

Chikungunya Fever in the United States: A Fifteen Year Review of Cases

Katherine B. Gibney,^{1,2} Marc Fischer,¹ Harry E. Prince,³ Laura D. Kramer,⁴ Kirsten St. George,⁴ Olga L. Kosoy,¹ Janeen J. Laven,¹ and J. Erin Staples¹

¹Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention (CDC), Fort Collins, Colorado; ²Epidemic Intelligence Service Program, CDC, Atlanta, Georgia; ³Focus Diagnostics, Cypress, California; and ⁴Wadsworth Center, New York State Department of Health, Albany, New York

Background. Chikungunya virus (CHIKV) represents a threat to the United States, because humans amplify CHIKV and vectors that transmit CHIKV are present.

Methods. We described the epidemiology of laboratory-confirmed chikungunya fever (CHIK) cases in the United States in 1995–2009 and compared states with CHIKV vectors with states with returning viremic CHIK cases. For 2006–2009, we evaluated reporting of CHIK cases to ArboNET, the arboviral surveillance system.

Results. In 1995–2009, 109 CHIK cases were identified in the United States; all adult travelers. Sixty-two subjects (57%) had recently visited India, and 13 (12%) had CHIKV viremia. Of the 26 jurisdictions with CHIK cases, 22 (85%) reported the presence of CHIKV vectors. Twelve viremic travelers returned to 6 states with CHIKV vectors. Of the 106 cases identified in 2006–2009, only 27 (25%) were reported to ArboNET, with a median of 122 days (range, 44–273 days) between illness onset and reporting.

Conclusions. No locally acquired CHIK cases were identified. However, several viremic travelers returned to states with CHIKV vectors and presented a risk for local transmission. Incomplete and delayed reporting made ArboNET less useful. To minimize the risk of CHIKV spread in the United States, healthcare providers and public health officials should be educated about recognition, diagnosis, and reporting of CHIK cases.

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that causes chikungunya fever (CHIK), an acute febrile illness characterized by severe and often debilitating arthralgia [1]. Since 2005, CHIK outbreaks of unprecedented magnitude have occurred in South Asia and islands in the Indian Ocean [2]. In India, >1.3 million CHIK cases were reported in 2006, with attack rates as high as 45% in some areas [2]. Although mortality is rare, the resulting morbidity is substantial [3]. During recent outbreaks, CHIK patients reported a median of 35 days off work, and >60% had persistent arthralgia at 18 months after their acute illness [4, 5].

CHIKV infection also occasionally results in more severe clinical manifestations, including neurological complications, myocarditis, hepatitis, and hemorrhage [1, 6].

Humans and other primates are the primary amplifying hosts of CHIKV, and infected travelers can potentially introduce the virus into nonendemic areas. The period of viremia following symptom onset has been reported to be ≤ 7 days [7, 8]. In 2007, a viremic traveler from India introduced CHIKV into northern Italy, resulting in >200 locally acquired cases [8]. The two most common CHIKV vectors, *Aedes aegypti* and *Aedes albopictus*, are well established in the United States [9], and introduction of the virus could lead to local transmission and outbreaks.

Timely recognition, appropriate diagnostic testing, and reporting of CHIK cases to public health officials are required to mitigate the risk of importation and spread of CHIKV in the United States. Currently, CHIKV testing in the United States is available at the Centers for Disease Control and Prevention (CDC), 1 state public health laboratory, and 1 commercial laboratory. CHIK

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Correspondence: Marc Fischer, MD, Arboviral Diseases Branch, Division of Vector-Borne Diseases, CDC, 3150 Rampart Rd, Fort Collins, CO 80521 (mfischer@cdc.gov).

