may result.<sup>12</sup>

The WHO has published guidelines for the management of severe dengue that highlight the critical importance of early administration of intravenous fluids and careful inpatient monitoring for those patients with suspected dengue and signs of plasma leakage.<sup>6</sup> Crystalloid solutions are used initially and changed to colloid or blood if initial management is unsuccessful. Once improvement (stable or gradually decreasing hematocrit, stable pulse and blood pressure, increasing urine output) is noted, the rate of intravenous fluid administration should be decreased and ultimately discontinued. Fluid overload is not uncommon in the management of severe dengue and has been noted in some series to cause as many deaths as shock itself<sup>6,150</sup>; appropriate fluid removal may be particularly important in decreasing mortality in the most severe presentations of DSS.<sup>150</sup>

The choice of specific fluids for initial management of severe dengue in children has recently been clarified. In a double-blind, randomized comparison of three fluids for initial resuscitation of dengue shock syndrome performed in a cohort of 383 Vietnamese children, Ringer's lactate was shown to be sufficient for children with moderately severe DSS. When severe shock was present, both Dextran 70 and 6% hydroxyethyl starch (both

colloid solutions) were efficacious in stabilizing cardiovascular status, although there were more adverse reactions among those receiving Dextran 70.<sup>148</sup>

Aside from careful fluid management, intensive care of DSS often involves correction of metabolic and electrolyte abnormalities and the administration of oxygen; individual cases may benefit from central venous monitoring and the use of inotropic agents.<sup>6,151</sup> The use of steroids in DSS has been studied, and, with the exception of one very small study in which high doses of methylprednisolone were given intravenously along with mannitol,<sup>152</sup> not shown to have significant effect on outcome.<sup>6</sup>

As mentioned above, bleeding is rare in children, as is the development of disseminated intravascular coagulation; both are more common in adults.<sup>12</sup> In children, the risk of bleeding appears to be most closely associated with duration of shock.<sup>153</sup> When bleeding is present, in both children and adults, use of blood products may be required, including transfusion of blood or fresh frozen plasma.<sup>9,12,151</sup> Thrombocytopenia is a hallmark of dengue infection; platelet counts as low as 5000 cells/ $\mu$ L have been reported.<sup>12</sup> As recovery proceeds, however, platelet counts briskly recover.<sup>12</sup> Platelet counts have not been shown to be predictive of hemorrhage in severe dengue,<sup>153</sup> and unless bleeding sufficient to warrant blood transfusion is present, there is no evidence supporting use of prophylactic platelet transfusion in dengue infection; indeed, such practice has been associated with an increased risk of complications.<sup>12</sup>

Just as for YF, and the other arboviral infections discussed in this review, there is no specific antiviral therapy available for dengue, although research into antiflaviviral drugs is an area of intense ongoing investigation.

### Dengue in Pregnancy

As with all dengue infections in adults, dengue in pregnancy may be severe and is not an uncommon event.<sup>154</sup> Development of DHF may be more common in pregnancy, and pregnant women may be more likely to develop DHF with primary infection than nonpregnant women.<sup>155</sup> Accurately diagnosing dengue infection in pregnancy requires knowledge of local dengue transmission patterns and a high index of suspicion, as nondengue pregnancy-associated conditions such as the HELLP syndrome can present similarly

(thrombocytopenia, hemoconcentration, elevated liver enzymes).<sup>155</sup> Complications of pregnancy and delivery may be more common with dengue infection, particularly when associated with severe thrombocytopenia, or plasma leakage and hemorrhagic tendencies as seen with DHF, which may compromise placental circulation.<sup>155</sup> In particular, first-trimester dengue infections may increase the risk of spontaneous abortion, and late third-trimester and intrapartum dengue infections may be associated with prolonged severe bleeding and adverse fetal outcomes.<sup>156</sup> As well, preterm birth has been associated with dengue infection during pregnancy.<sup>155,156</sup>

Vertical transmission of dengue virus has been reported but is not believed to be common<sup>154,156</sup>, in a cohort of 64 acute dengue infections during pregnancy recently reported from Malaysia, only one case of vertical transmission occurred.<sup>154</sup> In the few cases of vertical dengue infection reported in the literature, fever and thrombocytopenia are common presenting findings, severe hemorrhagic manifestations are rare, and long-term sequelae appear to be uncommon.<sup>156</sup>

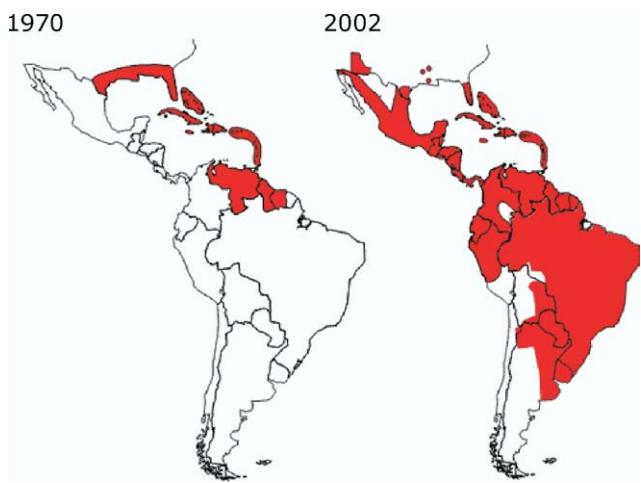
### Dengue Prevention: Dengue Vaccine

As with YF, the lack of specific therapy for dengue infection puts a high onus on the need for prevention. Unlike YF, however, there is not currently an available dengue vaccine, and dengue control has, accordingly, proven much more difficult than for YF. Chief among factors making development of a safe and effective dengue vaccine difficult are the existence of multiple dengue serotypes, and the fact that sequential infection with different dengue strains is associated with the development of DHF, through the putative mechanisms described above.<sup>108,137</sup> Accordingly, a dengue vaccine must yield persistent protective immunity against all four dengue serotypes simultaneously.<sup>108</sup> YF, as previously mentioned, has only a single serotype, making YF vaccine's development considerably simpler.<sup>94,108</sup> At the moment, two live-attenuated dengue vaccines are in phase II development.<sup>108</sup> One of these, a live-attenuated dengue-YF chimeric virus, was created by placing dengue envelope genes into the genome of the 17D YF vaccine and will soon undergo phase III trials in children in Thailand.<sup>108,157</sup> It is hoped that one or both of these vaccines will be widely available by the mid-2010s.<sup>157</sup>

### Dengue Prevention: *Aedes aegypti* Control

As is the case for *Anopheles* with respect to the impact on malaria transmission from control of its vector, so, too, is elimination or substantial reduction in *Ae. aegypti* densities a proven and effective means for prevention of its principal associated infections: YF, dengue, and, as discussed below, chikungunya virus.<sup>87</sup> *Ae. aegypti* is exquisitely well-adapted to modern human life, preferring to feed exclusively, if able, on humans, and having developed breeding habits facilitated by modern patterns of human habitation, particularly in the tropical developing world.<sup>94</sup> Lack of reliable water supply forces the storage of water on premises, and a lack of public refuse collection generates a large supply of environmental debris that collects rainwater and makes excellent *Ae. aegypti* habitat.<sup>88</sup> *Ae. aegypti* prefers breeding in clean water in such containers,<sup>94</sup> and the presence of discarded cans, plastic containers, and, particularly, tires in the home environment have been shown to be significant independent risk factors for infection during a dengue outbreak.<sup>158</sup> Poor urban infrastructure abounds in the tropical developing world, particularly in the haphazardly constructed peri-urban developments that ring many large urban areas in such settings, and in which human overcrowding has synergized with available *Ae. aegypti* habitat to create for dengue conditions in which it thrives, confirmed by dengue's explosive growth in the past two decades.<sup>120,121</sup>

