MAJOR ARTICLE

A Family Cluster of Infections by a Newly Recognized Bunyavirus in Eastern China, 2007: Further Evidence of Person-to-Person Transmission

Chang-jun Bao,[1,a] Xi-ling Guo,[2,a] Xian Qi,[1,a] Jian-li Hu,[1,a] Ming-hao Zhou,[3,a] Jay K. Varma,[4] Lun-biao Cui,[2] Hai-tao Yang,[3] Yong-jun Jiao,[2] John D. Klena,[4] Lu-xun Li,[5] Wen-yuan Tao,[6] Xian Li,[2] Yin Chen,[2] Zheng Zhu,[2] Ke Xu,[1] Ai-hua Shen,[5] Tao Wu,[2] Hai-yan Peng,[2] Zhi-feng Li,[1] Jun Shan,[1] Zhi-yang Shi,[2] and Hua Wang[3]

[1]Department of Acute Infectious Diseases Control and Prevention, [2]Pathogenic Microorganism Institute, and [3]Headquarters, Jiangsu Provincial Centre for Disease Control and Prevention, Nanjing, China; [4]Centers for Disease Control and Prevention, Atlanta, Georgia; [5]Lishui County Centre for Disease Control and Prevention, and [6]People's Hospital of Lishui County, Nanjing, China

Background. Seven persons in one family living in eastern China developed fever and thrombocytopenia during May 2007, but the initial investigation failed to identify an infectious etiology. In December 2009, a novel bunyavirus (designated severe fever with thrombocytopenia syndrome bunyavirus [SFTSV]) was identified as the cause of illness in patients with similar clinical manifestations in China. We reexamined this family cluster for SFTSV infection.

Methods. We analyzed epidemiological and clinical data for the index patient and 6 secondary patients. We tested stored blood specimens from the 6 secondary patients using real time reverse transcription polymerase chain reaction (RT-PCR), viral culture, genetic sequencing, micro-neutralization assay (MNA), and indirect immunofluorescence assay (IFA).

Results. An 80-year-old woman with fever, leucopenia, and thrombocytopenia died on 27 April 2007. Between 3 and 7 May 2007, another 6 patients from her family were admitted to a local county hospital with fever and other similar symptoms. Serum specimens collected in 2007 from these 6 patients were positive for SFTS viral RNA through RT-PCR and for antibody to SFTSV through MNA and IFA. SFTSV was isolated from 1 preserved serum specimen. The only shared characteristic between secondary patients was personal contact with the index patient; none reported exposure to suspected animals or vectors.

Conclusions. Clinical and laboratory evidence confirmed that the patients of fever and thrombocytopenia occurring in a family cluster in eastern China in 2007 were caused by a newly recognized bunyavirus, SFTSV. Epidemiological investigation strongly suggests that infection of secondary patients was transmitted to family members by personal contact.

In December 2009, a novel bunyavirus—named severe fever with thrombocytopenia syndrome bunyavirus (SFTSV)—was isolated from a patient in central China. Genomic sequencing indicated that the SFTSV comprises a third group within the genus phlebovirus, family *Bunyaviridae* [1]. Illness caused by this novel virus is characterized by sudden onset of fever and respiratory tract or gastrointestinal symptoms, followed by a progressive decline of whole white blood cell and platelet counts.

Three viruses in the family *Bunyaviridae* including Crimean-Congo hemorrhagic fever (CCHF) virus from the genus nairovirus, Rift Valley fever (RVF) virus from the genus phlebovirus, and Old World and New World hantaviruses, such as Andes virus, causing Hemorrhagic

Received 30 May 2011; accepted 8 September 2011; electronically published 25 October 2011.

[a]C. B., X. G., X. Q., J. H., and M. Z. contributed equally to this work.

Correspondence: Hua Wang, MD, Professor and Director, Jiangsu Provincial Centre for Disease Control and Prevention, 172, Jiangsu Rd, Nanjing 210009, Jiangsu Province, China (hua@jscdc.cn).