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is not a nationally notifiable condition. However, since 2006, state health departments could report CHIK cases to ArboNET, a national surveillance system that collects data on arboviral infections among humans, animal hosts, and vectors. We reviewed the epidemiology of all CHIK cases identified in the United States from 1995 through 2009, assessed the risk of local CHIKV transmission, and evaluated CHIK reporting to ArboNET. This information can be used by clinicians, laboratory personnel, and public health officials to help recognize future CHIK cases and to reduce the risk of subsequent spread and outbreaks.

METHODS

Case Finding

We identified all positive CHIK test results from 1995 through 2009 at CDC, the Wadsworth Center of the New York State Department of Health, and Focus Diagnostics. Since 1995, clinical specimens submitted to the CDC Arbovirus Diagnostic Laboratory (Fort Collins, CO) have been tested for evidence of CHIKV infection upon request or if a patient had a history of recent travel to an endemic area. Specimens are tested by enzyme-linked immunosorbent assay (ELISA) for CHIKV immunoglobulin (Ig) M and IgG antibodies [10, 11]. Specimens with a positive, equivocal, or indeterminate result for IgM antibodies are evaluated for CHIKV-specific neutralizing antibodies using plaque reduction neutralization tests (PRNT) with a 90% cutoff value (PRNT₉₀) [12, 13]. Serum specimens collected <7 days after onset of illness might also be tested for CHIKV RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) and CHIKV isolation using Vero cell culture [14]. Since 2005, Wadsworth Center has performed CHIKV PRNT, RT-PCR, and isolation in Vero cell culture. Since 2008, Focus Diagnostics has performed an immunofluorescence assay (IFA) for CHIKV IgM and IgG antibodies [15] and RT-PCR for CHIKV RNA. To our knowledge, there are no data comparing the relative sensitivity or specificity of the available CHIKV diagnostic assays.

Case Definition

We defined a CHIK case as a patient with ≥ 1 of the following laboratory findings in serum: (1) CHIKV or CHIKV RNA detected by viral isolation or RT-PCR, (2) ≥ 4 -fold rise in CHIKV neutralizing antibodies between acute- and convalescent-phase specimens, (3) CHIKV IgM antibodies, or (4) an equivocal or indeterminate result for CHIKV IgM antibodies but evidence of CHIKV neutralizing antibodies. Patients who had CHIKV isolated or CHIKV RNA detected were classified as being viremic.

Data Collection

For all CHIK cases identified at the CDC and Wadsworth Center, information was collected on sex, age, state from which

the specimen was submitted, date of illness onset, date of specimen collection, travel destination, and dates of travel. For cases identified at Focus Diagnostics, information was routinely available on sex, age, and date of specimen collection; state from which the specimen was submitted was available for some cases. The day of symptom onset was defined as day 0. For cases without a specific onset date noted, sample collection date was used as a surrogate for the month of illness onset. The presence of possible CHIKV vectors (ie, *Ae. aegypti* and *Ae. albopictus*) in a given state was determined by reports to ArboNET from 2002 through 2009.

Data Analysis

Data were analyzed using SAS statistical software, version 9.2 (SAS Institute), and mapped in the geographic information system (ArcView, version 9.3.1 [ESRI]). Categorical variables were described as proportions, and continuous variables were described by median and range. To assess the risk for local CHIKV transmission, we compared states that reported the presence of CHIKV vectors with states with laboratory-confirmed and viremic CHIK cases. We evaluated the completeness and timeliness of national CHIK surveillance by comparing CHIK cases identified through the 3 diagnostic laboratories from 2006 through 2009 with cases reported to ArboNET.