Efforts to control *Ae. aegypti* have been described as applicable on a continuum from "top down" (vertical) to "bottom up" (horizontal).<sup>19</sup> Vertically structured, disciplined campaigns such as those described above (including strategic house-to-house inspections) that yielded the eradication of *Ae. aegypti*, and, thus, YF, from much of the Americas in the early and mid 20th century provide excellent examples of top down approaches.<sup>88</sup> Focusing on larval source reduction, these campaigns, and similar, modern campaigns in countries with strong central governments such as Singapore and Cuba, have been very successful in controlling *Ae. aegypti* and, accordingly, dengue disease.<sup>19</sup> Such strategies have not been without issues, chiefly those of cost and ability to be implemented in countries with less effective power structures.<sup>19,88</sup> It has been suggested that once control is achieved, top down mosquito control programs are difficult to sustain<sup>19</sup>; programs less burdensome on the public system such as ultra-low-volume spraying of insecticides from



**FIG 7.** Reinfestation of the Americas with *Ae. aegypti* (distribution of *Ae. aegypti* in the Americas in 1970, at the end of the mosquito eradication program, and in 2002). (Reproduced with permission of the U.S. CDC.) (Color version of figure is available online.)

trucks or planes, while visible signs of action on the part of officialdom, have been shown ineffective.<sup>19,88</sup> Indeed, the inability to maintain control of *Ae. aegypti* has been the case in much of the world, particularly in the Americas, where the gains against *Ae. aegypti* seen by the mid 20th century have today been mostly eroded.<sup>19</sup> As shown in Figure 7, *Ae. aegypti* has long since returned, and, along with it, epidemic dengue on an unprecedented scale.<sup>19,120,121</sup>

Horizontal approaches assign responsibility where the impact of *Ae. aegypti*-vectored infections are most felt: the communities in which the infections take place.<sup>19,88</sup> However, the nature of *Ae. aegypti* dictates that community-based control depends on full participation by the community; no matter how free of breeding sites is one's household, if one's neighbor allows breeding sites, the risk of infection still exists for those in *Ae. aegypti*'s range. In addition to the elimination of physical breeding sites (containers that can hold water), control of *Aedes* larval maturation can be achieved by multiple means, including use of larvicides and larvivorous fish and copepods.<sup>87</sup> Generally, approaches utilizing these methods initiated solely at the community level have been unable to provide sustainable dengue control.<sup>87,159</sup>

It has been suggested that approaches that combine both vertical (directed through the Ministry of Health or other central authority) and horizontal (delivery by community-level structures) approaches may be more successful at effective and sustainable *Ae. aegypti*

control.<sup>88,159</sup> An example of such an approach is the centrally organized, but community-delivered, approach using mass cultured copepods of the genus *Mesocyclops* as biological control agents over the development of *Ae. aegypti* larvae in wells and water storage sites in communes distributed throughout Vietnam.<sup>88</sup> The vertical element of this approach is organized under the oversight of the Ministry of Health's National Dengue Control Committee, while the horizontal element, and concrete actions leading to dengue control, is organized at the commune level where health collaborators carry out monthly inspection of homes, deliver health education messages, and assist with periodic cleanup campaigns and the distribution of *Mesocyclops*.<sup>88</sup> This strategy has been able to eliminate *Ae. aegypti* from numerous communes throughout northern and central Vietnam and has resulted in the absence of dengue cases in many communes since 2001, despite high rates of dengue in untreated communes in the surrounding area.<sup>88</sup>

While this particular approach is especially well-suited for areas where large water storage containers are major breeding sites for *Ae. aegypti*, the potential for similar approaches combining vertical elements with locally effective *Ae. aegypti*-control methods delivered horizontally is great wherever communities and their oversight structures perceive dengue to be a serious problem.<sup>88</sup> A particularly attractive antilarval agent that may have wide applicability as an effective intervention in integrated *Ae. aegypti*-control programs is the insect growth regulator, pyriproxyfen, which inhibits the development of adult *Ae. aegypti* and is nontoxic, effective at very low concentrations, available in a variety of formulations, and able to be dispersed to untreated water containers by tainted *Ae. aegypti*.<sup>87,160</sup>

The recently issued report of an expert panel examining the deficiencies in and proposing solutions for *Ae. aegypti* control advises that while, historically, *Ae. aegypti* control has targeted the larval stage of mosquito development, more attention need be paid to strategies that target adult *Ae. aegypti*—the developmental form of *Ae. aegypti* that actually transmits disease.<sup>87</sup> Interventions effective along these lines include the use of curtains and water container covers treated with insecticide, which have been shown to reduce *Ae. aegypti* levels on the community level in Mexico and Venezuela, benefiting nonintervention households as well as intervention sites.<sup>161</sup> Indoor residual spraying, as for *Anopheles* control, has been

successfully used for *Ae. aegypti* control as well, yet is not currently recommended by WHO as an *Ae. aegypti* control strategy.<sup>162</sup> ITNs, as described for malaria prevention, have also been shown effective in the prevention of other nocturnally passed vector-transmitted diseases, including leishmaniasis, Chagas disease, and lymphatic filariasis.<sup>161,162</sup> Recently, ITNs were shown effective in reducing *Ae. aegypti* (which rest indoors after blood feeding and may contact treated netting and be killed) densities in Haiti.<sup>162</sup> As was seen with insecticide-treated materials as mentioned above, this resulted in a community protective effect and may have affected dengue transmission.<sup>162</sup>

Perhaps no intervention designed to control dengue is as effective as general socioeconomic development. As has been described, socioeconomic factors (poverty, lack of infrastructure) are key drivers of *Ae. aegypti* habitat and subsequent dengue infection. Indeed, while the emergence of dengue in the U.S. is a distinct possibility, owing to the widespread presence of *Ae. aegypti*<sup>163</sup> (and even more widespread distribution of *Ae. albopictus*, an able, if inefficient, vector for dengue,<sup>12,164</sup> now present in at least 36 U.S. states<sup>163</sup>), recent dengue transmission in the continental U.S. has been restricted to limited numbers of cases in south and southwest Texas, along the U.S.-Mexico border.<sup>163,165</sup> Indeed, in a dengue outbreak in the Laredo metropolitan area in 1999, antidengue IgM prevalence in Nuevo Laredo (Tamaulipas) was 16%, while in Laredo (Texas) it was only 1.3%, despite *Ae. aegypti*-infested containers being more abundant in Laredo.<sup>165</sup> In this analysis, the absence of air conditioning (which creates and is associated with an artificial environment that is quite inhospitable to both mosquito survival and the extrinsic incubation period for dengue) was significantly associated with IgM seropositivity (OR: 2.6; 95% CI: 1.2-5.6), and the mean distance between domiciles was 50% greater in Laredo, with lower numbers of occupants per domicile.<sup>165</sup>