Clinical Infectious Diseases 2011;53(12):1208–14

1058-4838/2011/5312-0006$14.00
DOI: 10.1093/cid/cir732

Fever Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS), respectively, from the genus hantavirus are recognized as able to induce hemorrhagic fever disease in humans. Cases most likely encounter these viruses via direct contact with infected animal tissues, inhalation of contaminated material, or being bitten by arthropod vectors such as mosquitoes, sand flies, or ticks [2]. Some SFTS patients have reported that they had seen or been bitten by ticks before their illness onset; in their original study, Yu et al [1] reported that there was no epidemiological evidence for person-to-person transmission. SFTSV was therefore proposed to be transmitted by contact with animals and/or vectors such as the *Haemaphysalis longicornis* ticks.

In May 2007, Jiangsu Province Centre for Disease Control and Provention (JS-CDC) was notified about a family in which 6 persons developed fever and clinical symptoms compatible with human granulocytic anaplasmosis (HGA) [3]. In October 2006, an outbreak of HGA had been reported from an adjacent province [4]; therefore, initial investigation of this family cluster focused on identifying *Anaplasma phagocytophilium*. Neither extracted DNAs nor antibodies to the *A. phagocytophilium*, however, were detected from patient blood specimens. Additional laboratory studies ruled out infections from HFRS virus, dengue fever virus, typhoid/paratyphoid *Salmonella* bacteria, leptospirosis, *Rickettsia*-like spotted fever, Pullman's typhus, tsutsugamushi fever, or Q fever. In December 2009, Chinese scientists identified SFTSV in patients with a similar clinical syndrome as the 2007 family cluster. In this paper, we describe the laboratory evidence gathered through molecular and serological analysis and assess the possible routes of SFTSV in the 2007 family cluster.

METHODS

Patients

The 2007 family cluster occurred in a hilly area about 110 km south from Nanjing in eastern China. The first patient (index patient, patient A) was an 80-year-old female who lived in a small village with her husband. She visited the village clinic on 19 April 2007, complaining of fever and chills. She was treated with gentamicin and dexamethasone. On 20 April 2007, she was admitted to the local county hospital with a temperature of 39.0°C. Laboratory testing performed on admission revealed leukopenia (WBC count, 3.1×10^9/L) and thrombocytopenia (PLT count, 48×10^9/L). Chest X-ray examination showed bronchopneumonia. On 21 April, the patient was discharged home for her birthday party, then readmitted to the local hospital on 23 April. At this time, the patient was noted to be confused and unable to speak. Her neck was supple. There were no focal neurological abnormalities. Her temperature was 38.2°C. Blood tests showed that her white blood cell (WBC) count had declined to 1.6×10^9/L and platelet (PLT) count to 30×10^9/L. On 25 April, she was transferred to a municipal hospital. Her condition continued to decline rapidly; on admission, she was noted to have elevated liver-associated enzyme levels (serum aspartate aminotransferase, 3869 U/L; alanine aminotransferase, 573 U/L; lactate dehydrogenase, 3094 U/L) and acute renal insufficiency (creatinine, 1883 umol/L; urea nitrogen, 1306 umol/L). The next day, she developed bleeding gums, ecchymosis at an intravenous line puncture site, melena, and fecal incontinence. On 27 April, a massive amount of fresh blood effused from the needle puncture site. Family members elected to withdraw intensive medical support, taking her home, where she died a few hours later.

Within 10 days of patient A's death, 6 of her family members developed similar symptoms. The elder son-in-law (patient B) of patient A developed symptoms first, with onset on 3 May 2007, 6 days after his mother-in-law's death. Symptoms subsequently developed in patient C (patient A's elder daughter, patient B's wife) and patient D (patient A's younger nephew) on 4 May, patient E patient A's younger son-in-law) and patient G (patient's elder nephew) on 5 May, and patient F (patient A's second daughter, patient E's wife) on 7 May. All the secondary patients were previously healthy. None of them lived with the index patient. The secondary patients were between 53 and 72 years of age (mean, 58.3 years), and 4 of them were men. All had fever of at least 37.5°C for 3–6 days (median, 4 days). All complained of having loose stool, 1–3 episodes per day for 1–2 days. Three male patients (patients B, D, and F) developed pleural effusion, bronchitis, and pneumonia, respectively, during hospitalization. Patient E, who had a history of hepatitis B virus infection, experienced the lowest WBC and PLT counts among the 6 secondary patients. However, they all recovered through supportive treatment and were discharged in good condition. A timeline of key events is shown in Figure 1, and clinical features are shown in Table 1.

