

were VGI, including a cluster of isolates with a single multilocus sequence type originating in the southeastern United States (10). The isolate in this case was identified as molecular type VGI and by multilocus sequence typing was shown to have the same sequence type as isolates from patients in Florida and Georgia and isolates from the environment in Washington.

Infections attributable to *C. gattii* are not confined to tropical and subtropical regions. The case we describe serves to extend the known range of this organism to include Illinois. Infections might be missed, given that many laboratories do not routinely differentiate *C. gattii* from *C. neoformans*. Mortality rates can range from 13% to 33% (4). Thus, clinicians and laboratorians must have increased awareness of this emerging infectious disease.

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Late or Lack of Vaccination Linked to Importation of Yellow Fever from Angola to China

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During March and April 2016, 11 yellow fever cases were identified in China. We report epidemic and viral information for 10 of these patients, 6 of whom had been vaccinated before travel. Phylogenetic analyses suggest these viruses nested within the diversity of strains endemic to Angola, where an outbreak began in 2015.

In December 2015, the first case of a major yellow fever outbreak was reported in Angola; the outbreak spread to Democratic Republic of the Congo (DRC) (<http://www.who.int/csr/don/13-april-2016-yellow-fever-angola/en/>). In addition to 965 confirmed cases in DRC during

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December 2016–February 2017 (<https://reliefweb.int/report/democratic-republic-congo/yellow-fever-outbreak-angola-and-democratic-republic-congo-ends>), the outbreak led to exportation to other countries. In China, 11 imported cases were reported during March and April 2016 (1); 1 case-patient subsequently died (2). We conducted a clinical-epidemiologic study on 10 of the 11 case-patients. The study was approved by the Review Board of Beijing Ditan Hospital (Beijing, China) and the Ethics Committee of State Key Laboratory of Pathogen and Biosecurity. We also obtained informed consent from recruited patients.

We confirmed the yellow fever diagnoses according to criteria established by the China National Health and Family

Planning Commission, in agreement with the recommendations of the World Health Organization (3). All case-patients were citizens of China who had stayed in Angola for a period of 5 months to 7 years before returning to China; 7 (70%) were male, the median age was 41 (range 17–50) years (online Technical Appendix Table 1, <https://wwwnc.cdc.gov/EID/article/24/7/17-1868-Techapp1.pdf>). Six case-patients reported a history of yellow fever vaccination; 4 of those were vaccinated <14 days before symptom onset. Case-patient 7 received vaccination in China 5 years before symptoms occurred, and case-patient 10 was vaccinated in Namibia 10 months before onset of illness. None had received fractional doses of yellow fever vaccine as advocated in some studies (4).