#### Advice for Travelers—Dengue

Until an effective dengue vaccine suitable for use in travelers is available, avoidance of dengue infection will continue to chiefly involve avoidance of mosquito bites.<sup>122</sup> *Ae. aegypti* tend to be “day-biters,”<sup>122</sup> and, unlike malaria, dengue transmission is common in urban areas in the tropics. As de-

scribed below, clothing that limits access of mosquitoes to skin and use of a mosquito repellent containing DEET are effective.<sup>122</sup> Infants, in particular, may benefit from taking their naps under a bed net. An appreciation of areas of ongoing dengue activity or outbreaks may help inform travelers of specific risk, and particular caution should be taken by pregnant women and infants traveling to areas with significant dengue activity; delay or deferral of travel may be preferable to risk of dengue infection. Data from Geo Sentinel, a global network that reports on travel-associated disease epidemiology, report that dengue was the second most common diagnosis in febrileReturned travelers from the developing world.<sup>166</sup> An important differentiating feature of dengue infection as compared with malaria is the short incubation period of dengue.<sup>122</sup> Fever that develops after less than 7 days of exposure in areas endemic for both malaria and dengue cannot, by definition, be due to malaria. Likewise, fever that develops more than 2 weeks after return to the U.S. or other dengue nonendemic region will be due to a diagnosis other than dengue.<sup>122</sup>

## Japanese Encephalitis Virus

JEV is the prototype species of the Japanese encephalitis (JE) serogroup of flaviviruses.<sup>7</sup> Ten in number (eight virus species with two subtypes), the JE serogroup shares clinical and ecological features, including maintenance in nature in enzootic cycles involving avian hosts and *Culex spp* mosquitoes as primary vectors.<sup>7,15,167</sup> Taken together, the JE serogroup of viruses is endemic worldwide with the exception of Antarctica<sup>7</sup>; the viruses and their specific geographic ranges are detailed in Table 7. This group of viruses infect humans incidentally and have a predilection for causing encephalitic disease.<sup>7,167</sup> Unlike in dengue and chikungunya infection, for the JE group viruses humans are dead-end hosts and do not participate in natural transmission cycles.<sup>7,167</sup>

JEV is a major public health threat in southern, eastern, and southeast Asia, where most of the 30,000 to 50,000 reported cases, and 10,000 to 15,000 deaths from JEV, occur annually.<sup>7,15,167</sup> These official statistics are widely considered to be significant underestimates, as in many Asian countries endemic for JEV, the infection’s burden is chiefly among rural children in regions where disease surveillance and reporting

**TABLE 7.** Japanese encephalitis serogroup of flaviviruses and their distribution

Virus	Geographic range
Japanese encephalitis virus	East, South, Southeast Asia Papua New Guinea Torres Strait/Northern Australia
West Nile virus (WNV)	Africa South, Central Europe India Middle East North America
Kunjin virus	Parts of Central and South America A subtype of WNV, found in Australia and Papua New Guinea
Murray Valley encephalitis virus (MVEV)	Australia Papua New Guinea Western Indonesian islands
Alfuy virus	A subtype of MVEV, found in Australia
St. Louis encephalitis virus	North, Central, and South America
Usutu virus	Africa
Koutango virus	Africa
Yaounde virus	Africa
Cacipacore virus	South America

Adapted from Mackenzie et al.<sup>7</sup>

may be inadequate.<sup>7,16</sup> The endemic region for JEV extends to northern China, parts of Siberia and Oceania, includes Papua New Guinea and northern Australia, and is shown in Figure 8.

Many endemic countries employ mass vaccination as part of childhood immunization schedules; in such settings, including Japan, Taiwan, and Korea, JE tends to affect adults more than children.<sup>16</sup> Where JE immunization is less extensively implemented, most infections occur in children less than 10 years of age, and more than 50% in children under age 5.<sup>16</sup> Transmission of JEV is year-round in tropical regions of the endemic zone, with a surge in transmission when rice cultivation begins and mosquito densities expand—chiefly between May and December.<sup>16</sup> In temperate countries (Japan, China, Korea), transmissions are much more common between June and October than at other times of year.<sup>16</sup> Throughout the endemic zone, and particularly where immunization coverage levels are low, large JEV outbreaks may be seen in some years, as in Uttar Pradesh (India), where as many as 5000 cases with 1300 deaths from JEV were recorded between July and November 2005.<sup>167</sup>

While JEV's enzootic cycle chiefly involves bird-mosquito-bird transmission (particularly wading birds that frequent areas of rice cultivation, such as herons and egrets),<sup>7,15,16,167</sup> domestic pigs play an important role in incident human infections.<sup>15,16</sup> In rural Asia,

pigs are commonly kept in the domestic environment and are prone to high levels of JE viremia, serving as “amplifiers” by infecting considerable numbers of mosquitoes and bringing virus into close proximity with humans.<sup>16</sup> Indeed, in much of endemic Asia the seroconversion rates of “sentinel pigs” are monitored by public health authorities as an indicator of JEV prevalence in a given area.<sup>16</sup>

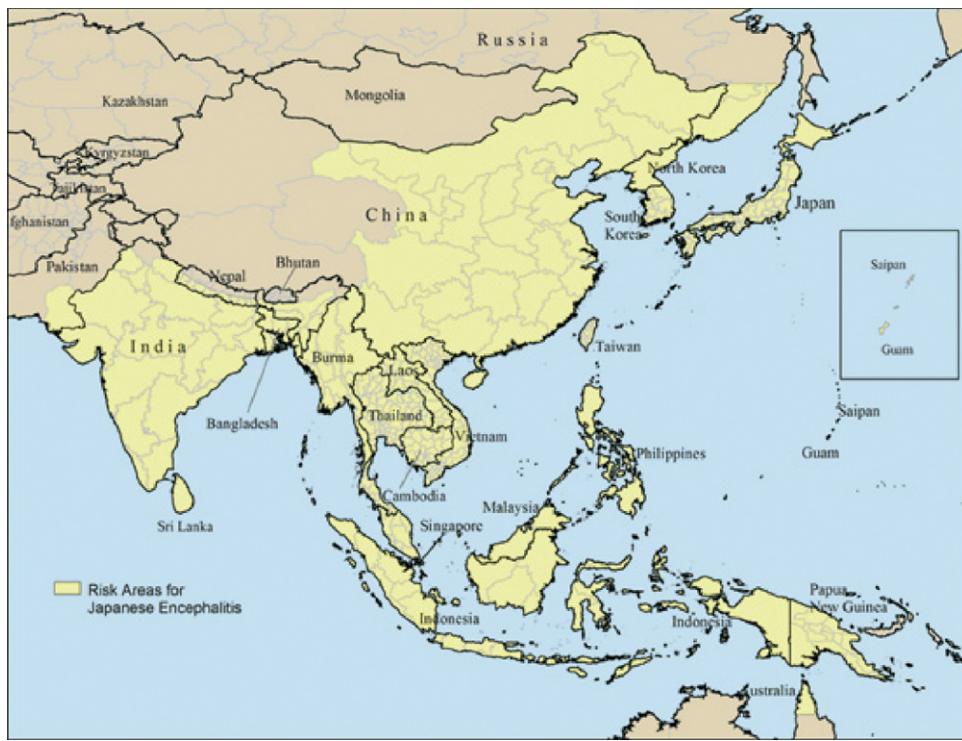
### Clinical Features

Serologic studies have shown that, in rural Asia, most of the population is exposed to JEV as children<sup>167</sup>; most infections, therefore, must be asymptomatic, with estimates of 1 in 25 to 1 in 1000 cases developing clinically apparent disease.<sup>7</sup> Prior infection with dengue virus, which is also common throughout Asia, plays a role in limiting the clinical impact of JE infection. Such infection generates cross-reacting antibodies which, while potentially confounding serologic testing (as discussed below), also seem to protect against severe JE disease.<sup>168</sup> Clinical presentation can vary from an undifferentiated febrile illness to a severe meningoencephalitic picture, with seizures, an altered level of consciousness, and acute flaccid paralysis resembling poliomyelitis not uncommon manifestations of JE progression.<sup>167,169</sup> As well, respiratory failure may occur,<sup>169</sup> and mechanical ventilation for this and other indications (increased intracranial pressure, airway protection in status epilepticus) is frequently necessary.<sup>169</sup>