RESULTS

Overall, 109 laboratory-confirmed CHIK cases were identified in the United States from 1995 through 2009, including 1 case each in 1996, 2001, and 2005, and 106 cases (97%) from 2006 through 2009 (Figure 1). From 2006 through 2009, a median of 26 CHIK cases were identified per year (range, 12–42 cases per year). The median age of all case patients was 48 years (range, 20–78 years), and 57 case patients (52%) were in the 40–59 year age group (Table 1). Sixty-two (57%) of the case patients were female. Illness onset occurred in every month except

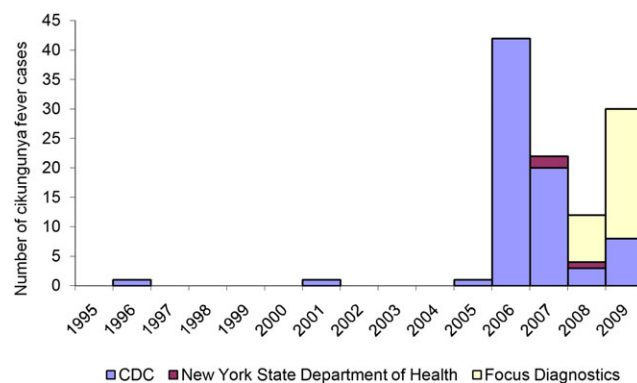


Figure 1. Chikungunya fever cases by testing laboratory and year, 1995–2009.

Table 1. Characteristics of Chikungunya Fever Cases Identified in the United States, 1995–2009 (N = 109)

Characteristic	No. of cases	(%) of cases
Age, years		
0–19	0	(0)
20–39	31	(28)
40–59	57	(52)
≥60	16	(15)
Unknown	5	(5)
Sex		
Female	62	(57)
Male	46	(42)
Unknown	1	(1)
Country or region where CHIKV infection acquired		
India ^a	62	(57)
Other Asian country ^a	9	(8)
Africa	6	(6)
Indian Ocean	2	(2)
Unknown ^b	31	(28)
Illness onset related to return to the United States		
>7 days before return to U.S.	18	(17)
≤7 days before return to U.S.	14	(13)
On day of return or in U.S.	14	(13)
Unknown ^b	63	(58)

^a One case went to both India and Sri Lanka.

^b Information available for certain cases tested at Centers for Disease Control and Prevention and Wadsworth Center.

March. However, 52 cases (48%) occurred during the months July–September, when vectors capable of transmitting CHIKV are likely to be most active (Figure 2).

Of the 78 cases with travel information available, all had traveled outside the United States immediately before or during their illness onset. Most (72 [92%]) had traveled to a region

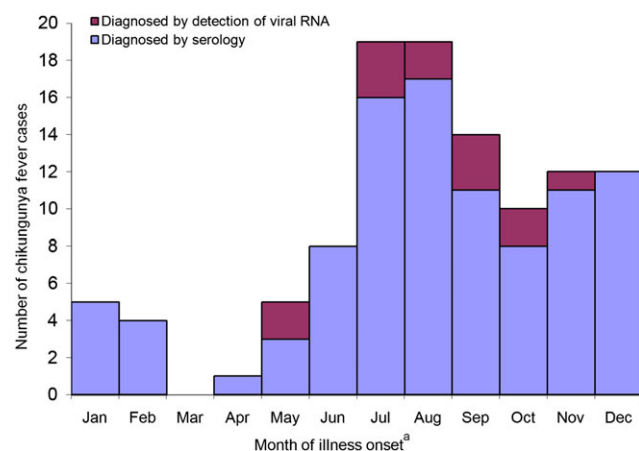


Figure 2. Month of illness onset of chikungunya fever cases identified in the United States, 1995–2009. ^aIf date of onset was missing, date of collection was used as a surrogate to determine month of illness onset.

during a known CHIK outbreak; only 6 cases (8%) were associated with travel to an endemic region in Africa (5 cases) or Asia (1 case) that were not known to be experiencing an outbreak at the time of travel. Of cases with a detailed travel history, both infections that occurred before 2006 were acquired in Africa, whereas 70 (92%) of the 76 cases that occurred since 2006 acquired their CHIKV infection during travel to Asia. India was the most common country of CHIKV acquisition for all years since 2006 (Table 1). Of the 46 cases with known dates of travel and illness onset, 28 (61%) returned to the United States within 7 days of illness onset or had illness onset in the United States.