Epidemiological Investigation

On 8 May 2007, we received a report that 5 patients with fever of unknown cause were admitted to a county hospital. Epidemiological investigation and active surveillance were immediately initiated. On 9 May, another patient was identified. A standardized questionnaire was used to collect demographic information, clinical manifestations, history of exposure to the index patient (where, when, and how contact was made), history of exposure to wild animals, and extent of outdoor activity. Furthermore, public health officials interviewed family members, neighboring villagers, and all hospital staff who had provided medical service for any of the patients, and cross-checked several written timelines of the outbreak. Medical records were also reviewed for the time of discovery of the index patient and the secondary patients' onset and progression of illness.

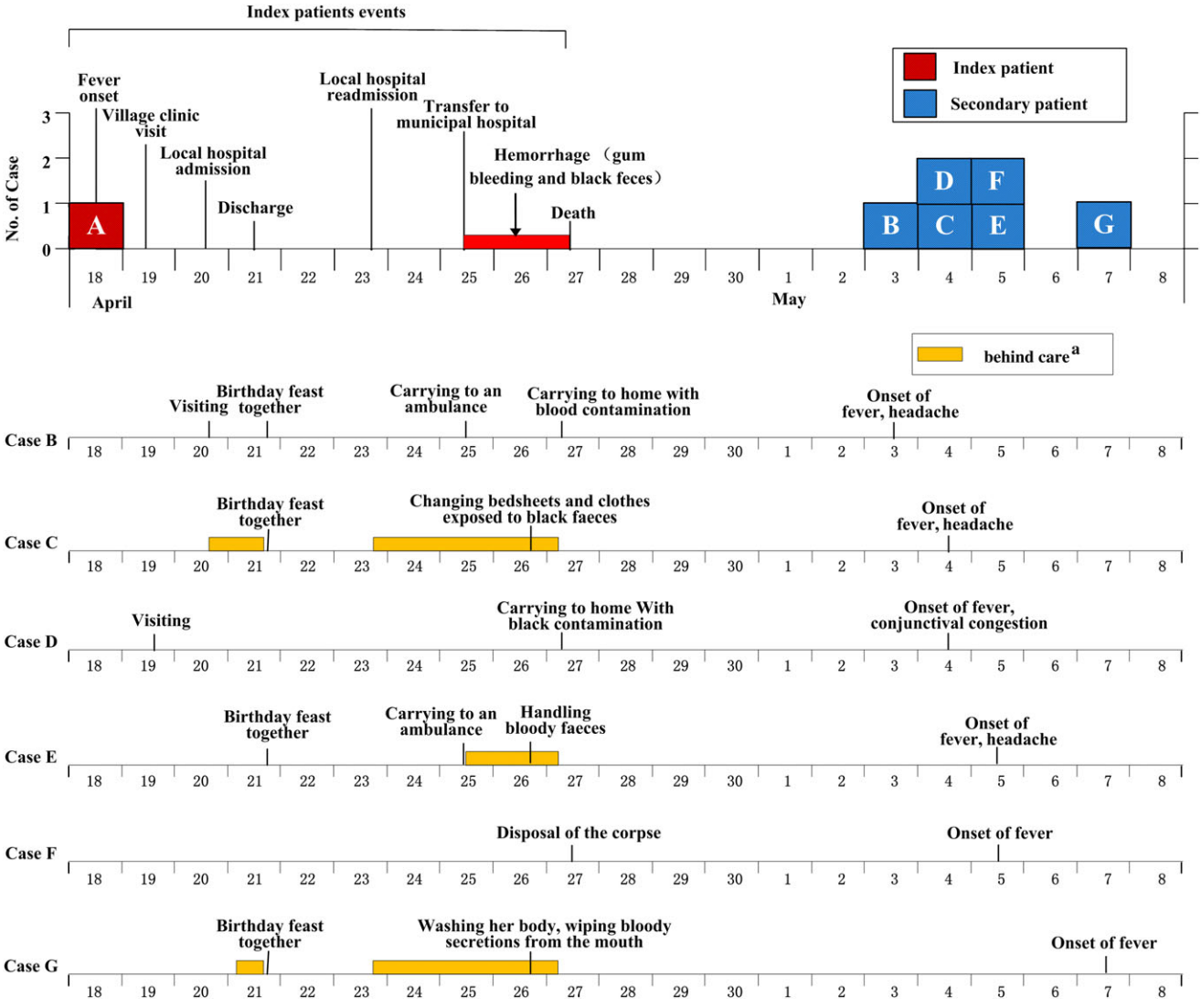

Figure 1. Epidemic curve shows progression of the family cluster and timeline of key events during the index patient's illness as well as pertinent exposure histories of secondary patients. [a]Exposure during period of providing bedside care may not have occurred continuously during the exposure period. Capital letters designate the corresponding secondary cases in the top and bottom panels.

By the time this family cluster was detected, the index patient had died and her body had been cremated; therefore, no specimens were available for further testing. Three serum specimens from each secondary patient were collected on 3 separate days (8 May 2007, 13 June 2007, and 17 September 2010) for a total of 18 specimens. All activities were conducted in accordance with the policies of the ethical committee of JS-CDC, and informed consent was obtained from the participants.

Laboratory Testing

In 2010, real-time reverse transcription polymerase chain reaction (RT-PCR) and serological testing were performed on blood samples (serum and EDTA blood) that had been collected from each secondary patient between days 3 and 10, after the onset of symptoms. All specimens had been stored at −70°C since initial testing in 2007.

RNA was extracted from serum or whole blood using a high pure viral RNA kit (Roche Diagnostics) according to the manufacturer's instructions. SFTS viral M and S genomic segments were amplified using specific primers and probes by RT-PCR assay. The primers and probes used in the real-time assay were synthesized according to the gene sequence of a SFTSV (GenBank accession numbers: HQ141601 to HQ141606).