As with the other arboviral illnesses discussed above, there is no specific treatment for JE.<sup>167</sup> At one point, interferon-alfa was believed to have a positive effect on JE,<sup>170</sup> but a randomized, double-blind, placebo-controlled trial of interferon-alfa in Vietnamese children with JE showed no association with outcome.<sup>159</sup> Acute management is supportive and oriented toward control of immediate complications such as mentioned above.<sup>167</sup> Anticonvulsants are needed in most cases, and inotropic support and mannitol are frequently employed when indicated.<sup>169</sup>

### Diagnosis

In endemic regions, JE is often initially a clinical diagnosis based on a high index of suspicion and JE's leading role as an etiology of encephalitic presentations, particularly in children in rural areas.<sup>16</sup> CSF findings are nonspecific, with a lymphocytic pleiocytosis typically present, along with mildly elevated glucose and protein levels.<sup>16,169</sup> Confirmatory diagnosis may be based on viral isolation or PCR techniques,



**FIG 8.** Areas endemic for Japanese encephalitis. (Reproduced with permission of the U.S. CDC.) (Color version of figure is available online.)

but, in practice, particularly in endemic areas, diagnosis is based on serological tests.<sup>16</sup>

In much of the region endemic for JEV, dengue virus is also endemic, and cross-reactions on serological tests for JEV or other flaviruses are common.<sup>16,169</sup> Many laboratories in the region utilize an IgM capture technique wherein paired serum samples and CSF samples are tested in parallel for IgM against both dengue and JEV in parallel.<sup>171</sup> Samples are considered IgM-positive for JEV if initial reactions to JEV are stronger than for dengue and can discriminate between peripheral JEV infections (only serum positive) and JEV central nervous system infections (CSF positive, even if serum negative).<sup>169,171</sup>

### Outcomes

Although lower in some reported series,<sup>169</sup> approximately 25 to 30% of acute, symptomatic JEV infections culminate in mortality, and as many as 50% of patients who recover survive with neurological sequelae.<sup>167,169</sup> In a large prospectively evaluated cohort of children with serologically confirmed JE recently reported from Malaysia, at discharge only 41% of survivors had full neurologic recovery; 3% had mild, 26% had moderate,

and 33% of survivors had severe neurological sequelae, including severe cognitive impairment with spastic quadripareisis and other manifestations graded incompatible with independent living.<sup>169</sup> After a median follow-up of almost 53 months, neurological outcome improved for 31/86 patients, while 15/86 experienced a further decline in neurological outcome and more than half of the entire cohort continued to experience neuropsychological manifestations, including behavioral disorders.<sup>169</sup> Other studies have reported similarly sobering long-term outcomes from symptomatic JEV infection.<sup>168</sup>

### Control Measures

As with the other mosquito-borne infections described here, control of JE is focused on the three following key interventions: reduction of mosquito populations, minimization of human exposure, and immunization.

Given the habits of the most important JE vectors (*Culex spp* that breed very effectively in rice paddies and other flooded ecosystems) and the nature of the agricultural environments common throughout much of JE's endemic region, mosquito control has proven difficult as a means of reducing the impact of JE.<sup>7,167</sup> Insecticides and chemical larvicides have been tried in

attempts to reduce mosquito breeding in rice paddies, yet to little effect.<sup>167</sup> Residual spraying has been felt ineffective given most *Culex spp* tendencies not to rest inside houses,<sup>16</sup> as *Aedes spp* do.<sup>52</sup> More success has been seen with larvicidal bacteria such as *Bacillus thuringiensis israelensis* (Bti) and *Bacillus sphaericus* Neide.<sup>172</sup> Bti have demonstrated efficacy in a diverse range of habitats against multiple species of mosquitoes (including rice paddies in Asia and against *Culex spp*<sup>173</sup>), while *B. sphaericus* are mainly used against *Culex spp*.<sup>172</sup> As described above, cyclopoid copepods, while much more effective against *Aedes spp*, in containers,<sup>88</sup> also have activity against *Culex spp*, and have shown a role in field studies in the augmentation of *Culex spp* control.<sup>174</sup>

Strategies to reduce human exposure to JE-infected mosquitoes have included the vaccination of pigs against JEV and the removal of pigs from human environments.<sup>16,167</sup> While swine vaccination has not reliably shown efficacy in reducing human JE infections,<sup>167</sup> where pig production has modernized to collective husbandry away from individual homes, JE infections have diminished, although other factors may be involved, including mass vaccination of children in many of the same countries (Japan, Korea, Taiwan).<sup>7,16</sup> Personal protection measures (including minimizing outdoor exposure, particularly around dusk, and applying mosquito repellents) are helpful<sup>167</sup> but difficult to apply consistently. The reality is that, particularly in much of rural Asia, the basic epidemiological factors that drive JE infection (wet agricultural areas, individual pig rearing, lack of personal mosquito protection) are ingrained in the rhythm of life and difficult to alter.

Immunization, therefore, is the mainstay of efforts to control JE infection. Inactivated mouse brain tissue-produced vaccines against JE have existed since the 1930s and have been used extensively in both residents of JE-endemic regions and travelers.<sup>175</sup> Routine immunization of children with inactivated JE vaccine has been standard practice for many years in wealthier Asian countries, including Japan, Korea, and Taiwan, and has been utilized as part of the Expanded Program on Immunization of the WHO in Thailand<sup>167</sup>; it is credited with markedly reducing the incidence of JE infection in these countries.<sup>16,167</sup> Costs have limited the availability of JE vaccines in more resource-limited parts of JE's endemic zone,<sup>15,175</sup> where they have been unable to be consistently and sustainably delivered to at-risk populations on a routine basis.

Historically, the most widely used of these was the Japanese Biken (JE-VAX), which requires three inoculations over 28 days and is associated relatively frequently with hypersensitivity reactions of varying degree (believed to be associated with a gelatin used as a stabilizer), and, very rarely (approximately 1:1,000,000), with severe neurological adverse events, such as acute disseminated encephalomyelitis.<sup>175,176</sup> Accordingly, routine immunization with JE-VAX was suspended in Japan in 2005, and it is no longer manufactured.<sup>176</sup> Supplies are expected to be exhausted over the next few years.<sup>177</sup>

Newer vaccines have been developed for JE, including a live-attenuated vaccine (SA-14-14-2) developed in China.<sup>175</sup> This vaccine has been shown to be effective and is now used extensively in China, India, Nepal, Korea, and Sri Lanka.<sup>177</sup> Structural genes from SA-14-14-2 have been incorporated into the YF 17D strain to produce a chimeric, live-attenuated JE vaccine, now in development.<sup>175,176</sup> An inactivated JE vaccine derived from Vero-cell culture (IC-51) has also been developed using the SA-14-14-2 genome and has been shown safe and immunogenic in comparison with JE-VAX.<sup>175-177</sup> Lacking both the gelatin and the neural tissue found in JE-VAX, this inactivated JE vaccine is expected to lack the hypersensitivity and severe neurological adverse effects associated with JE-VAX,<sup>177</sup> but further data are needed, particularly from careful postmarketing surveillance.<sup>176</sup>