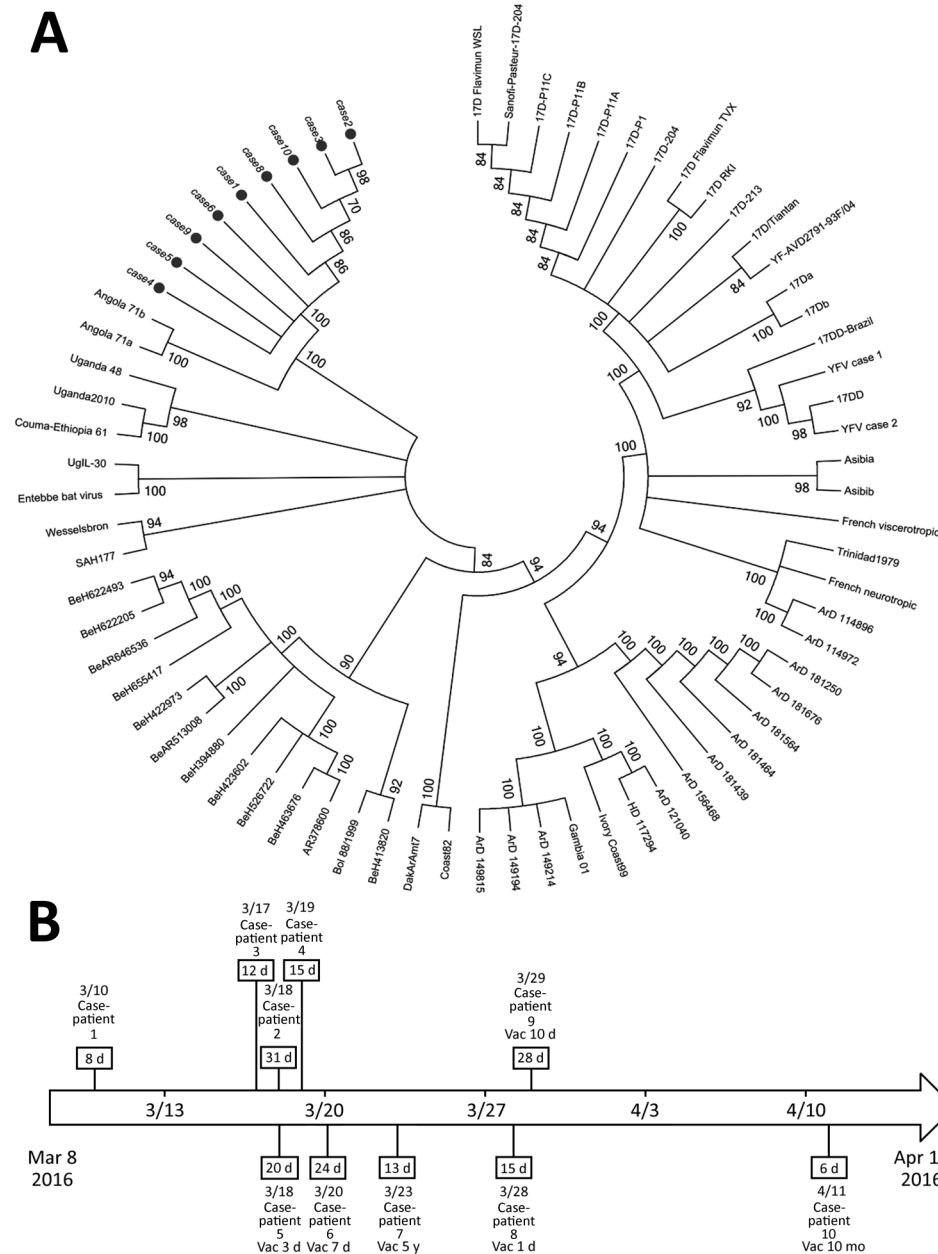


Figure. Phylogenetic analysis of yellow fever viruses and clinical courses for persons with yellow fever cases imported from Angola to China. A) Phylogenetic relationships among the yellow fever viruses from samples obtained from 9 case-patients (black circles). An unrooted dendrogram with maximum-likelihood by genome sequences represents the phylogenetic relationships. Clusters with bootstrap support values <70 were integrated; bootstrap values are shown on the branches. B) Dates of hospital admission, detection of virus in urine, and vaccination status for the 10 case-patients investigated. Case-patients 1–4 were not vaccinated. Numbers in boxes indicate longest interval from symptom onset to urine virus sequence detection. Vac, interval from previous vaccination to symptom onset.

We tested blood samples from all case-patients for yellow fever–specific antibodies by ELISA. We also extracted RNA from blood and urine samples by using the QIAamp MinElute Virus Spin Kit (QIAGEN, Valencia, CA, USA) for reverse transcription PCR virus detection. Phylogenetic analysis (Figure, panel A) of samples from 9 case-patients showed that the sequences were very closely related to each other and resembled the wild-type strain implicated in the Angola outbreak (2). We evaluated virus sequences of 5 of the 6 vaccinated case-patients; all showed the same wild-type strain. For the remaining patient (case-patient 7), RNA extraction was unsuccessful. She had been vaccinated 5 years before her illness, excluding the possibility of a vaccine-related adverse event.

Clinically, all 10 case-patients had acute onset of fever lasting 1–7 days; the highest temperature was 39.5°C (online Technical Appendix Table 2). The most common symptoms were fatigue, headache, dizziness, and myalgia. Of 10 case-patients, 8 had been treated for malaria before yellow fever was confirmed. Eight case-patients, including 2 of the 4 unvaccinated case-patients, had relatively mild symptoms. Case-patients 1 and 2, both unvaccinated, had severe disease; signs and symptoms were jaundice, vomiting, hemorrhaging (petechiae, ecchymosis, and gastrointestinal bleeding), and oliguria, as well as high levels of liver enzymes (alanine aminotransferase 11,425 and 3,710 u/L, respectively) and total bilirubin (>100 µmol/L). We also noted bleeding tendency, reflected by a high international normalized ratio and thrombocytopenia. Case-patient 1 deteriorated rapidly as a result of severe kidney and liver damage; biopsy showed evidence of panlobular and confluent hepatocyte necrosis (2). His CD4 T cell count was low at 155 cells/µL, but we excluded HIV co-infection. Despite continuous hemofiltration and hemodialysis and mechanical ventilation support, he died 9 days after symptom onset. The remaining 9 patients recovered after hospitalization, which lasted for a median of 16 (range 11–52) days.

Case-patients 1 and 2 also showed strong inflammatory responses as reflected by high plasma level of interleukin 6. Yellow fever virus nucleic acid continued to be detectable in urine during week 1 after symptom onset; case-patient 2 had the longest interval of detection at 31 days (Figure, panel B).