Viral culture was performed on aliquots of specimens testing positive by RT-PCR. For virus isolation, 2 or 3 blind passages through Vero cells, as previously described, were performed [1, 5].

Modified microneutralization assay (MNA) and indirect immunofluorescence assays (IFA) were performed essentially as described previously for immunoglobulin G (IgG)-specific

Table 1. The Clinical Features of Patients Involved in a Family Cluster Occurred in 2007, Eastern China

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G
General information[a]							
Age, years, and gender	80, female	59, male	59, female	54, male	53, male	72, male	53,female
Occupation	Farmer	Farmer	Farmer	Farmer	Security guard	Farmer	Farmer
Relationship with patient A	NA	Son-in-law	Elder daughter	Nephew	Son-in-law	Nephew	Younger daughter
Clinical manifestations[a]							
Date of onset	April 18	May 3	May 4	May 4	May 5	May 5	May 7
Temperature, °C	39.2	39.0	36.9	38.0	38.9	37.9	39·3 °C
	(39.3)	(40.0)	(39.0)	(39.7)	(40.0)	(38.2)	(39.4 °C)
Respiratory symptoms	Cough	Cough	None	Cough, hemoptysis	Cough	Cough, short of breath	None
Gastrointestinal symptoms	Diarrhea	Nausea, vomiting, diarrhea	Vomiting, diarrhea	Diarrhea	Diarrhea	Nausea, vomiting,	Diarrhea
Others	Dysphoria, coma, confusion	Myalgia, headache	Myalgia, headache	Myalgia, headache	Myalgia, conjunctival congestion	Myalgia, headache	Myalgia, headache
Complications	Bronchopneumonia	Bronchitis	None	Pneumonia	None	Pleural effusions	None
Treated with dexamethasone or hydrocortisone	Yes	Yes	No	No	Yes	Yes	Yes
Days of hospitalization	6	17	10	25	16	11	11
Blood counts[a]							
White blood cells count ($\times 10^9$/L)	3.1 (1.6)	4.0 (2.2)	3.6 (2.9)	4.0 (2.5)	1.3 (0.9)	3.2 (2.2)	3·5 (2·6)
Lymphocytes count ($\times 10^9$/L)	0.9 (0.3)	0.7 (0.7)	0·7 (0.7)	0·7 (0.7)	0.3 (0.3)	1.3 (0.9)	0.7 (0.7)
Platelets count ($\times 10^9$/L)	48 (30)	91 (20)	64 (27)	67 (3)	71 (15)	22 (22)	74 (36)
Urine and stool routine tests[a]							
Proteinuria	NA	+	−	3+	3+	NA	−
Hematuria	NA	+	−	−	±	NA	+
Fecal occult blood	−	−	−	+	−	−	NA
Serum biochemistry[a]							
Alanine amino transferase (U/L)	573.0	31.2 (174.9)	11.4 (52.4)	21.7 (130.8)	39.1 (255.7)	70.6 (110.0)	22.2 (124.1)
Aspartate amino transferase (U/L)	3869.0	49.0 (324.0)	24.0 (63.4)	57.0 (405.9)	93.0 (472.9)	177.3 (177.3)	33.0 (127.7)
Creatinine (U/L)	188	69 (69)	41 (87)	82 (63)	109 (109)	72 (87)	53 (87)
Lactate dehydrogenase (U/L)	3094	295 (1266)	267 (267)	382 (1334)	555 (992)	704 (704)	293 (481)
Coagulation[a]							
Prothrombin time (s)	NA	12.1	NA	12.6	12.6	NA	NA
Activated partial thromboplastic time (s)	NA	25.3	NA	23.1	25.4	NA	NA
Fibrinogen (g/L)	NA	3.48	NA	6.17	3.39	NA	NA