### Advice for Travelers—Japanese Encephalitis

While for residents of endemic areas the benefits of JE vaccination are clear, they may be less so for travelers. The odds of a traveler to the JE endemic zone contracting symptomatic JE infection have been estimated by the U.S. CDC at approximately one in a million,<sup>178</sup> although other estimates confer a higher risk.<sup>179</sup> Official guidance on the topic varies. The WHO recommends JE vaccination for travelers with extensive outdoor exposure in rural areas of an endemic region during the transmission season and for expatriates living in an endemic region through a transmission season or longer.<sup>180</sup> The CDC gives similar advice for expatriates and for travelers recommends vaccine for persons spending a month or longer in endemic areas during the transmission

season, and, under certain circumstances (travel to areas experiencing epidemics and persons whose activities place them at high risk of exposure), for persons spending less than 30 days in an endemic area.<sup>178</sup>

While the risk of contracting JE while traveling clearly varies with the type and duration of travel, there have been several recent case reports of JE infection in travelers, including in travelers with short and underappreciated risk of JE exposure.<sup>179,181,182</sup> Careful attention to the traveler's plans must be paid by the provider of travel medicine advice, and the current epidemiology of JE transmission in the region traveled to well understood, in order for an informed decision to be made regarding the need for JE immunization. The risk of side effects with JE-VAX, its multidose schedule (which was advised to be completed 10 days before departure to allow time for ascertainment of potential delayed hypersensitivity reactions), and its cost were impediments in the past for many travelers.<sup>175-177,183</sup> Some travel medicine providers feel that once one of the potentially more safe and simpler to administrate vaccines described above is available, there will be a case to be made for wider use of JE vaccine in travelers.<sup>183</sup>

## West Nile Virus

While other arboviruses cause neuroinvasive disease in North America (California serogroup viruses, St. Louis encephalitis virus, and eastern equine encephalitis virus among them),<sup>168,184</sup> since its detection during an outbreak of meningoencephalitis in New York in 1999, WNV has become the most prevalent cause of such in the U.S., responsible for 9 of every 10 cases of arboviral meningoencephalitis reported.<sup>184</sup> As mentioned above, WNV is a member of the JE group of flaviviruses, and, like JEV, exists in nature in enzootic cycles chiefly involving birds as natural amplifying hosts.<sup>13,89,184,185</sup> Humans are infected incidentally when bitten by mosquitoes that have fed on viremic birds.<sup>89</sup> With its expansion throughout much of the Americas (North America and parts of the Caribbean, Central and South America) since introduction in 1999, the endemic range of WNV, first characterized in Uganda in 1937,<sup>89</sup> in addition to the Americas, now covers much of Africa, Europe, the Middle East, and

Central Asia<sup>13</sup>; a related subtype, Kunjin virus, is seen in Australia.<sup>13</sup> In addition to causing severe human disease, WNV has also proven highly virulent to horses and to corvid birds (crows, jays, and magpies), collection and testing of dead specimens of which have become a key part of WNV surveillance in the U.S.<sup>185</sup>

*Culex spp* are the chief vectors of WNV in the U.S., and in the U.S. and other temperate locales WNV is transmitted chiefly in the summer and early fall.<sup>185</sup> In the tropics, WNV may be transmitted year-round, and in both ecological zones outbreaks of WNV may be seen.<sup>13</sup> As with JEV, large outbreaks of WNV neuroinvasive disease may be associated with certain, possibly more virulent, genotypes.<sup>168</sup> Although in development, there currently is no available human vaccine against WNV, whereas an inactivated vaccine is used in horses.<sup>168</sup>

The natural history of WNV infection in humans ranges from subclinical to fatal meningoencephalitis. Severe neuroinvasive disease typically develops after an incubation period of 5 to 15 days and a short febrile prodrome<sup>168</sup> is more frequent with increasing age and is associated with high and sustained viremia.<sup>13</sup> The majority (roughly 80%) of WNV infections, however, are asymptomatic, and the vast majority of symptomatic (roughly 95%) infections manifest as nonsevere clinical illness (West Nile fever) rather than severe disease.<sup>13</sup> While most severe disease manifests as meningoencephalitis, acute flaccid paralysis is also seen.<sup>185</sup> Case fatality rates in severe neuroinvasive WNV infection generally range from 5 to 15%; in the U.S. in 2006, the case fatality rate was 10.8%.<sup>185</sup> Uncomplicated West Nile fever is typically characterized by abrupt onset of fever along with myalgias and headache, frequently with gastrointestinal symptoms as well.<sup>13</sup> A diffuse maculopapular rash may be seen, as may generalized lymphadenopathy, and recovery is the rule, typically in less than a week, although many patients experience prolonged fatigue and, occasionally, depression.<sup>13</sup>

When clinically apparent in the pediatric population, WNV is generally mild, and neuroinvasive disease is rare; in most years, <5% of all severe WNV cases in the U.S. are in patients under age 18.<sup>89</sup> In utero transmission is very rare but has been reported,<sup>89</sup> as has the probability of WNV transmission through breast milk.<sup>89</sup>

The presentation of WNV is clinically indistinct, and serology has been the mainstay of WNV diagnosis.<sup>13,89,184,185</sup> A detectable IgM in CSF or serum on

acute presentation, with/or development of a fourfold rise in convalescent titer 2 to 3 weeks later, is diagnostic for WNV.<sup>13</sup> Even with a positive IgM on presentation, a convalescent titer is needed for confirmation, as IgM to WNV can persist in serum for extended periods, and, in theory, a positive IgM on presentation may, in rare cases, not be indicative of acute infection.<sup>13</sup> Nucleic acid amplification techniques are also available.<sup>184</sup> When serology is used for diagnosis, a battery of serologies versus other flaviviruses (as clinicoepidemiologically suggested) should also be tested for, as cross-reactions between flaviviruses are common.<sup>168</sup>

While ribavirin has been used empirically in patients with WNV disease, there is no evidence that it has an impact on clinical outcomes; as for the other flavivirus infections described here, there is no established effective antiviral therapy.<sup>89,168</sup> Care is supportive, including management and control of seizures present in about 10% of adults with WNV meningoencephalitis.<sup>168</sup>

### Avoidance of Mosquito Bites

As with the other mosquito-transmitted infections described here, the mainstay of WNV infection prevention is avoidance of mosquito bites. While broad public mosquito-control methods may be beneficial in this regard, personal protection is important. Avoiding exposure during peak periods of mosquito activity (dawn and dusk), and application of insect repellent containing DEET to skin and clothes (permethrin can also be applied to clothes) when exposure cannot be avoided, may significantly reduce the possibility of receiving an infective bite.