Overall, the clinical courses of these imported yellow fever cases in China were similar to others reported in the published literature: mild diseases in most case-patients, but high fatality rates among severe cases (5). China is not a yellow fever–endemic area, but importation of the virus was not surprising, considering the high number of travelers between Angola and China (6). Unfortunately, vaccination coverage was not high for Chinese travelers bound for Angola; among this cohort, only 2 had been vaccinated before travel to a yellow fever–endemic area. Travelers

may be worried about vaccine-associated viscerotropic disease (7), but this condition did not occur among the vaccinated case-patients in our study, who all had a moderate disease, requiring hospitalization of 11–29 days. The World Health Organization had recommended vaccination at least 10 days before entering a yellow fever–endemic area, but late vaccination in travelers is common (8).

Our observations highlight the importance of timely immunization to achieve protection during an outbreak within a yellow fever–endemic area. Vaccination efficacy and long-term protection are other concerns highlighted in this study: 2 patients were infected despite vaccination received 1–5 years previously. Although most international guidelines did not recommend booster administration of vaccine, its possible role in outbreak settings demands further research (9,10).

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Enterovirus A71 Infection, Thailand, 2017

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An outbreak of hand, foot and mouth disease among children in Thailand peaked in August 2017. Enterovirus A71 subgenogroup B5 caused most (33.8%, 163/482) cases. Severe disease (myocarditis and encephalitis) was observed in 1 patient. Coxsackievirus A6 was detected in 6.0% (29/482) of patients, and coxsackievirus A16 was detected in 2.7% (13/482) of patients.

Hand, foot and mouth disease (HFMD) and herpangina, caused primarily by enterovirus A, commonly affect children and result in painful blisters in the buccal cavity and on the soles of the hands and feet. In rare situations, enterovirus infection can lead to severe neurologic complications, notably aseptic meningitis, encephalitis, acute flaccid paralysis, and death in young children (1).

A nationwide outbreak of HFMD caused by coxsackievirus A6 (CV-A6) affected many children in Thailand in 2012 (2). Since that time, ≈50,000 cases of HFMD

have been reported annually to the Thailand Ministry of Public Health (3); CV-A6 and CV-A16 are the main causative agents. Most reports were based on clinical symptoms; laboratory-based confirmations are rare. Consequently, the incidence increased awareness and the need for diagnostic-based epidemiologic surveillance. As of September 25, 2017, a total of 59,071 cases of HFMD have been reported (4). We determined the prevalence and viral etiology of enterovirus infections among patients with clinical HFMD and herpangina in Thailand during 2017.

The study was approved by the Chulalongkorn University Faculty of Medicine Institutional Review Board (institutional review board no. 002/60). We tested clinical specimens from 482 children requiring hospital care for HFMD (n = 435) and herpangina (n = 47) that were submitted to King Chulalongkorn Memorial Hospital (Bangkok, Thailand) during January 1–October 30, 2017, from 12 provinces with reported HFMD outbreaks (online Technical Appendix Figure 1, <https://wwwnc.cdc.gov/EID/article/24/7/17-1923-Techapp1.pdf>). The study population was 273 boys and 209 girls (sex ratio M:F 1.3:1; age range 4 days to 45 years; mean ± SD age 2.9 ± 4.0 years; median age 2.0 years).

We subjected specimens to 2 real-time reverse transcription PCRs (RT-PCRs). The first RT-PCR identifies enterovirus A71 (EV-A71), CV-A6, and CV-A16 (5). We then subjected virus-positive samples to full-length virus capsid protein 1 (VP1) gene amplification by using a conventional RT-PCR and nucleotide sequencing to identify EV-A71 subgenogroups (6). The second RT-PCR is a pan-enterovirus real-time RT-PCR, which also detects the glyceraldehyde-3-phosphate dehydrogenase gene (internal control). We subjected samples to a conventional RT-PCR that used CODEHOP degenerate primers to identify enterovirus serotypes other than EV-A71, CV-A6, and CV-A16 (7). We also performed molecular typing by using phylogenetic analysis and nucleotide sequence comparisons of strains. Sequences were deposited in GenBank (accession nos. MG843892–844136).

Enterovirus infections were detected throughout the year; increased frequency was observed in the rainy season (June–September) (online Technical Appendix Figure 1). Enteroviruses were identified in 67.4% (325/482) of samples. EV-A71 was most frequent (33.8%, 163/482), followed by CV-A6 (6.0%, 29/482), and CV-A16 (2.7%, 13/482). Analysis of partial VP1 sequences showed that almost all (99.4%, 162/163) of EV-A71 was subgenogroup B5: only 2 samples were subgenogroup C4 (Figure 1A). Full-length VP1 analysis also confirmed our EV-A71 subgenogroup assignment (online Technical Appendix Figure 2).