Of the 109 CHIK cases identified, 76 (70%) had diagnostic testing performed at CDC, 3 (3%) at Wadsworth Center, and 30 (28%) at the commercial laboratory (Figure 1). CHIKV RNA was detected by RT-PCR in 13 (12%) of the 109 cases. All viremic cases were tested <7 days after illness onset, and all had illness onset in the months of May–November. Of the 39 cases with known date of illness onset who had CHIKV RT-PCR performed, 8 (80%) of 10 were positive when tested ≤3 days after illness onset, 5 (50%) of 10 were positive on day 4–6, and none of 19 were positive after day 6. Twelve (92%) of the 13 cases with CHIKV RNA detected also had viral isolation attempted. CHIKV was isolated in 7 (58%); all of the culture-positive specimens were collected ≤4 days after illness onset. An additional 14 cases returned to the United States <7 days after illness onset but did not have viral isolation attempted or RT-PCR testing performed.

For the remaining 96 CHIK cases (88%), the diagnosis was determined on the basis of the detection of anti-CHIKV antibodies. Of case patients tested for anti-CHIKV antibodies in the first week of illness, 13 (54%) of 24 had IgM antibodies detected, 6 (25%) of 24 had IgG antibodies detected, and 13 (62%) of 21 had neutralizing antibodies detected. Of the 51 cases tested after the first week of illness, 47 (92%) were IgM positive, 42 (82%) were IgG positive, and 51 (100%) had CHIKV-specific neutralizing titers. Of the 4 specimens that were not IgM positive after the first week, one was in the equivocal range (day 32 of illness) and 3 had indeterminate reactions (days 57–93); all had CHIKV-specific neutralizing titers. Of the 38 cases tested >4 weeks after illness onset, 36 (95%) were CHIKV IgG positive. The 2 samples that were not IgG positive had indeterminate reactions; both had IgM and neutralizing antibodies detected.

Information identifying the state or district from which specimens were submitted was available for 94 CHIK cases. Specimens that tested positive for CHIKV infection were submitted from 25 states and the District of Columbia (DC) (Figure 3). California (24 [26%]) and Illinois (14 [15%]) submitted the highest number of samples testing positive for CHIKV. Of the jurisdictions with CHIK cases, 85% (21 states and DC) reported having potential CHIKV vectors present in their state or district. The 13 viremic cases originated in 7 states;