Abbreviation: NA, not applicable.

[a] Data are measurement at admission (peak or nadir measurement during hospitalization). For the coagulation, above-mentioned markers were measured only 1 time on 15 May 2007. NA = Not applicable or not available.

antibodies to SFTSV [6]. For MNA, briefly, 100 50% tissue culture infective dose (TCID50) units of virus were pre-incubated with serial 2-fold dilutions of serum and then used to infect Vero cells in 96-well microtiter plates. For IFA, fixed Vero cells infected with SFTSV were incubated with diluted human serum and stained with fluorescein-labeled anti-human IgG secondary antibodies. Antigens for the testing were produced from a strain isolated from a patient in 2010.

RESULTS

Patient A was in a good physical condition before the onset of illness and was known to collect tea leaves from her tea garden on a hillside around the village where she lived. Her family recalled that she did not leave the village within 1 month preceding disease onset. The village where she lived is located in a typical hilly area with a population of ~150. No obvious change in mosquito density nor rising morbidity or mortality of poultry and livestock at that time was observed through an ecological survey.

Except for patient E, the other 5 secondary patients also lived in the same village but in separate houses or in an adjacent village <3 km away. Patient E worked as a security guard for a supermarket in another county ~40 km away. After hearing of his mother-in-law's illness, he returned to the village and took part in her birthday party on April 21. He provided bedside care after she was readmitted to the local hospital.

All 6 secondary patients denied a history of insect bites, exposure to wild animals, or participation in hunting activity in the month preceding illness onset. All, however, participated in the index patient's birthday party (April 21–22). Five patients, except patient G, reported contact with bloody secretions and/or handled feces of the index patient with unprotected hands during her hospitalization. Patient G, the index patient's nephew, also reported that he touched the blood of the index patient while handling her corpse.

An additional 85 persons were identified as patient A's contacts. Only 2 individuals lived in the household of the index case: the index case and her husband. However, another 19 individuals had contact with the index case but did not acquire infection. An additional 21 relatives and 45 medical personnel (1 from the village clinic, 38 from the county hospital, 6 from the regional hospital) also had contact. It is estimated that 192 persons attended patient A's funeral. Only 2 of the 19 family members reported exposure to patient A's blood with their bare hands. Public health officials interviewed all additional contacts and found that none became ill.

RNAs extracted from serum/blood specimens from the 6 secondary patients collected during the acute phase of their illness were identified as SFTS viral RNAs using RT-PCR. Positive results were confirmed through retesting of samples at China CDC. SFTSV was isolated from 1 preserved serum collected in May 2007 from 1 secondary patient (patient E) after 3 blind passages. Complete genomic sequencing and analysis of this isolate (GenBank accession number: JF837593 to JF837595) showed that it shared 96.0%–99.7% homology in nucleotide sequence with 2 strains (JS03 and JS04) isolated from sporadic patients in Jiangsu Province, 2010. Additional sequence of SFTSV M-segments (~406bp-498bp) from 3 other secondary cases (patients B, D, and G) showed no nucleotide changes with patient E, indicating that these viruses were most likely from the same origin. Serum obtained from the 6 secondary patients collected in their acute phase were negative (the titer of neutralization antibodies was <1:10) for antibodies to SFTSV by MNA, but paired convalescent-phase specimens obtained from those patients were positive. Additionally, seroconversion was further demonstrated by IFA. A summary of the results of diagnostic testing is shown in Table 2.