### Chikungunya

In the Makonde language of East Africa, the word chikungunya means “that which bends up”<sup>186</sup>; indeed, infection with chikungunya virus characteristically results in a febrile arthralgia that is often incapacitating.<sup>14</sup> Chikungunya is a member of the genus *Alphavirus*, a group of 28 distinct viruses, 6 of which, including chikungunya, can yield arthritic manifestations in humans.<sup>14</sup> These are listed in Table 8 and include Ross River Virus, the most common arboviral disease in Australia (on average, more than 4000 cases reported annually), which like chikungunya causes a febrile illness characterized by rash and arthritic manifestations which may persist.<sup>187</sup>

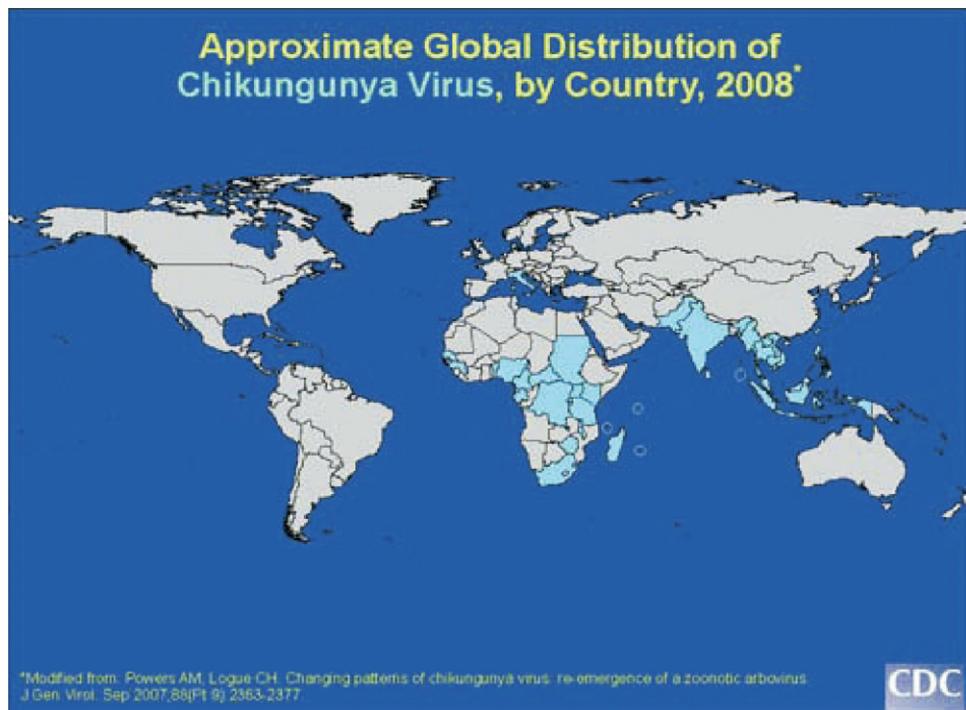
**TABLE 8.** Arthritogenic alphaviruses: geographic distribution and epidemiology

Alphavirus	Geographic distribution	Cases
Chikungunya	Africa Indian Ocean South, Southeast, East Asia West Pacific	Recurrent epidemics Sustained epidemic with millions of cases since 2005 across East Africa, Indian Ocean, S and SE Asia, Italy
Ross River	Australia West Pacific	Up to 8000 annually
Barmah Forest	Australia	500-1500 annually
Sindbis Group	Africa Australia Asia Scandinavia, Russia (subtypes)	100-200 annually (Posgosta subtype—Finland) Up to 30 annually (Ockelbo subtype—Sweden) Otherwise, rare
O’nyong-nyong	Central and East Africa	Small, sporadic epidemics; historical epidemics with millions of cases (1959-1962)
Mayaro	South America	Small, sporadic epidemics
Igbo Ora	Central Africa	Rare

Adapted with permission from Suhrbier and Linn.<sup>188</sup>

Arthritogenic alphaviruses are maintained in nature in enzootic cycles involving mosquitoes and vertebrates, generally birds and mammals.<sup>188</sup> Like many of the other infections described here, human infections are incidental and occur after receipt of a bite from an infected mosquito.<sup>188</sup> A distinctive feature of infection with this group of alphaviruses is that almost all symptomatic infections in adults manifest with arthritic symptoms; infections in children are often milder and difficult to distinguish from other febrile conditions, although in children with chikungunya infection, painful arthritic manifestations are not unusual.<sup>188</sup> Cases are generally sporadic and occur in small numbers, although epidemics may be seen.<sup>14,188</sup>

Figure 9 details the current global distribution of chikungunya. Until emerging in East Africa, the Indian Ocean, India, and elsewhere in South and Southeast Asia after 2004, chikungunya, first described in Tanzania in 1952, had been considered an uncommon and somewhat obscure tropical infection, generally confined to the African continent (although chikungunya had been seen occasionally in India since 1963, as well as occasionally elsewhere as epidemics in South and Southeast Asia).<sup>14</sup> Traditional chikungunya vectors include, chiefly, many different *Aedes* species, as well as, occasionally, *Culex*, *Mansonia*, and *Anopheles* species.<sup>14</sup> Most Asian epidemics have been urban,



**FIG 9.** Global distribution of chikungunya virus, 2008. (Reproduced with permission of the U.S. CDC.) (Color version of figure is available online.)

focused, and vectored by *Ae. aegypti* and, occasionally, by *Ae. albopictus* (the Asian Tiger Mosquito).<sup>14</sup>

Since 2004, a substantial chikungunya epidemic with origins in Kenya (2004) and the Comoros (2005) has been underway in the Indian Ocean, India, and South and Southeast Asia.<sup>14,186,188,189</sup> Several million cases have been seen, including thousands in returned travelers to Europe and the Americas,<sup>189</sup> and local transmission of chikungunya, likely imported by an infected traveler, was reported in Italy in 2007.<sup>190</sup> The current chikungunya epidemic was particularly severe on the Indian Ocean island of La Reunion.<sup>14,186,188-191</sup> Of a population of 770,000, there were 265,000 clinical cases (34% incidence) in 2005 and 2006<sup>191</sup>; overall seroprevalence was 35%, indicating very few asymptomatic infections.<sup>191</sup> As well, relatively high mortality (1:1000 cases), which is traditionally rare with chikungunya, was seen on La Reunion, including in infants and young children.<sup>191,192</sup>

The extraordinary nature of this epidemic appears, with its unprecedented incidence rate in the Indian Ocean (as well as on La Reunion, relatively high incidences were seen in 2005 and 2006 on Mauritius, the Seychelles, and the island of Mayotte),<sup>14</sup> to have been driven by several features, including increased

tourist numbers and the introduction of the virus into nonimmune populations.<sup>14</sup>

Perhaps though the most important factor in chikungunya's re-emergence in the region is its acquisition of an adaptive mutation allowing it to be efficiently vectored by *Ae. albopictus* (traditionally considered to have a low vector capacity) in addition to its traditional vector, *Ae. aegypti*.<sup>189,191</sup> This mutation (a single base-pair, valine for alanine at position 226 of the E1 gene, known as A226V<sup>189</sup>) appears to have occurred in 2005 or 2006 when chikungunya arrived in La Reunion and other Indian Ocean islands where *Ae. albopictus* has displaced *Ae. aegypti*, and, as well as conferring fitness to be vectored by *Ae. albopictus*, may be associated with the more virulent nature of chikungunya infections with this variant, as well its ability to be transported by infected travelers to new areas where outbreaks occur.<sup>189,191</sup> The A226V variant was also noted in the outbreak mentioned above in Italy, where transmission was also by *Ae. albopictus*.<sup>190,191</sup> This phenomenon—an independent adaptive mutation meeting a necessity of transmission by *Ae. albopictus*—is known as evolutionary convergence, and its observation in nature is considered extremely rare.<sup>189</sup> As well, chikungunya's ability to so

converge is considered to have potentially serious implications for its potential to cause outbreaks in Europe and the Americas where introduced *Ae. albopictus* is becoming widespread.<sup>189</sup>

## Clinical Manifestations

Chikungunya typically presents as an acute illness characterized by the abrupt onset of fever and arthralgia, which is often incapacitating, after an incubation period that averages 2 to 4 days.<sup>14</sup> Headache, myalgias, pain along the spine, and conjunctival injection are common associated symptoms, and a maculopapular rash most prominent on the trunk and facial edema are commonly developed signs.<sup>14</sup>