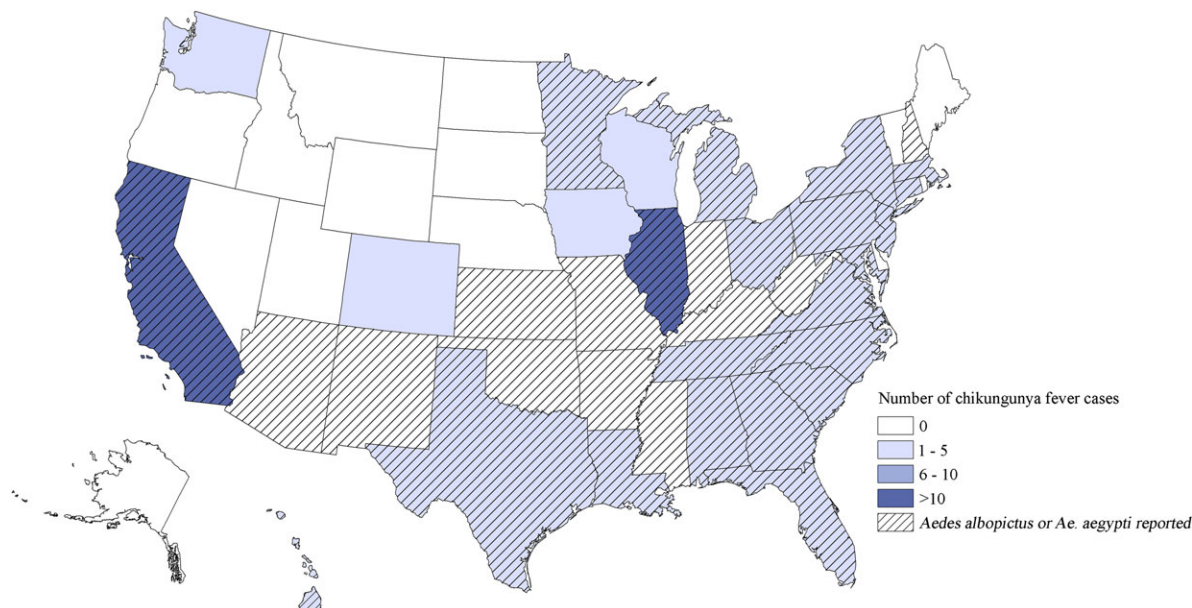


Figure 3. Chikungunya fever cases identified (1995–2009) and presence of Chikungunya virus vectors reported (2002–2009) by state.

of these, 12 viremic cases returned to 6 states (California, Illinois, Massachusetts, Minnesota, New York, and Pennsylvania) that reported presence of potential CHIKV vectors in ≥ 1 location in their state.

Of the 106 CHIK cases identified from 2006 through 2009, only 27 (25%) were reported to ArboNET. The majority (25 [93%]) of the 27 cases were reported in 2006 and 2007. All reported cases had laboratory testing performed at the CDC (24 cases) or Wadsworth Center (3 cases). The time between onset of CHIK illness and reporting of the CHIK case to ArboNET was a median of 122 days (range, 44–273 days).

DISCUSSION

The epidemic potential of CHIKV has recently been observed in South Asia and islands of the Indian Ocean [2]. The potential for a viremic traveler to introduce CHIKV into a nonendemic country, resulting in local spread, was demonstrated in Italy in 2007 [8]. Moreover, outbreaks of dengue virus (which shares vectors with CHIKV) have occurred in Hawaii, Texas, and Florida in the past decade [16–18], reinforcing the possibility of imported arboviruses causing epidemics in the United States. Although the outbreak of CHIKV in Italy was contained after intensive vector control efforts [8, 19, 20], the sustained local transmission of dengue virus over ≥ 2 seasons in Key West, Florida [18], and the established presence of *Ae. aegypti* and *Ae. albopictus* in parts of the United States [9] suggest that local transmission of CHIKV could potentially be maintained if it were introduced in the right location and during the right

season. Timely recognition, appropriate diagnostic testing, and reporting of cases to public health officials are needed to mitigate the risk of importation and spread of CHIKV in the United States and other nonendemic countries.

Until 2006, the diagnosis of CHIK in a US traveler was rare. However, over the past 4 years, a median of 26 CHIK cases have been identified in the United States each year. All cases were adult travelers, and most were returning from areas with ongoing CHIK epidemics. Many of the travelers became ill in the United States or returned to the United States within a week of becoming ill, suggesting that they might have been viremic while in the United States. Furthermore, many returned to a state that has reported vectors capable of transmitting the virus. As occurred in Italy in 2007 [8], the first evidence of local CHIKV transmission may come from the diagnosis of CHIK in a patient with no history of recent travel. For these reasons, healthcare providers and public health officials need to be aware of CHIK, including its clinical manifestations and methods of diagnosis, so that suspected cases are tested appropriately and potentially viremic cases are counseled to avoid mosquito bites to prevent subsequent transmission.

The age and sex of CHIK cases imported to the United States are similar to those of CHIK cases reported in travelers returning to Europe [7, 21–23]. However, although cases returning to the United States, Singapore, and Australia were primarily acquired in India, Sri Lanka, and Malaysia [24–26], most European cases were acquired in islands in the Indian Ocean, presumably reflecting differences in travel patterns and cultural ties between regions. The lack of pediatric cases identified in the United States

may reflect the age of travelers, differences in testing practices among pediatric and adult patients, or a reduced likelihood of symptomatic disease among infected children, compared with adults [27].