DISCUSSION

Although only recently identified, SFTSV appears to have been responsible for a family cluster of fever, thrombocytopenia, and leukopenia in eastern China in May 2007. We confirmed infection in all 6 secondary patients using multiple methods. SFTS viral RNA was detected using RT-PCR in acute-phase blood specimens from patients. Serum MNA and IFA documented seroconversion of specific IgG antibody to the novel virus between acute phase and convalescence phase serum samples. Finally, SFTSV was successfully isolated from 1 of the preserved specimens through 3 blind passages. Laboratory evidence demonstrated that the 6 secondary patients had recent infections with SFTSV, in accordance with the definition of a confirmed case issued by Chinese Ministry of Health in October 2010 [7].

Infection was most probably transmitted by direct contact between the index patient and 6 family members. Person-to-person transmission has been documented with other viruses of the family *Bunyaviridae* such as CCHF virus and Andes virus [8–11]. The phenomenon of person-to-person transmission has also been observed in a more recent outbreak (October 2010) in eastern China [12]. Four pieces of epidemiological evidence gathered in this investigation indicate that the most likely transmission route of SFTS in this cluster was person-to-person. First, all subsequent patients had a history of contact with patient A's blood or feces while providing bedside care during her hospitalization or handling her corpse after death, suggesting a possible mechanism of transmission. Patient E lived and worked in another county, but he developed illness 15 days after he returned to patient A's village and participated in events there. Second, all subsequent illnesses began during a brief period (from May 3 to 7), suggesting that infection was probably due to a common, single-point exposure. This hypothesis was

Table 2. Results of Diagnostic Testing of a Family Cluster Occurred in 2007, Eastern China

Patient	Relationship	Gender, age	Outcome	MNA[a]		IFA[b]			RT- PCR, 2007
				AP	CP	AP	CP	2010	
Patient A	Mother (Index patient)	F, 80	Fatal	NT	NT	NT	NT	NT	NT
Patient B	Elder son-in-law	M, 59	survived	<10	1280	<10	1280	80	Positive
Patient C	Elder daughter	F, 59	survived	<10	1280	<10	1280	80	Positive
Patient D	Nephew 1	M, 54	survived	<10	640	<10	2560	320	Positive
Patient E[c]	Younger son-in-law	M, 53	survived	<10	640	<10	1280	80	Positive
Patient F	Nephew 2	M, 72	survived	<10	640	<10	1280	80	Positive
Patient G	Younger daughter	F, 53	survived	<10	640	<10	1280	160	Positive

Abbreviations: F, female; M, male; MNA, microneutralization assay; AP, acute phase; CP, convalescent phase; IFA, indirect immunofluorescence assay; RT-PCR , real time reverse transcription polymerase chain reaction.

[a] MNA, AP: The serum specimens were collected on 8 May 2007. CP: The serum specimens were collected on 13 June 2007.

[b] IFA, AP: The serum specimens were collected on 8 May 2007. CP: The serum specimens were collected on 13 June 2007. 2010: The serum specimens were collected in 17 September 2010.

[c] The novel virus was isolated from the patient's serum collected in May 2007.

supported by the results of SFTSV M-segments sequences alignment from 4 of the subsequent patients. Third, all 6 secondary patients seroconverted to SFTSV positivity, and antibodies against SFTSV were still detected from the serum of the secondary patients collected >3 years after recovery. In contrast, a serological survey of 180 farmers from the same village or an adjacent village in 2010 found no one with antibodies to the SFTSV. Fourth, patient A's clinical symptoms were consistent with SFTS, although her diagnosis was not laboratory confirmed because no specimens were available for testing.