Comparison of full-length VP1 nucleotide sequences of subgenogroup B5 viruses between strains isolated in Thailand during this study and those previously isolated in

Late or Lack of Vaccination after Angola Outbreak Linked to Yellow Fever, China

Technical Appendix

Technical Appendix Table 1. General characteristics of the case-patients in China who had confirmed diagnoses of yellow fever after being in Angola during the 2015–2017 outbreak (n = 10)

Characteristic	No. median	Range (%)
Male gender	7	(70)
Age (years)	41	(17–50)
Duration of stay in Angola	<1 y	4 (40)
	1–3 y	1 (10)
	3–5 y	2 (20)
	>5 y	3 (30)
Place of diagnosis	Beijing	5 (50)
	Fuzhou	5 (50)
Month of symptom onset	March	9 (90)
	2016	
	April 2016	1 (100)
History of yellow fever vaccination	6	(60)
Days of hospitalization	16	(11–52)
Deceased	1	(6)

Technical Appendix Table 2. Clinical and epidemiologic characteristics of yellow fever cases imported to China from Angola in March and April 2016 (n = 10)

Characteristic	Case-patient No.									
	1	2	3	4	5	6	7	8	9	10
A) Epidemiologic history										
Date of arrival in China	3/9	3/18	3/17	3/19	3/11	3/19	3/21	3/21	3/27	4/11
Date of symptom onset	3/8	3/11	3/9	3/6	3/10	3/17	3/18	3/13	3/12	4/15
Date of hospital admission	3/10	3/18	3/17	3/19	3/18	3/20	3/23	3/28	3/29	4/11
Date of confirmed diagnosis	3/16	3/18	3/18	3/20	3/24	3/24	3/25	3/30	3/2	4/13
Previous vaccination	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Interval from vaccination to symptom onset	NA	NA	NA	NA	3 d	7 d	5 y	1 d	10 d	10 mo
B) Clinical signs and symptoms										
Fever	+	+	+	+	+	+	+	+	+	+
Highest temperature recorded C°	39.3	39.1	38.5	38	ND	39	37.3	39.3	39	39.5
Days of fever	1	7	7	3	1	6	1	2	5	3
Hemorrhage	+	+	ND	ND	ND	ND	ND	ND	ND	ND
Oliguria	+	+	ND	ND	ND	ND	ND	ND	ND	ND
Other symptoms	H, D, M, J, V, F	D, M, J, V, F	D, M, F	H, D, M, F	H, M, F	H, D, M, V, F	F	H, D, M, F	H, D, M, F	H, D, M, F
Shock	+	ND	ND	ND	ND	ND	ND	ND	ND	ND
Days in hospital	6	52	28	26	15	27	17	12	11	29
Outcome	Died on day 9	Rec	Rec	Rec	Rec	Rec	Rec	Rec	Rec	Rec

Characteristic	Case-patient No.									
	1	2	3	4	5	6	7	8	9	10
C) Laboratory findings at diagnosis										
Hemoglobin (g/dL)	16.1	17.0	13.7	15.3	13.1	13.9	12.9	11.8	14.1	15.2
Leukocyte ($\times 10^9/L$)	6.23	3.01	3.91	6.06	5.51	2.1	9.41	5.59	6.54	3.07
Platelet count ($\times 10^9/L$)	70	70	90	302	204	65	295	254	373	60
ALT (U/L)	11425	3710	323.3	312.8	81	805	139	44	259	1418.1
AST (U/L)	21467	6460	158.8	101.6	49	857	75	40	61	714.1
Total bilirubin ($\mu\text{mol/L}$)	100.6	166.2	8.3	12.2	5.4	8.9	4.7	13	15	14.8
GGT (U/L)	ND	331.5	294	248.7	49	43	139	20	177	631.6
CK (U/L)	670.2	470.4	167.3	58.7	83	140	405	177	176	162.2
Creatinine ($\mu\text{mol/L}$)	650.1	89	67.2	65.6	56	79	61	60	71	78
BUN (mmol/L)	19.33	6.18	4.13	2.72	2.6	4.2	3.4	7.3	4.6	5.56
IL-6 (pg/ml)	182.6	137.2	<1.5	<1.5	2.79	12.12	10.68	5.77	3.4	ND
CD4(cells/ul)	155	333	1163	717	648	ND	ND	467	1500	798
D) Urine virus sequence detection										
Days from symptom onset	8	31	12	15	20	24	13	15	28	6
Result (CT value)	33.5	25.22	30.95	35.22	39.40	39.39	U	37.06	37.29	23.77

NA, not applicable; ND, no data; +, U, undetectable; H, headache; D: dizziness; M: myalgia; J: jaundice; V: vomiting; F: fatigue.