The period of viremia following symptom onset has been reported to be ≤ 7 days [7, 8], which is consistent with our finding of isolating CHIKV up to 4 days and detecting CHIKV RNA by RT-PCR up to 6 days after onset of illness. Previous reports from Europe have indicated that CHIKV RNA could be detected in all patients up to day 4 of illness [7, 28]. However, in our study, some cases did not have CHIKV detected by RT-PCR within this period. This may be due to differences in test characteristics or may relate to inaccurate documentation of date of illness onset. Importantly, IgM and neutralizing antibodies were detected in $<65\%$ of samples collected within the first week of illness; therefore, negative antibody results in the first week of illness cannot be used to rule out CHIKV infection. Samples taken within the first week of illness that test negative for anti-CHIKV IgM or neutralizing antibodies ideally should be tested for CHIKV by culture or by RT-PCR, and a convalescent sample should be collected after day 7 of illness to repeat the serological testing. Two studies have shown that anti-CHIKV IgM antibodies can persist for 18 months in one-third to one-half of CHIK patients; therefore, a positive CHIKV IgM test result occasionally may reflect past rather than recent CHIKV infection [4, 29].

At the present time, reporting of CHIK cases to ArboNET is incomplete and delayed, and ArboNET is unlikely to assist in the recognition of an outbreak of this disease. Steps that may improve the completeness and timeliness of CHIK reporting include: education of healthcare providers regarding recognition, diagnosis, and reporting of CHIK cases; improvement of communication between commercial laboratories and state and local public health departments; and the classification of CHIK as a nationally notifiable condition.

This analysis has several limitations. It is likely that we have underestimated the number of CHIK cases in the United States, because (1) patients may not present for medical care, (2) healthcare providers may not recognize the clinical features of CHIK or submit specimens for appropriate testing, and (3) testing may miss cases if performed early (before production of IgM) or late (after IgM levels wane). In addition, we have reported cases identified at CDC, 1 state public health laboratory, and 1 commercial laboratory only. As far as we are aware, these are the only laboratories in the United States that offer testing for CHIKV. However, additional laboratories may offer CHIKV testing, especially as commercial assays become more widely available. Information on the detection of CHIKV vectors was presented at the state level, when in fact the distribution of the vectors may be limited to focal areas within a state and may not overlap with the location of CHIK cases. Vector distributions in

the upper Midwest (eg, Michigan or Minnesota), the Plains, and the arid West may reflect single observations due to seasonal introductions rather than sustained, established populations that occur in other areas. Reporting of these vectors to ArboNET was not reliable before 2002; therefore, the period of vector surveillance presented in this paper (2002–2009) is shorter than that of CHIK cases identified (1995–2009). Finally, demographic and travel information was missing for some cases, and this may impact how representative the data are for all cases.

There is neither an available vaccine to prevent nor a specific antiviral therapy to treat CHIKV infection. All travelers to endemic areas should be advised to take precautions to avoid mosquito bites to reduce the risk for CHIK and other vector-borne infectious diseases. These precautions include using insect repellent, wearing permethrin-impregnated clothing, sleeping under permethrin-impregnated bed nets, and staying in accommodations with screened or air-conditioned rooms [30]. The majority of the CHIK cases identified in the United States became ill while still overseas, highlighting the need for travelers to be informed about the risk of CHIKV acquisition overseas, the symptoms associated with the illness, and ways to seek appropriate medical care while overseas. Increasing awareness of travelers and clinicians about this disease should facilitate diagnosis of cases when they occur. In addition, improving CHIK surveillance in the United States may result in rapid and targeted public health interventions to prevent local transmission, potentially limiting the spread of CHIKV in the United States.

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