By contrast, no obvious evidence thus far showed that SFTSV can transmit through inhalation or droplets based on the following reasons. First, the pulmonary symptoms of the index case and 4 of the secondary cases developed in their later phase as a complication. Second, the medical staff who provided services for the index patient and patients who stayed in the same ward with the index patient did not become ill. Third, in 2010, when another family cluster was identified, no viral RNA was detected from collected throat swab and feces specimens from patients in their acute phases (unpublished data). Two additional family members reported that they provided bedside care or handled the corpse of patient A but did not develop symptoms. It is not clear why these individuals did not develop illness, but this might be linked to the manner of interaction, frequency, or duration of contact with the acute patient, or to infectious dose, individual susceptibility, and immune status [11].

We believe it is plausible that the index patient acquired her infection from the environment. She used to pick tea leaves in a grove filled with grasses and shrubs. In 2007, a survey identified dozens of ticks belonging to the species *Haemaphysalis longicornis* in this tea grove. SFTSV has been detected from this species of ticks [1]. Unfortunately, all of the ticks collected in 2007 were discarded after testing DNA for *A. phagocytophilium*; all were negative by PCR. Although it is possible that secondary cases contracted the infection from the environment, and the timing of the disease reflects different incubation times, we believe that this hypothesis is less likely. First, except for these 6 family patients, no other cases from the same area were reported at that time. Second, 5 secondary patients except patient E lived in the same village or an adjacent village preceding their illnesses, but their daily works mainly involved raising silkworms, which does not require frequent fieldwork; all denied tick bites or exposure to wild animals before disease onset. Finally, the incubation period of most SFTSV infections ranges from 5 days to 2 weeks, according to most studies to date. If the secondary cases shared a common exposure with the index patient, we would have expected their dates of illness onset to be earlier than May 3.

Confirmation of the etiological agent for the family cluster demonstrates that the novel virus may be traced back to at least the year 2007 or earlier. The SFTSV, however, caused several outbreaks in central China with a high case fatality, inciting panic in affected and surrounding provinces since 2009 [7]. Given this situation, together with the potential for increased transmission and resulting consequences of SFTS infection, more attention to the epidemiology and biology of this pathogen is required.

Our study suggests a transmission mode not previously reported for SFTS, and the public health significance needs further evaluation. In the past 2 years, almost all SFTS patients confirmed by China CDC occurred sporadically and were geographically dispersed [1, 7]. Therefore, the emergence of person-to-person transmission, coupled with the severity of SFTS, suggests that hospitals should strengthen infection control when patients with similar clinical symptoms initially present. This should include systematic and ongoing training of hospital personnel in infection control measures, restricting visitation and provision of bedside care for suspected SFTS patients by family members, and providing appropriate personal protective equipment to all caregivers. In addition, corpses of patients who

have died from hemorrhagic disease should only be handled by trained and properly outfitted persons.

To the best of our knowledge, the SFTSV is unique to China, and no epizootic has yet been reported. Whether the novel virus also exists in other regions of the world or if it has the capacity of spread to previously unaffected areas, as RVF virus, is unknown. One death among 7 patients corresponds to the 12% fatality rate found in the 171 sporadic patients reported by Yu et al [1] is as high as that of RVF virus in humans [1, 13–15]. In addition, because it is easily cultured and associated with a high mortality rate, together with no currently available effective antiviral drugs or vaccines, the virus should be considered a potential candidate as weapons for bioterrorism, and restrictions on its distribution and handling should be established and enforced [16, 17]. It is therefore critical to establish uniform laboratory diagnostic methods and conduct surveillance on suspected viral hemorrhagic fever patients in countries that have similar geographic location and climatic conditions as China [16]. Failure to do so may result in viral identification only after a large outbreak has occurred.

Notes

Authors and Contributors. Chang-jun Bao coordinated field epidemiology, all data analysis, and manuscript writing; Xi-ling Guo did viral isolation, indirect immunofluorescence assay; Xian Qi and Zhi-feng Li did the RT-PCR and micro-neutralization testing; Jian-li Hu and Ke Xu conducted field investigation and data collection; Ming-hao Zhou and Hai-tao Yang consulted study design and implementation; Jay K. Varma and John D. Klena consulted on data analysis, interpretation, and manuscript revision; Lun-biao Cui and Jun Shan did molecular diagnosis and genomic sequencing and analysis; Yong-jun Jiao, Xian Li, Yin Chen, Zheng Zhu, Tao Wu, Hai-yan Peng and Zhi-yang Shi were involved in viral antigens preparation and serological diagnosis; Lu-xun Li and Ai-hua Shen assisted or were involved in patient identification, contact follow-up, specimen collection; Wen-yuan Tao provided clinical data; Hua Wang was the project coordinator, responsible for the project design and implementation, and supervised all aspects of fieldwork, laboratory activities and data analysis.