In children, more substantial skin and mucous membrane involvement may be seen, including bullous eruptions and the appearance of petechiae and bleeding from the gums.<sup>14</sup> Frank hemorrhagic fever is rare but has been reported.<sup>14</sup> The presence of pharyngitis and upper respiratory tract symptoms are also more common in children, particularly infants and young children.<sup>186</sup> While chikungunya, unlike dengue and JEV, is generally considered to have a milder course in children than in adults<sup>193</sup> (particularly the elderly, in whom the vast majority of the fatalities seen in the La Reunion epidemic took place<sup>191</sup>), symptoms severe enough to require hospitalization are not uncommon, and neuroinvasive disease (discussed below) may be seen.<sup>14,193</sup>

Recovery generally occurs within 7 to 10 days, although arthritic manifestations may persist for some time, most commonly in the principal joints affected during the acute phase of the illness—wrists, hands, and ankles—but also occasionally affecting the large joints.<sup>14,186</sup> While the precise mechanisms underlying the joint manifestations seen with alphavirus infections, including chikungunya, are unclear,<sup>14,187</sup> approximately 75% of patients infected with chikungunya experience such symptoms.<sup>14</sup> In approximately one-third of cases, arthritic symptoms persist for more than 3 months, and in 15% for more than a year; very long-term persistence (5 years) has been described.<sup>14</sup> In some outbreaks, higher fractions of affected individuals may suffer prolonged, persistent arthralgias.<sup>194</sup> In a retrospective study of 88 patients on La Reunion with documented chikungunya infection in the recent outbreak, 56 (63.6%) reported persistent arthralgia 18 months postinfection, with continuous pain and pain impacting negatively on everyday activities present in approximately 50% of those affected.<sup>194</sup> Even in persistent cases, laboratory tests for markers associated with

rheumatic disease tend to be normal, as do radiographic findings,<sup>14</sup> although early in the course of disease erythrocyte sedimentation rate and C-reactive protein may be mildly elevated, and a neutrophilia may be noted.<sup>188</sup>

## Diagnosis

Chikungunya infection is typically a clinical diagnosis; in areas affected by the ongoing epidemic, cases are often seen in large numbers in a given area, and the clinical syndrome of febrile arthralgia with or without rash is characteristic. Serologic diagnosis may be available in some centers but is not as widely available nor as standardized as for diagnosis of dengue and related flaviruses<sup>14</sup>; cross-reactions, particularly with other alphaviruses, may occur.<sup>14,187</sup> IgM is generally assessable by day 2 to 4 of illness, and IgG may be detected in convalescent samples.<sup>14</sup> RT-PCR can detect chikungunya infection as early as the onset of symptoms but is generally not routinely available.<sup>14</sup>

### Chikungunya or Dengue?

The most important infection in the differential of chikungunya presentations is dengue. The presence of arthralgia in particular aids in distinguishing chikungunya from dengue, as the two infections are both present at high incidence where their ranges overlap (particularly in India and elsewhere in South and Southeast Asia), and otherwise present similarly; indeed, co-infection may occur.<sup>14</sup> Distinguishing the two has important implications: patients with dengue infection need to be observed for development of DHF, while chikungunya-infected individuals require expectant guidance on the potential likelihood of persistent arthritic manifestations. In addition to arthralgia being more frequent with chikungunya, as compared with dengue, chikungunya also generally presents with a more sudden onset, a shorter febrile period, and a higher likelihood of rash.<sup>186</sup>

### Severe Chikungunya

Traditionally, severe disease associated with chikungunya infection has been considered quite rare.<sup>191,194</sup> Yet in the 2005 to 2006 outbreak on La Reunion, more than 200 deaths attributed to chikungunya were reported,<sup>191,193</sup> mainly from cardiopulmonary failure or neuroinvasive disease,<sup>193</sup> although chikungunya was implicated in cases of multi-organ failure, as well,

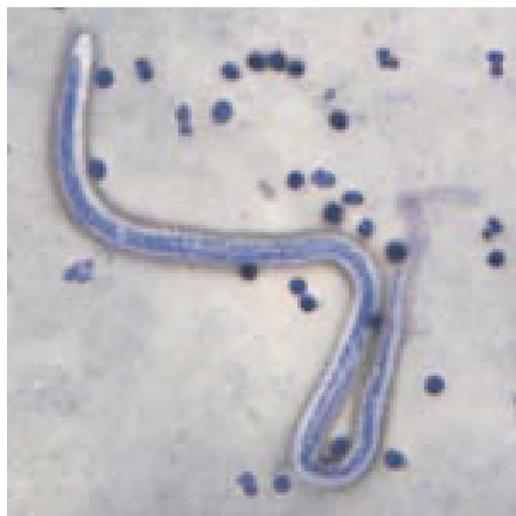
that occurred during this outbreak.<sup>14,193</sup> Neuroinvasive disease has also been seen in the ongoing outbreak in India.<sup>14</sup> It has been suggested that the mutation that has allowed chikungunya's evolutionary convergence with *Ae. albopictus* may underlie chikungunya's recently observed increased virulence,<sup>191</sup> but other factors may also be involved.

While clinical manifestations of chikungunya in young children tend to be mild, severe neonatal infections associated with mother-to-child transmission (MTCT) of chikungunya have been reported.<sup>192</sup> While the overall rate of chikungunya MTCT in a prospective study of 739 women infected during pregnancy with chikungunya in the La Reunion outbreak was 2.5% (19/739), among women with intrapartum viremia the MTCT rate was 48.7% (19/39).<sup>192</sup> Vertical transmission was noted exclusively in the presence of intrapartum viremia and in near-term deliveries with an average of 38 weeks' gestation.<sup>192</sup> Cesarean delivery was not protective.<sup>192</sup> Vertically infected neonates were universally asymptomatic at birth, and clinical illness manifested by fever and ill appearance (100%) and thrombocytopenia (89%) developed at a median of 4 days of age.<sup>192</sup> Encephalopathy developed in 9/19 cases and hemorrhagic fever in another.<sup>192</sup> Four of the neonates with severe disease developed persistent neurological sequelae.<sup>192</sup>

### Treatment and Prevention

There is currently no effective antiviral treatment for chikungunya, and symptom management typically focuses on control of fever and arthralgia, and on management of sequelae of severe infection, such as seizures.<sup>14,186</sup> While nonsteroidal anti-inflammatory drugs are helpful in both the acute phase of chikungunya and the long-term management of persistent arthralgias,<sup>14,188</sup> aspirin is generally avoided unless dengue infection has been carefully excluded, such that the risk of exacerbating hemorrhagic tendencies is avoided.<sup>188</sup> Particularly in small children, febrile seizures may be noted with otherwise uncomplicated chikungunya.<sup>186</sup>

As well, there is no available vaccine for chikungunya, and attack rates, as previously mentioned, may be quite high during outbreaks. Control focuses on control of the principal epidemic vectors, *Ae. aegypti* and *Ae. albopictus*.<sup>14</sup> Infection with chikungunya is believed to generate lifelong protective immunity.<sup>14</sup>



**FIG 10.** "W. bancrofti microfilaria." (Courtesy of CDC-DPDx.) (Color version of figure is available online.)

### Filariasis

Filariae are tissue-dwelling nematodes, and, globally, lymphatic filariasis is a leading cause of permanent disability.<sup>17</sup> As its pathology is chiefly due to the impact of adult parasites, its impact on young children is reasonably limited.<sup>17,195</sup> However, adolescent and young adult populations experience considerable morbidity from lymphatic filariasis. Pediatric and adolescent populations are reasonably limited.<sup>17,195</sup>