Acknowledgments. We acknowledge the technical support and assistance with gene sequence of the novel bunyavirus of the National Institution for Viral Disease Control and Prevention, China Centers for Disease Control and Prevention (CDC). We are grateful to Nanjing First Hospital, Lishui County Hospital of Traditional Chinese Medicine, and Lishui County People's Hospital for providing medical records, and to Xiao-jun Lu and Lei Hong (staff from Nanjing Municipal CDC) for field epidemiological investigation and ecological survey support. We thank Prof Jun Zhang (University of Xiamen), senior lecturer Shannon Rutherford (Griffith University, Australia), and Dr Robert Fontaine (US CDC) for useful discussions and help with manuscript preparation. We also thank other colleagues from both our centre and affected areas who are not on the manuscript but provided suggestions and comments in the process of manuscript preparation or with sample collection.

Financial support. This work was supported by China Mega-Project for Infectious Disease [2009ZX10004-904] from Ministry of Science and Technology and Ministry of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of manuscript.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med **2011**; 364:1523–32.
2. Marty AM, Jahrling PB, Geisbert TW. Viral hemorrhagic fevers. Clin Lab Med **2006**; 26:345–86. viii.
3. Dumler JS, Madigan JE, Pusterla N, Bakken JS. Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment. Clin Infect Dis **2007**; 45((Suppl 1)):S45–51.
4. Zhang L, Liu Y, Ni D, et al. Nosocomial transmission of human granulocytic anaplasmosis in China. JAMA **2008**; 300:2263–70.
5. Bowen MD, Trappier SG, Sanchez AJ, et al. A reassortant bunyavirus isolated from acute hemorrhagic fever cases in Kenya and Somalia. Virology **2001**; 291:185–90.
6. Li C, Liu F, Liang M, et al. Hantavirus-like particles generated in CHO cells induce specific immune responses in C57BL/6 mice. Vaccine **2010**; 28:4294–300.
7. Ministry of Health of People's Republic of China. National guideline for prevention and control of severe fever with thrombocytopenia syndrome (2010 edition). Beijing, **2010**. The Ministry of Health of People's Republic of China. http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohwsyjbgs/s8348/201010/49272.htm
8. Martinez VP, Bellomo C, San JJ, et al. Person-to-person transmission of Andes virus. Emerg Infect Dis **2005**; 11:1848–53.
9. Harxhi A, Pilaca A, Delia Z, Pano K, Rezza G. Crimean-Congo hemorrhagic fever: a case of nosocomial transmission. Infection **2005**; 33:295–6.
10. Padula PJ, Edelstein A, Miguel SD, Lopez NM, Rossi CM, Rabinovich RD. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. Virology **1998**; 241:323–30.
11. Lazaro ME, Cantoni GE, Calanni LM, et al. Clusters of hantavirus infection, southern Argentina. Emerg Infect Dis **2007**; 13:104–10.
12. Bao CJ, Qi X, Wang H. A novel bunyavirus in china. N Engl J Med; 365:862-5.
13. Bird BH, Ksiazek TG, Nichol ST, Maclachlan NJ. Rift Valley fever virus. J Am Vet Med Assoc **2009**; 234:883–93.
14. Madani TA, Al-Mazrou YY, Al-Jeffri MH, et al. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. Clin Infect Dis **2003**; 37:1084–92.
15. Nguku PM, Sharif SK, Mutonga D, et al. An investigation of a major outbreak of Rift Valley fever in Kenya: 2006–2007. Am J Trop Med Hyg **2010**; 83((Suppl 2)):5–13.
16. Mandell RB, Flick R. Rift Valley fever virus: an unrecognized emerging threat? Hum Vaccin **2010**; 6:597–601.
17. Sidwell RW, Smee DF. Viruses of the Bunya- and Togaviridae families: potential as bioterrorism agents and means of control. Antiviral Res **2003**; 57:101–11.