While there are many filarial parasites, only the three that cause lymphatic filariasis (*Wuchereria bancrofti* [Fig 10], *Brugia malayi*, and *Brugia timori*) are vectored by mosquitoes, the others being vectored by flies or, in the case of *Dracunculus* (Guinea worm), by copepods.<sup>196</sup> More than 120 million persons worldwide are estimated to be infected with one of the three lymphatic filariasis parasites,<sup>17</sup> with the vast majority (90+%) infected with *W. bancrofti*, widely distributed throughout tropical Africa, Asia, the Pacific and the Americas, and mostly in sub-Saharan Africa and India.<sup>196</sup> *B. malayi* is restricted to areas of Southeast Asia, China, and a very small focus in southwestern India, while *B. timori* is restricted to the island of Timor and a few other small islands of Indonesia.<sup>196</sup>

The adult forms of the lymphatic filarial parasites reside in the lymphatic vessels of their human hosts.<sup>196</sup> There they mate and may live for as long as 20 years, the females producing microfilariae, which make their way to the circulation and may be ingested by feeding mosquitoes (a large number of various

species).<sup>196</sup> Development to infective third-stage larvae within the mosquito takes at least 10 to 12 days, after which time these may enter through the host's skin when the mosquito again feeds.<sup>196</sup> Larvae migrate to the lymphatics to develop into adult worms, producing microfilariae after a minimum of 8 months for *W. bancrofti* and 3 months for *B. malayi*.<sup>196</sup> In most of their range, there is a daily periodicity in microfilaremia. For *W. bancrofti* and *B. malayi*, this is chiefly nocturnal, with peak blood concentrations around midnight.<sup>196</sup> Accordingly, these filaria are chiefly vectored by night-biting mosquitoes<sup>196</sup>; microfilaria may be absent in midday blood collections, an important point for parasitological diagnosis, which is based on the detection of microfilaria on Giemsa-stained blood smears, best taken at the time of day when microfilaria levels peak.<sup>196</sup>

The debilitating manifestations of chronic lymphatic filariasis are due to destruction of the lymphatic vessels by adult worms and particularly include lymphedema, elephantiasis, and hydrocele.<sup>196</sup> Indeed, hydrocele is the most common chronic manifestation of filariasis due to *W. bancrofti*.<sup>196</sup>

While it is distinctly uncommon for children to demonstrate signs of chronic filariasis, signs and symptoms of early filarial infection are more commonly seen.<sup>195</sup> Adolescents, in particular, are more likely to experience a syndrome due to an acute inflammatory response to dying adult worms, which manifests as fever and constitutional symptoms (myalgias, headache), lymphangitis involving an extremity, and lymphadenitis.<sup>195</sup> Tropical pulmonary eosinophilia (TPE), while more common in males ages 20 to 30 years, may occasionally be seen in children.<sup>195,196</sup> Caused by an immunological reaction to microfilariae in the lungs, TPE presents as paroxysms of cough and wheezing, chiefly at night, impressive eosinophilia (often over 3000 cells/mm<sup>3</sup>), and occasionally fever and weight loss. Serum IgE is often markedly elevated (>1000 IU/mL), as are antimicrofilarial antibodies, although microfilaremia is absent.<sup>195,196</sup> TPE responds well to diethylcarbamazine (DEC); this is often used as a criterion in making a diagnosis of TPE.<sup>195,196</sup>

## Management

While there are little data to support the use of antifilarial drugs in the management of acute lymphangitis and lymphadenitis,<sup>195</sup> antifilarial drugs are commonly used both in the management of chronic lymphatic filariasis and for its control.<sup>17,195-197</sup> DEC

has traditionally been used, with activity against both microfilaria and, to some degree, adult worms.<sup>195,197</sup> However, it must be used with caution in areas where onchocerciasis (West and Central Africa, parts of the Americas) and loiasis (broadly in West and Central Africa) co-infections may be seen; there is an increased risk of ocular side effects when DEC is used when *Onchocerca volvulus* infection is present, and use of DEC when *Loa loa* microfilaremia is present may result in encephalopathy.<sup>197</sup> Ivermectin and albendazole (given along with either DEC or ivermectin) also are used in the management of lymphatic filariasis, and, like DEC, are effective against microfilaria but have incomplete activity against the adult worms responsible for chronic symptoms.<sup>197</sup> There may be a role for doxycycline (in children older than age 8 and nonpregnant adolescents) in the management of lymphatic filariasis, as a strategy directed against *Wolbachia*, intracellular bacterial symbionts of filarial, the depletion of which by doxycycline kills the majority of adult worms.<sup>198</sup>

## Global Eradication of Lymphatic Filariasis

Lymphatic filariasis (LF) has been targeted for global eradication by the year 2020, within the framework of the Global Program for the Elimination of Lymphatic Filariasis (GPELF).<sup>17</sup> Using vector control, DEC, or a combination thereof, elimination of LF through interruption of transmission has proven feasible in some areas, including China and South Korea.<sup>17</sup> Current efforts of the GPELF recommend a single-dose of DEC (6 mg/kg, one dose) (or, as described above, ivermectin where DEC cannot be used), generally with albendazole (400 mg, one dose), given annually as mass drug administration to the general population in LF endemic areas for 5 years, a sufficient period to interrupt LF transmission.<sup>17,195</sup> In some countries, table salt fortified with DEC is being used for a period of 1 to 2 years.<sup>17</sup> ITNs have been shown to reduce LF transmission and augment filariasis control efforts<sup>199</sup>; indeed, in many locales, *W. bancrofti* is vectored by the same *Anopheles sp.* mosquitoes that transmit malaria, and programs integrating ITN distribution with mass drug administration have successfully improved ITN ownership and usage, aiding control efforts for both infections.<sup>199</sup>

## Concluding Remarks

As discussed here, mosquito-borne diseases have a disproportionate impact on poor populations in the developing world, particularly with respect to children. Where vaccination is widely available, as for YF, disease control has been readily achievable, although poor immunization coverage and the expansion of *Ae. aegypti* populations may allow outbreaks to become more frequent in future years. Japanese encephalitis control, too, has been achieved in higher income endemic countries where vaccine coverage has been high and modern animal husbandry practices prevail; expansion of vaccine programs in lower income endemic countries would likely, too, yield improved JE control. While no vaccine exists for the prevention of filarial infection, the natural history of filariasis lends itself to the application of an eradication program.

For the diseases described here for which effective and affordable vaccines do not yet exist, the prospects for control are much less clear. As described above, complete and sustained mosquito control is a complicated endeavor; by nature, the chief mosquito vectors, particularly *Ae. aegypti*, exploit the gaps opened by the facts of modern life in many poor, developing settings: weak central authority, favorable ecology, and the inescapable effect of poverty and neglect.

Indeed, it is fair to say that Africa's devastating malaria burden and the uncontrolled expansion of dengue, in particular, await the one intervention with the power to bring them under sustainable control: safe vaccines with long-lasting effect, affordable to the poorest of countries, and universally available to the infants and children who need them most urgently. While these visions are being revealed and their application brought to scale, it will remain of critical importance that existing effective interventions, such as ITNs and IPT in the case of malaria, be fully utilized, that the children of today may benefit while we await tomorrow's advances.

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